

Estimating Incidence of Infectious Diseases
in
Canada Beyond Surveillance

by

Maria Major

A thesis

presented to the University of Waterloo

in fulfilment of the

thesis requirement for the degree of

Doctor of Philosophy

in

Public Health Sciences

Waterloo, Ontario, Canada, 2024

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Statement of Contributions

Maria Major was the sole author for Chapters 1 and 5, which were written under the supervision of Dr. Susan Horton and were not written for publication.

This thesis consists in part of three manuscripts written for publication; one which has been published and two additional manuscripts being prepared for publication. Exceptions to sole authorship of material are as follows:

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Chapter 2: Study 1

As the lead author of the research in study 1, I conceptualized and conducted the systematic literature, inspired by previous work by Fred Angulo in the US, under the supervision of Susan Horton. Laura Jiménez assisted with the literature review and screening. I conducted

all the data analysis, led the data interpretation, and wrote the first draft of the manuscript. My co-authors assisted in data review, interpretation, and manuscript development.

I wish to thank Jackie Stapleton, MLS, Liaison Librarian, University of Waterloo Library, for her assistance in development of the search strategies for this review and Arsh Maira Muhammad Muhyiddin, University of Waterloo, Health Studies (Honours, Co-op) student, for her assistance in development of Figure 1. I wish to thank Laura Jiménez for her assistance through the conduct of the literature review, for managing the administrative tasks associated with the literature and creation of the data tables, as well as preparing and formatting the manuscript for publication.

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Citation:

Major M, Majowicz SE, Oremus M, Jimenez LJ, Angulo FJ, Horton S. Systematic literature review of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) seroprevalence surveys in Canada through April 2021. *IJID Reg.* 2022 Sep;4:157-164. doi: 10.1016/j.ijregi.2022.07.010. Epub 2022 Jul 29. Received 9 April 2022; Received in revised form 23 July 2022; Accepted 25 July 2022 2772-7076/©2022 Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license.

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Supplementary material associated with this published work can be found in Appendix A, as well as in the online version at doi:[10.1016/j.ijregi.2022.07.010](https://doi.org/10.1016/j.ijregi.2022.07.010).

Chapter 3: Study 2

I am the lead investigator of the research in study 2, which is being funded by my employer, Pfizer ULC. I conceptualized and initiated the study, hired IQVIA to assist with the development of the protocol and billing code algorithm as well as the data extraction with Manitoba Population Research Data Repository (MPRDR). I have led the data analysis and interpretation for this thesis.

Members of the study team were involved with the protocol development, consulted upon the algorithm, and were involved in data interpretation and development of an abstract developed for submission to the Canadian Immunization Conference in May 2024, as well as a manuscript planned for submission to a peer-reviewed journal in 2024.

Study team members are Susan Horton (University of Waterloo), Mark Loeb (McMaster University), Natalie Nightingale (IQVIA), Calum Neish (IQVIA), Irene Wang (IQVIA), Saranya Nair (IQVIA), Kate Halsby (Pfizer, UK), Sarah Jeanette Willis (Pfizer, US), Holly Yu (Pfizer, US), Frederick J. Angulo (Pfizer, US), and James Stark (Pfizer, US).

Chapter 4: Study 3

As lead author, I conceptualized this study, constructed the Markov model, defined the data sources and parameters. I wrote the paper for this thesis and plan to prepare a manuscript in late 2024. I reviewed the model with Ashleigh Tuite, PhD, MPH, MSc, an experienced modeler and professor at the University of Toronto, Dalla Lana School of Public Health.

Abstract

Introduction

Public health surveillance provides valuable information about the epidemiologic trends of infectious diseases but is not designed to provide exact estimates of population-level disease incidence. Case reporting to public health surveillance may be impacted due to a variety of reasons: clinical misdiagnosis, sensitivity and specificity of laboratory testing assays producing false negative results, incomplete case information, failure to report to public health, patient access to healthcare resources, etc. Estimating the true incidence of a disease is particularly important when conducting health economic assessments that evaluate the value of public health interventions. Equally important is to investigate sources of bias in reporting by evaluating differences in case ascertainment by sub-group (age, race, socioeconomic status (SES), gender, etc). The aim of my thesis is to explore alternative methods of estimating incidence of infectious disease of public health importance and where possible, explore potential sources of bias.

Study 1: Using Seroprevalence to Estimate Incidence of SARS-CoV-2 in Canada

For study 1, a systematic literature review was conducted of SARS-CoV-2 seroprevalence studies in Canada. Disease incidence was estimated from seroprevalence studies, which were then grouped by region and age. Estimated incidence was compared to reported cases by calculating under-ascertainment ratios for each study. Under-ascertainment of cases was highest at the beginning of the pandemic, as access to testing was limited early on. Over time, the under-ascertainment declined, perhaps due to increased access to testing, but may have

been confounded by reports of reduced assay sensitivity of thresholds to lower titre levels over time. This work was published in July 2022.

Study 2: Estimating Incidence of Lyme Disease in Manitoba using Administrative Data

Lyme Disease (LD) is a growing public health threat in Canada due to the impact of environmental factors that favour the expansion of *Borrelia burgdorferi*-infected ticks (*Ixodes scapularis*) into Canada. It is widely accepted that LD cases are under reported in Canada, but there are no empirical estimates that quantify true incidence of disease. An algorithm developed by the Center for Disease Control, using administrative healthcare billing codes (ICD-9, ICD-10) for Lyme and prescription data, was clinically validated in several endemic Lyme regions within the US. Access to administrative claims databases is province specific with variation in the types of linked datasets available for research. To ensure compliance with the validated CDC protocol, we needed to have physician billing codes that were specific for LD, hospital discharge abstracts, emergency room visits and antibiotic prescriptions. Our investigation was limited to the eastern Canadian provinces, which is the only habitat for *I. scapularis* in Canada. Manitoba was selected as an ideal province to conduct this study as it met all the database criteria as well as provided access to public health serology test results for LD, which was not available to the CDC in their study. The algorithm was adapted to the Manitoba database and a protocol was submitted to the Manitoba data custodian for extraction. The primary objective was to estimate the incidence of LD from 2010-2021, overall, by patient characteristics (e.g., age, sex), and by local residential area. Secondary objectives were to describe the demographic and clinical characteristics of LD cases, and to estimate the clinical stage of patients based upon reported symptoms. The yearly incidence of Lyme cases identified

using this method were between 5.1 and 11.0 times higher than those reported to public health surveillance during the study period. There were no clear trends in the under-ascertainment over time. Due to the limitations of using administrative billing data, it was not possible to estimate the clinical stage of identified cases.

Study 3: Modeling the impact of elevated LD incidence on population health in Manitoba, Canada

LD is an emerging and growing public health threat in Canada due to climate change factors responsible for the rapid expansion of *Borrelia burgdorferi*-infected ticks (*Ixodes scapularis*) into densely populated areas. Under-reporting cases to public health and delays early treatment can lead to serious and persistent sequelae. The objective of this study was to construct a cohort LD model to assess the impact of elevated incidence on health-related quality-of-life.

The health-related quality-of-life impact of LD in Manitoba over a 10-year period resulted in loss of 13.8 QALYs for the base case (reported incidence) and 73.4 QALYs for the elevated incidence scenario. Our model estimated average direct healthcare costs of \$210 for the base case and \$1,029 for the elevated incidence scenario, although these costs were taken from an Ontario costing study from reported cases which may underestimate the true cost of treatment of more complicated cases that are untreated during the early clinical stages of LD. Receipt of costing data from Manitoba is expected in June 2024 and will replace the Ontario LD costing estimates. The model was most sensitive to variations in incidence rates and time spent with persistent sequelae, namely arthritis, neurologic sequelae, and Post-treatment Lyme

Disease Syndrome (PTLDS). Our model demonstrated that elevated incidence rates that account for under-reporting of LD in Manitoba have a substantial impact on health-related quality-of-life.

Conclusion

Using two infectious diseases of public health significance, lessons were learned by characterizing their under-ascertainment within the context of access to care, access to testing, and identified equity issues that impact case ascertainment and low disease awareness. The validity of HR-QoL or health economic estimates is questionable in light under-ascertainment. The goal of quantifying under-ascertainment of disease and evaluating the health-related quality-of-life impact provided important insights into burden of disease. Understanding the specific transmission patterns and immune profiles stimulated by exposure were important in designing the studies and interpreting results. Linked administrative datasets are an efficient method of conducting research while preserving patient privacy. Future efforts would benefit from increasing the kind of datasets included in provincial databases, such as inclusion of electronic health records to gather symptom-related data, as well as seroprevalence data from studies conducted by Canada Blood Services or public health. Methods to quantify the level of uncertainty of incidence estimates play an important role in the development and assessment of public health initiatives.

Acknowledgements

I would like to extend my sincere gratitude to everyone who has helped me with this doctoral dissertation. Your assistance, guidance, and patience, when many things did not go as planned and everything seemed to take longer than expected, is greatly appreciated. Your unwavering support, even during a global pandemic, is the reason I have reached this important milestone.

Firstly, I would like to thank my supervisor, Dr Susan Horton, for the guidance she has provided throughout the completion of my PhD. From helping me select courses that would supplement my knowledge and support the development of my thesis, to helping me shape my thesis, you were there for me at the beginning, middle and end of this journey. When my thesis took longer than expected, extending past the date of your retirement from the University of Waterloo, you stuck with me through to the end, for which I will be eternally grateful! Your mentorship was invaluable to me. As a mature student, I always felt comfortable coming to you with questions or advice on my work; you created most supportive learning environment I could imagine. I hope the contribution of my future work will live up to the personal investment you have made in my education.

To Mark Oremus, from the development of my thesis proposal you have always been there providing immediate and ongoing feedback that has been very valuable in shaping this doctoral work. Thank you very much for your help editing and revising this dissertation, as well as improving the structure of this work. You may have read this dissertation as many times as I have! From taking your epidemiology course at the beginning of my PhD, to the preparation of this dissertation, your impact has been immeasurably important to where it is today.

To Shannon Majowicz, thank you for your keen insights that have improved the quality of my work over these years, in the development of this dissertation. You challenge me to think deeply about the importance of my work and how it contributes to the broader body of academic literature. You have raised the bar and I think I will always hear your voice in my head as I write future manuscripts. (I hope one day I get to the stage where I will not need to check my work for double-spaces after punctuation!)

To Fred Angulo, you have been an important mentor to me, encouraging me in the development of this doctoral work. You have shown me important applications that have inspired the direction of my thesis and how it could be applied in a Canadian setting. Thank you for the time and effort you have devoted to shaping and reviewing this work, when I know how busy you have been in providing important epidemiologic support for the COVID vaccine development and evaluation.

To Laura Jiménez, your assistance has been greatly appreciated, through the conduct of the systematic literature review, managing many of the administrative and technological tasks, extraction, and creation of the data tables, as well as preparing and formatting the manuscript for publication. You helped me beyond the scope of your time as a summer intern, and continued to help in formatting this dissertation while you completed your graduate work at Dalhousie University. Your commitment and drive are exemplary, and I am confident that you have a very bright future ahead of you!

To my family, Rod, Everett, and Jack, thank you for your love and support that have made these past 12 years of part-time graduate studies and full-time work possible. You are and have always been my priority and the reason I get up in the morning. I love you!

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List of Abbreviations

CDC	Centers for Disease Control and Prevention
CITF	COVID-19 Immunity Taskforce
COVID-19	Coronavirus Disease of 2019
CNDSS	The Canadian Notifiable Disease Surveillance System
DAD	Discharge Abstract Database
DIN	Drug Identification Number
DPIN	Drug Program Information Network
ED	Emergency Department
EM	<i>Erythema Migrans</i>
ELISA	Enzyme-Linked Immunosorbent Assay
HR-QoL	Health-Related Quality-of-Life
ICD	International Classification of Diseases
IQR	Interquartile Range
LD	Lyme Disease
LOINC	Logical Observation Identifiers Names and Codes
MC-MS	Medical Claims-Medical Services
MHIR	Manitoba Health Insurance Registry
MPRDR	Manitoba Population Research Data Repository
NACRS	National Ambulatory Care Reporting System
OHIP	Ontario Health Insurance Plan
PHAC	Public Health Agency of Canada
PTLDS	Post-treatment Lyme Disease Syndrome

QALY	Quality-Adjusted Life Year
RHA	Regional Health Authority
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2

1. Chapter 1: General Introduction

1.1. Background

Epidemiologic surveillance is the systematic collection and analysis of health data for the purpose of evaluating the need for public health intervention (Centers for Disease Control, 1988). Public health surveillance for infectious diseases in Canada is an indispensable component of safeguarding the nation's well-being. Through a comprehensive network of monitoring systems and data collection, Canadian public health authorities diligently track the prevalence, spread, and impact of infectious diseases within the population. By scrutinizing various indicators such as disease incidence, demographic patterns, and geographic trends, public health professionals gain crucial insights into emerging threats, enabling timely interventions to mitigate risks and protect public health (Government of Canada, 2024b). This proactive approach is underpinned by a collaborative framework involving federal, provincial, and territorial health agencies, with the goal of providing a coordinated response to infectious disease outbreaks across the country. Advancements in technology and data analytics have enhanced the efficiency and effectiveness of surveillance efforts, empowering policymakers, and healthcare providers with actionable information to guide strategic decision-making (Government of Canada, 2021a).

The methodology and characteristics of public health surveillance systems vary to meet the specific goals such as detecting or monitoring outbreaks, monitoring trends and identifying contacts of cases for the purposes of administering prophylaxis. Based upon the public health significance, surveillance systems consist of a balance of the following attributes: simplicity, flexibility, acceptability, sensitivity, predictive value positive, representativeness, and timeliness

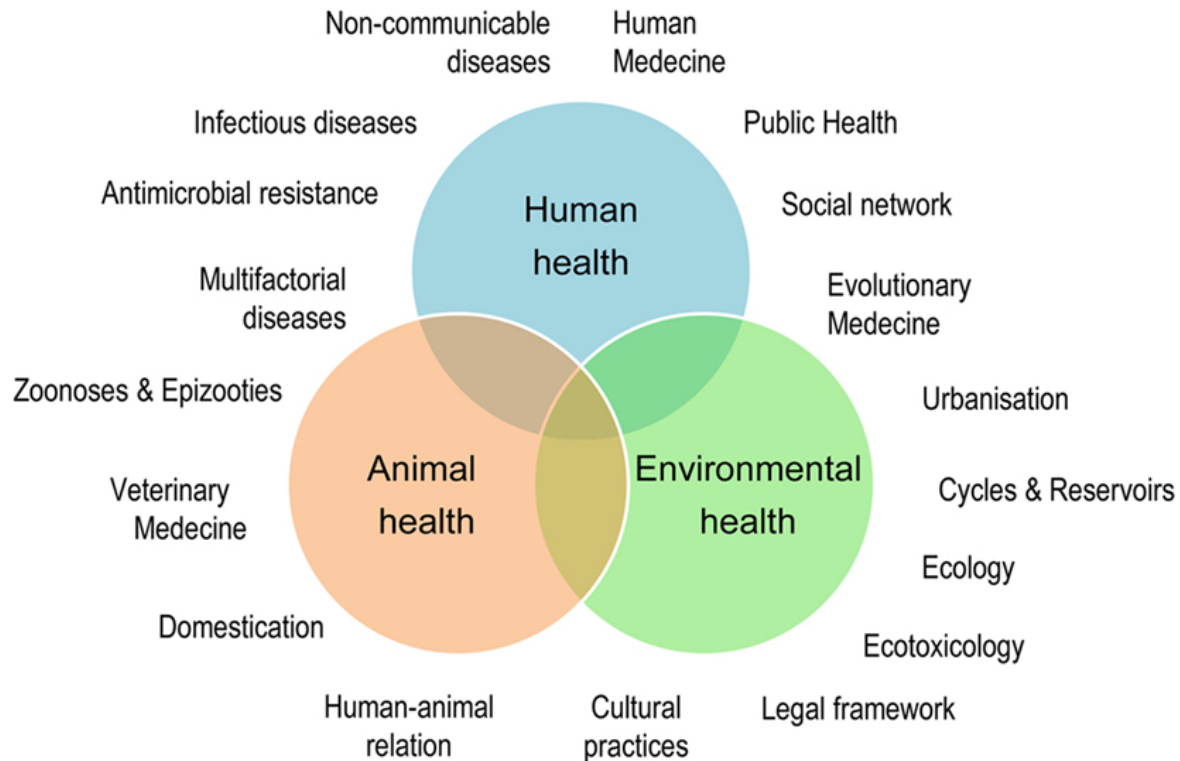
(Centers for Disease Control, 1988). The ability of public health surveillance systems in meeting those goals is important however there are no accepted frameworks currently used to evaluate the quality of surveillance systems and limited peer-reviewed literature in this field (Ramlackhan et al., 2023). Barriers to funding, capacity, and access to surveillance pose a serious threat to the validity of this data, impacting the integrity of public health policy (Smith et al., 2023). As Canada continues to confront evolving health challenges such as the elevated risk of zoonotic diseases and pandemics, fueled in part by ecological and climate change factors, investment in public health surveillance remains pivotal in promoting resilience and safeguarding the health and well-being of its citizens, by the generation of robust public health policy decision-making (Peyre et al., 2022).

The Coronavirus Disease of 2019 (COVID-19) pandemic underscored the critical importance of understanding infectious disease epidemiology and surveillance in Canada but uncovered substantial barriers. With its rapid spread and devastating impact on global health and economies, the pandemic highlighted the necessity for robust surveillance systems capable of detecting, monitoring, and responding to emerging infectious threats effectively (Government of Canada, 2021b). In Canada, the pandemic exposed gaps in public health infrastructure and highlighted the need for coordinated efforts among various levels of government and healthcare institutions to combat such crises. Specifically, pandemic preparedness and surveillance capacity were liabilities in the early stages of the pandemic, which created barriers and delays in implementing important health policy decisions such as masking in public (Government of Canada, 2021a). The pandemic emphasized the need to collect and utilize healthcare evidence (Government of Canada, 2021b). A qualitative study that

evaluated the impact of public health system centralization and integration on COVID-19 responses in 3 Canadian provinces (Alberta, Ontario, and Quebec), found that centralized, integrated systems led to quicker and more effective COVID-19 responses (Smith et al., 2023). As Canada continues to navigate the complexities of infectious disease control and prevention, the lessons learned from the COVID-19 pandemic will undoubtedly inform future strategies to better protect public health and ensure preparedness for future outbreaks.

Zoonotic infections represent 61% of infectious diseases of public health importance, and 75% of emerging infectious disease pathogens (Taylor et al., 2001). The One Health concept provides a holistic framework that is built upon the interconnectedness of human health, animal health and ecosystem health (Figure 1) (Destoumieux-Garzon et al., 2018). The emergence of zoonotic infections is directly related to the health of ecosystems, which impacts the spread of infectious agents through vector organisms and their hosts (Destoumieux-Garzon et al., 2018). Monitoring zoonotic infections in a manner that reflects the One Health approach adds additional challenges in the development of surveillance systems, due to the multi-disciplinary coordination needed at the policy-level, the institutional-level and the operational-level (Bordier et al., 2020).

Figure 1: The One Health concept: a holistic, transdisciplinary, and multisectoral approach of Health.



Source: (Destoumieux-Garzon et al., 2018)

An emerging zoonotic threat in Canada is LD, the most commonly reported vector-borne disease in Canada, caused by *Borrelia burgdorferi* (*B. burgdorferi*) *sensu stricto*, which is transmitted to humans by *Ixodes pacificus* (*I. pacificus*) or western blacklegged tick in British Columbia and *Ixodes scapularis* (*I. scapularis*) or blacklegged tick in central and eastern Canada (Gasmi et al., 2022). LD may be transmitted when an infected tick, typically a nymph or adult female, feeds on a human for an extended period. Deer, rodents, and birds are the reservoir for the bacterium and infect the tick hosts that feed upon them. They are also responsible for disbursement of ticks into new areas. The ticks in turn, feed on humans leading to LD infections (Gasmi et al., 2019).

Provinces and territories use inconsistent surveillance methods to track the expansion of *I. scapularis* and *B. burgdorferi* and to generate maps of LD high risk areas (Robinson et al., 2023). Passive tick surveillance involves the submission of ticks by citizens, either by mail, or more recently through an online platform, where individuals can upload pictures of ticks to an app for species verification and geo-tracking of its location (eTick, 2021). Active surveillance is when ticks are collected by field surveillance experts in the wild, using specific methods such as tick dragging or ticks collected from animal capture (Robinson et al., 2023). An assessment of these methods have found that dragging alone has high specificity and low sensitivity, but may be sufficient to define a high risk area, because the capture of ticks through this method indicates a high density of ticks established in the habitat (Ogden et al., 2014). Climate change factors and the increased urbanization of society have favoured an expansion of the *I. scapularis* habitat, due to encroachment of forested areas and increases in ambient temperature, that are projected to increase the size and number of high-risk areas in Canada (Ogden et al., 2024). Due to inconsistent methods and rapid tick expansion, tick maps are not a comprehensive method of assessing risk of LD acquisition.

LD is a multi-system disease with the clinical manifestations categorized into 3 stages, early localized LD, early disseminated LD, and late disseminated LD. The stages can overlap but may also occur in progression, generally in patients who are untreated during the early stages of infection. Early localized LD is the acute phase of the illness, which occurs between 2 – 30 days after a tick bite. Up to 80% of patients present with *erythema migrans* (EM), the characteristic bullseye rash. Patients may also experience flu-like symptoms such as fever, malaise, myalgia, headache, and lymphadenopathy. Laboratory testing using the recommended two-tiered

method has low sensitivity ($\approx 40\%$) during this stage, as individuals usually have not generated sufficient antibody level, which may lead to false negative results (Charlton et al., 2021; Lindsay et al., 2014). Early disseminated disease occurs between 1 – 3 months post-tick bite, usually when patients are not treated during the early stage of disease and the bacterium disseminates via the bloodstream and lymphatic system to other body sites causing damage mainly in the musculoskeletal system. Complications include but are not limited to, multiple EM lesions, neurologic manifestations, aseptic meningitis, cranial neuropathy (Bell's palsy), and Lyme carditis (Government of Canada, 2022). Late disseminated disease occurs more than 3 months post-tick bite and can persist for months to years. Complications include Lyme arthritis, Baker's cyst, meningitis, and subacute mild encephalopathy, all of which can affect memory and concentration (Murison et al., 2023).

Early treatment for LD is important to prevent progression of disease and acquisition of persistent sequelae. Many physicians in Canada follow the Infectious Disease Society of America treatment guidelines for treatment of LD (*personal communication from Dr. Mark Loeb*) (Lantos et al., 2021). For this reason, post-exposure prophylactic treatment after a tick bite can be obtained without a prescription in pharmacies in most high risk provinces (Canadian Pharmacists Association, 2023). In Manitoba, individuals who have been bitten by a tick may seek prophylactic treatment with 1 dose of doxycycline if the following conditions apply: the tick can be reliably identified as an adult or nymph blacklegged tick (*I. scapularis*), and the tick was attached for > 36 hours or tick is engorged, and the tick bite was acquired from a high risk area (anywhere in southern Manitoba, south of the 53rd parallel, with suitable habitat), and doxycycline is not contraindicated (Manitoba Health, 2021). Treatment of early-stage disease is

typically a 2-week course of antimicrobial therapy, such as doxycycline and requires a physician's assessment (Government of Canada, 2022). Five to ten percent of patients may experience prolonged symptoms due to LD which is referred to as Post-Treatment Lyme Disease Syndrome (PTLDS). Treatment of persistent symptoms, without signs of active infection, with antibiotics is not recommended (Centers for Disease Control, 2022; Lantos et al., 2021).

LD has been a notifiable disease in Canada since 2009, and provinces and territories (P/T) voluntarily reported cases to the Public Health Agency of Canada (PHAC) through the Canadian Notifiable Disease Surveillance System (CNDSS) (Gasmi et al., 2022). Confirmed and probable LD cases may be reported to public health, using the most current case definition of LD developed in 2016. Confirmed case definition is clinical evidence of illness with laboratory confirmation by one of the following methods: isolation of *B. burgdorferi* from a clinical specimen as specified by current guidelines or detection of *B. burgdorferi* DNA by PCR testing on synovial fluid, cerebrospinal fluid, EM tissue biopsies or blood and by methods specified by current guidelines. Confirmed cases can also be diagnosed clinically, in an individual who resides in a high-risk area and has laboratory confirmation of infection from a positive serologic test using the two-tiered approach. The two-tiered testing approach uses an ELISA first, then if positive, is followed by a western blot assay that target *B. burgdorferi* proteins (Government of Canada, 2022). Probable cases can be registered to surveillance if there is clinical evidence of LD, without history of residence or visit to a LD risk area, with laboratory confirmation or may be diagnosed clinically in patients with EM, without laboratory confirmation but with a history of residence in or visit to a LD risk area (Government of Canada, 2022). Reported LD cases in

Canada have risen from 144 cases reported in 2009 to 3,147 cases reported in 2021, of which 95.6% were from Ontario, Québec, and Nova Scotia (Public Health Agency of Canada, 2023c).

In 2011, PHAC developed the LD Enhanced Surveillance (LDES) system to collect additional information on location of tick exposure, clinical findings, and laboratory reports. Eight provinces participate in the enhanced surveillance including British Columbia, Alberta, Manitoba, Ontario, New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador (Murison et al., 2023). Clinical characterisation of reported LD surveillance data from LDES (excluding Quebec and Manitoba) indicate that LD is a bimodal disease, with peak incidence rates in children aged 5-9 years and adults over 60 years, with a male predominance (Murison et al., 2023). LD is a seasonal disease in Canada, based upon the climatic suitability for tick survival, leading to peak incidence from May through September, but late disseminated cases were more likely to be diagnosed January through March, about 8 months after initial infection (Murison et al., 2023). In the eastern provinces of Nova Scotia and New Brunswick, most reported cases were of the early localized disease stage, while in Ontario, most reported cases were of the late disseminated disease stage, indicating that cases were not identified and treated early (Murison et al., 2023). Over time, diagnosis of cases shifted towards the early localized disease stage, which may reflect an improvement in early detection and treatment, however the proportion of cases diagnosed in the late disseminated stage in Ontario is higher than is seen in the US (Centers for Disease Control, 2022; Murison et al., 2023).

1.2. Rationale for Study

The overarching theme of my thesis is to explore different study methods and approaches to estimate the burden of two infectious diseases of public health importance in Canada. This research focused on addressing gaps in the understanding of two infectious disease that have under-recognized or mischaracterized burden of disease, namely SARS-CoV-2 and LD. Early in the pandemic, SARS-CoV-2 was a novel pathogen with unknown mechanism of transmissibility from person-to-person. Understanding of transmission patterns of previous coronavirus outbreaks initially led to health policy initiatives that focused on restriction of testing to travellers from specific regions. In addition, early issues with laboratory capacity led to strained surveillance and under-assessment of case reporting (Government of Canada, 2021a). Seroprevalence surveys conducted during that period were useful to estimate the spread and case count of COVID-19 in the absence of accurate surveillance data.

Despite the increases in reported cases in recent years, most public health experts believe that LD is substantially underreported in Canada (Lloyd & Hawkins, 2018; Ogden et al., 2024). Reasons for underreporting may include lack of awareness, misdiagnoses, failure to seek health care, or lack of reporting to public health surveillance. Expansion of tick habitats may also be the cause of increased risk areas and increased density in current high-risk areas. A modelling study that estimates the impact of climate change and other ecologic factors on tick habitat expansion into densely populated areas of Canada, projects that after correcting for under reporting (by a factor of 13), that the annual LD case count will rise to between 120,000 and 500,000 by 2050 (Ogden et al., 2024).

In the US, 16 states are classified as high-incidence jurisdictions, which is defined by the Centers for Disease Control and Prevention (CDC) as an incidence of 10 cases per 100,000, per year, for 3 consecutive years (Centers for Disease Control, 2022). Notably, based upon cases reported to public health surveillance, the only province that would be classified as high incidence in Canada using the CDC definition is Nova Scotia (Public Health Agency of Canada, 2023b; Public Health Agency of Canada, 2023c; Gasmi et al., 2022). In the US, despite the established areas of high incidence and high awareness of disease, cases were believed to be under-reported to surveillance. To estimate the under-ascertainment of LD cases, the CDC developed an algorithm using administrative claims (physician billing codes for Lyme, with antibiotic prescription within 30 days), to extract proposed cases from a large claims database (Kugeler et al., 2021; Schwartz et al., 2021). Annual incidence of LD diagnoses estimated from this study from 2010 – 2018 were between 49 to 88 cases per 100,000 persons, approximately 6–8 times higher than cases reported through notifiable disease surveillance (Schwartz et al., 2021). A validation study was conducted in Massachusetts, USA, during July 2000 through June 2019 by performing chart reviews on a subset of LD cases identified by the CDC algorithm. The positive predictive value (PPV) for confirmed, probable, or suspected cases was 93.8% (95% CI 88.1%–97.3%); the PPV was 66.4% (95% CI 57.5%–74.5%) for confirmed and probable cases only, validating that this was a reasonable method that could be used to identify cases from administrative claims data (Cocoros et al., 2023). While LD cases are believed to be under-reported in Canada, a similar study such as the one described in the previous paragraph has not yet been conducted in any Canadian public health jurisdiction.

Estimating infectious disease burden extends beyond the realm of public health surveillance, offering invaluable insights into the broader societal impact and facilitating more comprehensive healthcare planning. Beyond merely counting cases, estimating disease burden allows for a deeper understanding of the associated morbidity, mortality, and economic consequences within communities. By examining factors such as quality-adjusted life years (QALYs), disability-adjusted life years (DALYs) and years of life lost (YLL), policymakers may gain a clearer picture of the true toll of infectious diseases on both individuals and society (GBD, 2020). Moreover, estimating disease burden aids in identifying vulnerable populations disproportionately affected by certain diseases, guiding targeted interventions to mitigate disparities in healthcare access and outcomes. This was observed by the Canadian Blood Services (CBS) seroprevalence studies, which utilized demographic data to identify that who resided in low income areas were at elevated risk of exposure to SARS-CoV-2 early in the pandemic, possibly due to crowded living conditions and the inability to isolate (Saeed et al., 2021). Using a holistic approach in the evaluation of infectious disease burden not only enhances epidemic preparedness, but also underscores the importance of investing in preventative measures and healthcare infrastructure to effectively combat infectious diseases.

1.3 Thesis Structure

This thesis consists of 3 studies:

Study 1: Systematic literature review of SARS-CoV-2 seroprevalence surveys in Canada through April 2021.

This previously published work (Major et al., 2022) is a systematic literature review of Canadian seroprevalence surveys for SARS-CoV-2, during the early stages of the pandemic. The

included studies were conducted using a variety of laboratory testing methods, specimen sources, and sample frames, which created too much heterogeneity to pool results in a meta-analysis. However, using an alternative approach known as synthesis without meta-analysis (SWiM), structured analyses were performed with the included studies, to evaluate trends over time and by geographic region, age-group, and sex (Campbell et al., 2020). Comparisons of seroprevalence estimates were made to surveillance reports by calculating the under-ascertainment ratios, which provided meaningful insights into SARS-CoV-2 surveillance criteria, natural immunity to SARS-CoV-2, and sensitivity of laboratory assays.

Study 2: Estimating Incidence of LD in Manitoba using Administrative Data

The incidence of LD in Canada is growing due to environmental factors that have been responsible for increasing the spread of ticks into densely populated areas of Canada. LD cases are under-reported to surveillance for several reasons. Individuals at early stages of disease have non-specific influenza-like symptoms, the characteristic bulls-eye rash does not happen in all cases or may be difficult to detect, and there could be low awareness of risk. In this study, we used a validated algorithm developed by the CDC to extract proposed Lyme cases from administrative health claims data. We developed a protocol that adheres to the CDC algorithm and submitted it to the Manitoba Centre for Health Policy (MCHP), who extracted the LD cases from the Manitoba Population Research Data Repository (MPRDR) for 2010 through 2021. Annual incidence rates were calculated for the overall population and by age group, sex, geographic region. Comparisons were made to reported rates to evaluate under-reporting of LD cases.

Study 3: Modeling the impact of elevated LD incidence on population health in Manitoba, Canada

We constructed a Markov state transition model for LD, to evaluate the difference in health-related quality-of-life scores between the reported rate of LD and the elevated incidence rate of LD from the administrative data study (Study 2, Major et al.) that identified un-reported Lyme cases. Health states included in the model were being well, early localized LD, early disseminated LD, late disseminated LD, PTLDS, dead, or recovered, with transitions to clinical manifestations and sequelae. The model had monthly cycles and ran for 120 cycles to capture incident cases, persistent sequelae, and PTLDS.

2. Chapter 2: Study 1 Systematic literature review of SARS-CoV-2 seroprevalence surveys in Canada through April 2021

Major M, Majowicz SE, Oremus M, Jimenez LJ, Angulo FJ, Horton S. Systematic literature review of SARS-CoV-2 seroprevalence surveys in Canada through April 2021. *IJID Reg.* 2022 Sep;4:157-164. doi: 10.1016/j.ijregi.2022.07.010.

2.1. Abstract

Objectives: To estimate the proportion of the population infected by SARS-CoV-2 in Canada through April 2021, 16 months into the coronavirus disease 2019 (COVID- 19) pandemic and 4 months after COVID-19 vaccines became available.

Methods: Publication databases, preprint servers, public health databases and the grey literature were searched for seroprevalence surveys conducted in Canada from 1 November 2019 to 10 July 2021. Studies were assessed for bias using the Joanna Briggs Checklist. Numbers of infections derived from seroprevalence estimates were compared with reported cases to estimate under-ascertainment ratios.

Results: In total, 12 serosurveys with 210,321 participants were identified. Three (25%) serosurveys were conducted at national level, one (8.3%) was conducted at provincial level, and eight (66.7%) were conducted at local level. All 12 serosurveys had moderate or high risk of bias. The proportion of the population infected by April 2021 was low (2.6%). The proportion of the population infected was higher in surveys of residents of long- term care facilities (43.0–86%), workers at long-term care facilities (22.4–32.4%), and workers in healthcare institutions (1.4–14%).

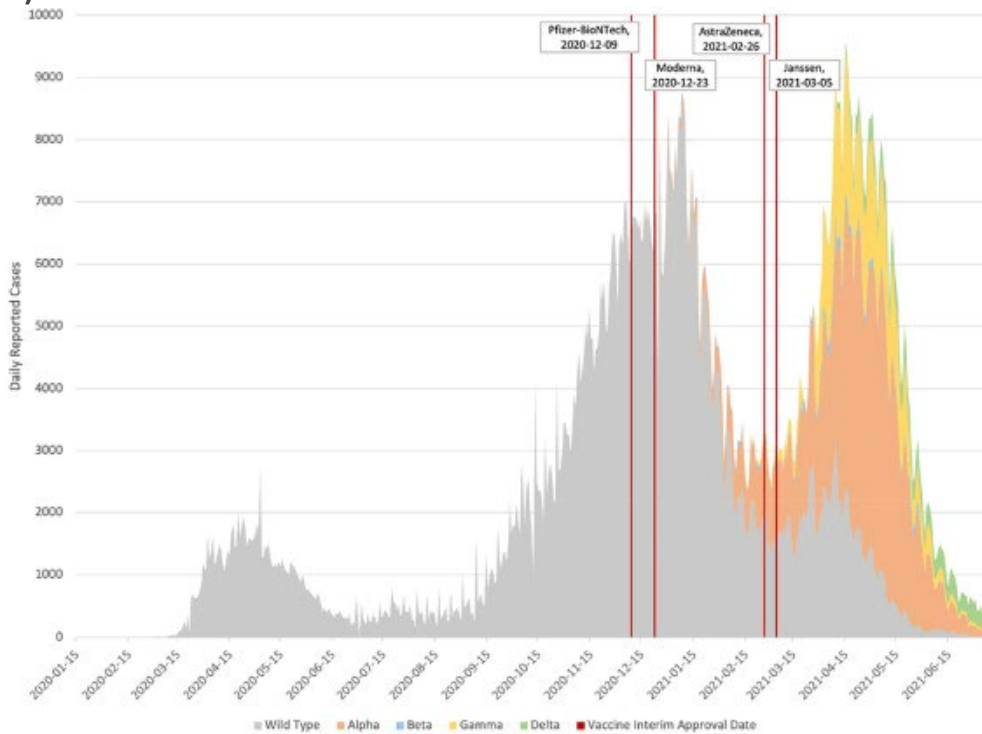
Conclusions: As of April 2021, the proportion of the population infected by SARS-CoV-2 was low in the overall population of Canada, but was high in healthcare facilities, particularly long-term care facilities, supporting the need for vaccines.

2.2. Introduction

The first reported case of coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, in Canada was in Toronto on 25 January 2020, in a traveller from Wuhan, China (Canadian Institute of Health Information, 2021). As of April 2021, 1,219,418 cases of COVID-19 and 24,219 deaths (Government of Canada, 2021b) had been reported in Canada (population 38,048,738) (Statistics Canada, 2021b). COVID-19 vaccines became available in Canada in December 2020, administered first to healthcare workers and residents of long-term care facilities. Vaccine availability remained limited in early 2021, with only 29% of the population aged ≥ 16 years receiving a first dose of vaccine by April 2021. Through mid-2021, Canada had experienced three waves of COVID-19 (Figure 2). The latter waves were of increasing magnitude and associated with the dissemination of SARS-CoV-2 variants B.1.1.7 (Alpha) and B.1.617.2 (Delta), which were more transmissible than the wild-type SARS-CoV-2 strain (Government of Canada, 2021b). To reduce community transmission, restrictive pandemic measures were enacted by each level of government, based upon the scope of their responsibilities. The federal government focused on international travel restrictions and border closures, with all other measures enacted by provincial/territorial/municipal governments. This led to substantial variability, ranging from the probusiness policies of Alberta to the most restrictive policies of the Atlantic provinces (Hale et al., 2021). The number of cases of COVID-19 reported in Canada is derived from provincial public health surveillance of laboratory-confirmed SARS-CoV-2. Laboratory confirmation is based upon molecular testing (real-time,

reverse transcription polymerase chain reaction) to detect SARS- CoV-2 genetic material from nasopharyngeal specimens (Ontario Ministry of Health, 2021).

Figure 2: Trends in cases of coronavirus disease 2019 in Canada (31 January 2020 – 10 July 2021)



The number of reported cases does not include all individuals infected with SARS-CoV-2 for several reasons. Asymptomatic and mild infections are unlikely to be laboratory tested for SARS-CoV-2 due to reduced access or lack of awareness for the need of testing, yet represent an important source of community transmission, estimated to be the cause of up to 44% of cases (He et al., 2020). Furthermore, limited testing capacity requires screening protocols which vary by jurisdiction, but generally prioritize access to symptomatic individuals (Hale et al., 2021). Laboratory-based surveillance also relies on reporting of laboratory-confirmed cases to surveillance. For these and other reasons, public health case counts under-ascertain the

number of individuals infected with SARS-CoV-2. Most patients infected with SARS-CoV-2 will generate a detectable immune response within a few weeks of infection (Charlton et al., 2021). Serological assays have been developed that can measure SARS-CoV-2 antibodies either by total antibody level or by individual isotypes, immunoglobulin G (IgG), immunoglobulin M (IgM) and immunoglobulin A (IgA), generated in response to SARS-CoV-2 proteins [nucleocapsid (N) or spike (S) protein] (Charlton et al., 2021). These assays are primarily used to estimate population-level exposure to SARS-CoV-2, but also have limited clinical uses. The long-term persistence of detectable antibodies is not known, although assays have been observed to lose sensitivity after approximately 4 months due to antibody waning following natural infection, increasing the potential for false-negative results (Perez-Saez et al., 2021). As available COVID-19 vaccines are based on the S protein, vaccine-induced immunity only generates antibodies to the S protein. This allows serological assays that measure antibodies to the N protein the ability to distinguish immunity derived from natural infection from that derived from vaccination. Many jurisdictions in Canada have conducted population-based SARS-CoV-2 serosurveys in accordance with the World Health Organization UNITY protocol, which guides the conduct of seroprevalence surveys to assess the prevalence of SARS-CoV-2 infection and monitor population immunity (World Health Organization, 2020). This review was conducted to understand the extent of SARS-CoV-2 infection in Canada through April 2021, and thereby estimate the extent of under-ascertainment by public health surveillance in the first 16 months of the pandemic and after 4 months of vaccine availability. The aims were to: (1) identify SARS-CoV-2 seroprevalence surveys conducted in Canada; and (2) provide a comparison of seroprevalence estimates over time, and by region and study method.

2.3. Methods

2.3.1. Information sources and search strategy

This systematic literature review was conducted in accordance with PRISMA guidelines (Table S1, see online supplementary material), and the protocol and search strategy were registered with PROSPERO (CRD42021246958) and the National Collaborating Centre for Methods and Tools (ID 401) (Major et al., 2021; Page et al., 2021). PubMed and Scopus were searched using a search strategy developed in consultation with a health sciences librarian. Pre-prints were searched on the MedRxiv and BioRxiv servers. A grey literature search was conducted by hand searching specific websites and online COVID-19 data repositories. Data disseminated by press release was searched using Google News advanced search. The search dates used were November 2019 to 10 July 2021 in order to factor in a time lag for publication of reports that would enable estimation of the extent of SARS-CoV-2 infection through April 2021. References in both of Canada's official languages (English and French) were included. Detailed search strategies can be found in Appendix A; Tables S2–S6. This review included studies that reported SARS-CoV-2 serological surveys conducted in Canada in humans, that estimated seroprevalence for a defined population in a distinct geographical area within a specified time period. Studies were included if they reported seroprevalence, sample size, sampling interval dates and sample frame. Studies included in this review used a validated serological assay to measure antibodies to SARS-CoV-2, either total antibodies or by individual isotype (IgG, IgM, IgA), generated in response to exposure to one or more of the SARS-CoV-2 proteins [N, S, receptor-binding domain (RBD)]. Cohort and cross-sectional studies were included, while all other designs (e.g., case–control studies, case reports, review articles, assay

validation studies) were excluded. The inclusion and exclusion criteria are shown in Appendix A; Table S7.

2.3.2. Data extraction and quality assessment

A single reviewer (LJJ) executed the searches and entered references into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia: www.covidence.org). A single reviewer (MM) screened articles, and a second reviewer (LJJ) verified and provided translation support for French language articles. Discrepancies regarding study inclusion were settled by consensus and expert input from co-authors (MM, LJJ, MO, FA). If two or more studies reported seroprevalence estimates from the same serological survey and period, the most current and complete study was included. Data items from the included studies were extracted and entered into an Excel (Microsoft Corp., Redmond, WA, USA) template by one author (LJJ), then reviewed by a second author (MM). Missing data items were marked as not reported. Data items collected for each included study were grouped into four categories: publication level information, serological assay characteristics, study characteristics and outcome level information (Table S8, see online supplementary material). An individual article was defined as a published or non-published study or report that provided one or more seroprevalence estimates. Individual articles that were part of a repeated cross-sectional assessment using identical methodology were grouped as companion studies but were analysed individually. The number of studies, articles and distinct seroprevalence estimates that were included in this study are shown in the PRISMA flowchart (Figure 3) and the full data extraction sheet is given in Appendix A; Tables S12–S14. Studies were defined as national, provincial, or regional, based upon the jurisdiction of sampling, with studies sampling most

provinces/territories being classified as national and studies sampling most health regions within a province classed as provincial. The Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data (JB Checklist) was adapted to assess the potential risk of bias for each included article (Munn et al., 2015). Risk assessment appraisals were conducted by one author (MM), in consultation with other members of the study team (LJJ, FA, MO). Overall risk of bias for included articles was classified as low, moderate, high, or unclear. The checklist and criteria for appraisals are shown in Appendix A; Table S9.

2.3.3. Synthesis methods

Data from the included articles were assessed using the SWiM (Synthesis Without Meta-analysis) reporting guidelines for systematic reviews (Campbell et al., 2020). Seroprevalence estimates were grouped by jurisdiction; classified as national, provincial, or local; then ranked by sampling interval to assess trends over time. Articles were grouped by target sample frame, classified as population-wide or population-specific. Sample sizes were also pooled to assess representation by age and jurisdiction and reported in structured tables. Descriptive methods were used to investigate sources of heterogeneity. Structured tables were created to visually inspect study characteristics, sampling method and assay characteristics, and to test algorithms used to determine their impact on seropositivity. Articles were also grouped by risk of bias. For serosurveys that used population-wide sample frames, seroprevalence estimates were used to estimate the cumulative number of cases of SARS-CoV-2 in Canada. To assess the extent of under-ascertainment by public health surveillance, national and provincial seroprevalence estimates were converted to an 'estimated' case count based upon the last day of the sampling interval, then compared with the corresponding cumulative reported case counts on that date,

to assess concordance. Estimated case counts were derived by multiplying seroprevalence estimates by the population estimate for the jurisdiction, obtained from Statistics Canada, on the final day of the sampling interval (Statistics Canada, 2021c). Confidence intervals for the seroprevalence estimates were used to produce confidence intervals for the estimated case counts using the same method. Reported case counts were extracted from the national COVID-19 case surveillance reporting databases (Government of Canada, 2021b). Ratios of estimated case counts to reported cases were calculated for each sampling interval to visually assess differences between estimated case counts and reported cases. To assess trends over time, regional reported seroprevalence assessments were grouped, ranked by sampling timeframe, and displayed in bar graphs. Serosurveys that assessed population-specific sample frames, such as healthcare workers and long-term care residents, were grouped into structured tables and ranked by sampling date. Population-wide and population-specific serosurveys that reported estimates for children aged < 19 years were combined and ordered by sampling date.

2.4. Results

2.4.1. Study Characteristics

This systematic literature review yielded 208 published or unpublished studies, of which 33 underwent full-text screening (Figure 3). Fifteen (45%) of these 33 articles met the exclusion criteria. The primary reasons for exclusion were duplicates ($n = 12$) or inappropriate outcome measures ($n = 3$). Of the 18 included articles, six (33%) had been published in peer-reviewed journals, two (11%) had been published as pre-prints, and 10 (55%) had been published as reports posted on websites (Appendix A; Table S13).

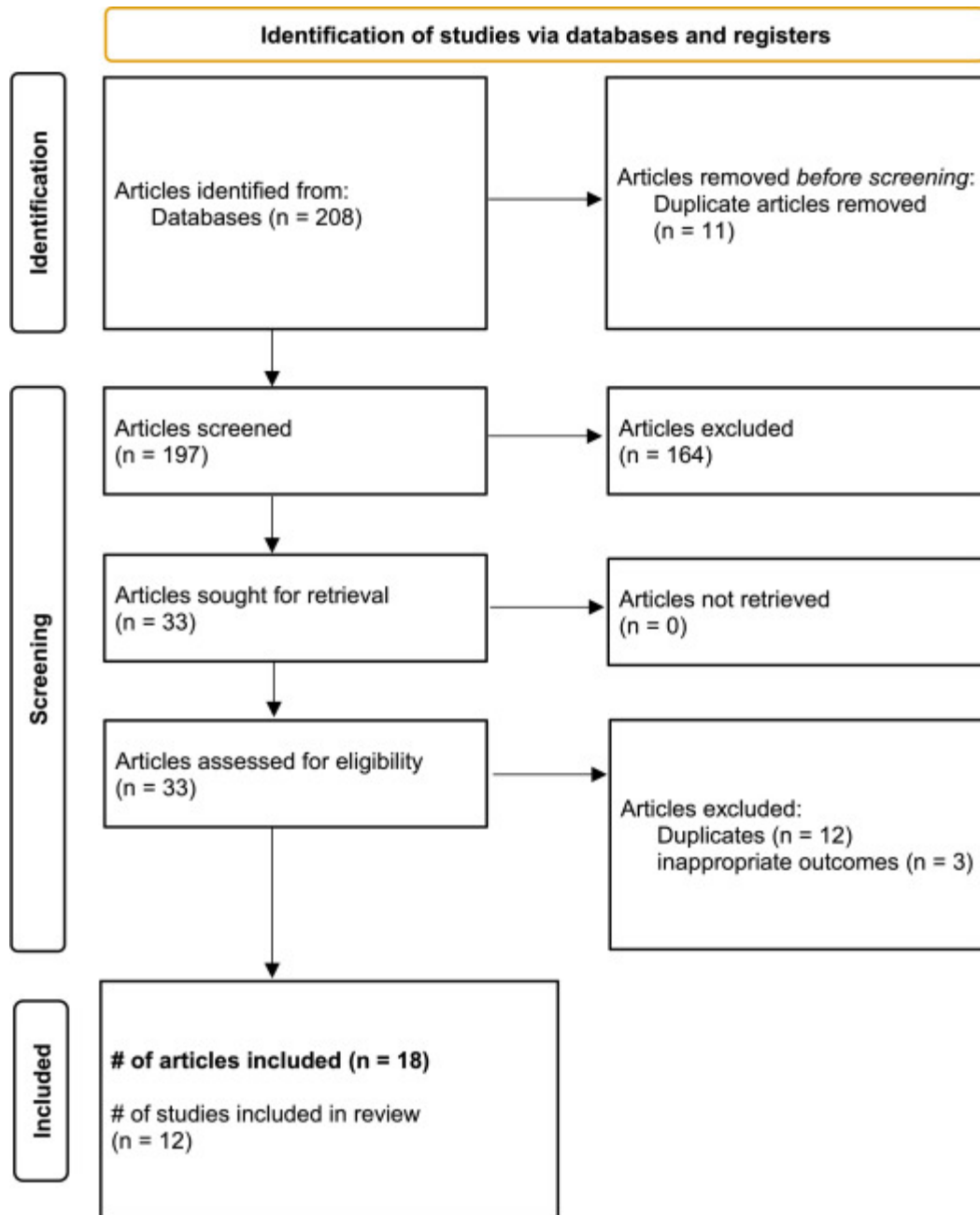


Figure 3: PRISMA Flowchart

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.

The seroprevalence results of the 18 articles were provided by 12 different serosurveys: four articles reported results (each at one different time point) from one serosurvey, four articles reported results (each at one or two different time points) from one serosurvey, two

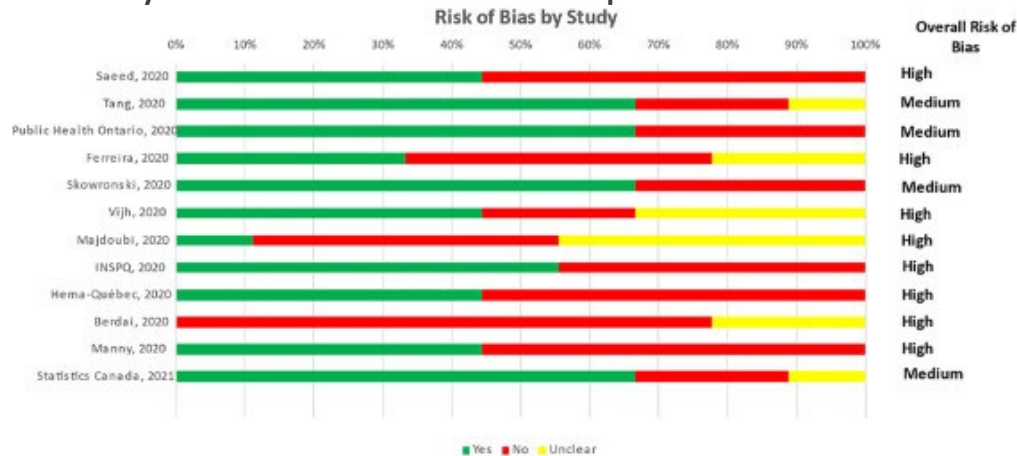
articles reported results (each at two time points) from two different serosurveys, and eight articles reported results (each at one time point) from eight different serosurveys (Appendix A; Table S13). The dates for seroprevalence estimates in the 18 articles ranged from 5 March 2020 to April 2021, and seroprevalence estimates ranged from 0% to 56% (Appendix A; Table S13). The 12 serosurveys in the 18 articles had a total sample size of 210,321 participants (Appendix A; Table S14). Of the 12 serosurveys, three (25%) were of national scope (with seroprevalence stratified by sex, age group, province and selected urban centres), one (8.3%) was Ontario-based (seroprevalence stratified by sex and age group), and eight (66.6%) were conducted in large urban centres (Table 1). Of the 12 serosurveys, six (50%) targeted a general population sample frame and six (50%) targeted specific populations, primarily children, healthcare workers, and residents of long-term care facilities (Table 1). The study participants in the 12 serosurveys included 57.4% from Ontario, 28.5% from western Canada (British Columbia, Alberta, Saskatchewan and Manitoba, including Northern Territories), 8.5% from eastern Canada (New Brunswick, Nova Scotia, Newfoundland and Prince Edward County) and 5.6% from Quebec; these regional groupings represent 40%, 32%, 6% and 22% of Canada's population, respectively (Appendix A; Table S13) (Statistics Canada, 2021a). In the 12 serosurveys, children aged < 19 years comprised 2.9% of the participants compared with 21% of the population (Statistics Canada, 2021a). Adults aged 20–64 years represented 75.4% of serosurvey participants compared with 60% of the population (Table 2) (Statistics Canada, 2021a).

Table 1: Characteristics of 12 serosurveys conducted in Canada (March 2020–April 2021).

Characteristic	Serosurveys n (%) (total n=12)
Geographical scope	
National	3 (25%)
Provincial	1 (8.3%)
Local	8 (66.7%)
Target population	
Population-wide	6 (50%)
Population-specific	6 (50%)
Sampling method	
Probability sampling	2 (16.7%)
Non-probability sampling	10 (83.3%)
Testing algorithm to determine seropositivity	
Positive to one test alone	8 (66.6%)
Positive to two or more tests	4 (33.3%)
Risk of bias	
High	8 (66.6%)
Moderate	4 (33.3%)
Low	0

Using the JB Checklist, four studies were assessed as moderate risk of bias and eight were assessed as high risk of bias (Figure 4). The main sources of bias were attributed to the representativeness of the sampling frame, sensitivity and specificity of the assay, lack of orthogonal testing algorithm to determine seropositivity, and non-probability sampling (Appendix A; Table S10).

Figure 4: Risk-of-bias assessment of the 12 severe acute respiratory syndrome coronavirus-2 serosurveys in Canada from March 2020 to April 2021.



2.4.2. Population-based seroprevalence estimates

Of the six serosurveys that targeted a general population sampling frame, two used residual specimens collected from the healthcare system, two used sera from blood donors, and two procured specimens prospectively (Table 3). Four of the six serosurveys determined seropositivity by testing positive using a single assay, while the remaining two serosurveys used an orthogonal approach (i.e., seropositivity to two or more assays). Estimates obtained using dried blood spots (DBS) were higher than those from residual sera or blood donors at national level (1.7% vs 0.7%) and in Ontario (2.35% vs 1.1% and 0.88%), but not in Quebec (1.56% vs 2.2%) in July 2020 (Table 3). The highest national seroprevalence estimates were reported by Tang et al. (2021) using DBS (2.5% in September 2020) and Statistics Canada (2021c) (2.6% in April 2021) (Table 3). The highest regional seroprevalence estimates were reported in western Canada in November 2020, with Manitoba at 8.6% and Saskatchewan at 4.2% (Table 3). The lowest seroprevalence estimates were reported in the eastern provinces, ranging from 0% to 1.3% (Appendix A; Table S13).

Table 2: Age of participants in the 12 severe acute respiratory syndrome coronavirus-2 serosurveys conducted in Canada (March 2020–April 2021)

Age groups	Sample size (n=199,621) ^a
Children (0–18 years)	5792 (2.9%)
Adults (19–64 years)	150,497 (75.4%)
Elderly (≥65 years)	43,332 (21.7%)

^a Excluding [Statistics Canada \(2021c\)](#) due to lack of reporting of sample stratification.

When seroprevalence estimates were compared with the cumulative SARS-CoV-2 case counts reported to public health surveillance, a varying degree of under-ascertainment was exhibited over the first 18 months of the pandemic. Under-ascertainment was particularly high

early in the pandemic, between March and November 2020, independent of jurisdiction, assay, or study method (Table 3). Using national data, the under-ascertainment ratio was highest at 6.1x in September 2020. Regionally, the ratio was highest at 8.8x in Ontario in July 2020 (Table 3). National and regional under-ascertainment ratios declined over time, with limited evidence of under-ascertainment of cases infected with SARS-CoV-2 by April 2021. The decline in under-ascertainment by public health surveillance nationally was also evident in Ontario, Quebec, British Columbia, Alberta, Saskatchewan, and Manitoba (Table 3).

Table 3: Population-wide under-ascertainment of cases of coronavirus disease 2019 by jurisdiction and sampling interval

Jurisdiction	Study	Dates samples were collected	Specimens	Seroprevalence (95% CI)	Estimated cases (n) (95% CI)	Reported cases (n)	Under-ascertainment ratio (95% CI)
Canada	Saeed et al., 2021 ^a	9 May–21 Jul 2020	Blood donor	0.7 (0.63–0.76)	265,859 (239,273–288,647)	111,684	2.4x (2.1–2.6)
	Tang et al., 2021	May–Jul 2020	Dried blood spot	1.7 (NR)	645,658	116,298	5.6x
	Tang et al., 2021	Aug–Sept 2020	Dried blood spot	2.54 (NR)	965,333	158,758	6.1x
Ontario	Canadian Blood Services, 2020 ^a	12–31 Oct 2020	Blood donor	0.88 (0.73–1.04)	334,470 (277,458–395,283)	235,444	1.4x (1.2–1.7)
	Canadian Blood Services, 2021 ^a	7–25 Nov 2020	Blood donor	1.51 (1.31–1.71)	573,921 (497,905–649,937)	347,466	1.7x (1.4–1.9)
	Canadian Blood Services, 2021 ^b	1–27 Jan 2021	Blood donor	1.99 (1.84–2.15)	757,170 (700,097–818,048)	761,226	1.0x (0.9–1.1)
	Statistics Canada, 2021c	Nov 2020–Apr 2021	Dried blood spot	2.6 (1.6–3.2)	989,267 (608,780–1,217,560)	1,219,418	0.8x (0.5–1.0)
	Public Health Ontario, 2020c	27 Mar–30 Apr 2020	Residual laboratory sera	0.5 (0.1–1.5)	73,445 (14,689–220,336)	16,187	4.5x (0.9–13.6)
	Public Health Ontario, 2020c	26–31 May 2020	Residual laboratory sera	1.5 (0.7–2.2)	220,852 (103,064–323,917)	27,859	7.9x (3.7–11.6)
	Public Health Ontario, 2020c	5–30 Jun 2020	Residual laboratory sera	1.1 (0.8–1.3)	161,958 (117,788–191,405)	35,068	4.6x (3.4–5.5)
	Saeed et al., 2021	9 May–21 Jul 2020	Blood donor	0.88 (0.78–0.98)	129,659 (114,925–144,393)	37,942	3.4x (3.0–3.8)
	Public Health Ontario, 2020b	4–31 Jul 2020	Residual laboratory sera	1.1 (0.8–1.3)	162,074 (117,872–191,542)	39,209	4.1x (3.0–4.9)
	Tang et al., 2021	May–Jul 2020	Dried blood spot	2.35 (NR)	346,249	39,209	8.8x (NR)
	Public Health Ontario, 2020a	1–31 Aug 2020	Residual laboratory sera	1.1 (0.8–1.3)	162,074 (117,872–191,542)	42,309	3.8x (2.8–4.5)
	Public Health Ontario, 2020d	3–30 Sept 2020	Residual laboratory sera	0.7 (0.4–0.9)	103,138 (58,936–132,606)	51,710	2.0x (1.1–2.6)
Public Health Ontario, 2020d	1–30 Oct 2020	Residual laboratory sera	1.2 (0.9–1.4)	176,802 (132,602–206,269)	74,715	2.4x (1.8–2.8)	
Canadian Blood Services, 2020	12–31 Oct 2020	Blood donor	0.87 (0.65–1.08)	128,182 (95,768–159,122)	75,730	1.7x (1.3–2.1)	
Canadian Blood Services, 2021a	7–25 Nov 2020	Blood donor	0.77 (0.56–0.97)	113,448 (82,508–142,915)	107,883	1.1x (0.8–1.3)	
Canadian Blood Services, 2021b	1–27 Jan 2021	Blood donor	1.82 (1.61–2.04)	268,545 (237,559–301,006)	260,370	1.0x (0.9–1.2)	
Statistics Canada, 2021c	Nov 2020–Apr 2021	Dried blood spot	2.5 (1.1–4.4)	368,880 (162,307–649,229)	463,364	0.8x (0.4–1.4)	
Quebec	Héma-Québec, 2020 ^b	25 May–9 Jul 2020	Blood donor	2.2 (1.9–2.56)	188,585 (162,869–219,445)	56,216	3.4x (2.9–3.9)
Tang et al., 2021	May–July 2020	Dried blood spot	1.56 (NR)	133,763	59,131	2.3x	
Statistics Canada, 2021c	Nov 2020–Apr 2021	Dried blood spot	3.2 (2.1–4.1)	274,386 (180,066–351,557)	349,773	0.8x (0.5–1.0)	
British Columbia	Saeed et al., 2021	9 May–21 Jul 2020	Blood donor	0.56 (0.42–0.69)	28,797 (21,598–35,483)	3328	8.7x (6.5–10.7)
Canadian Blood Services, 2020 ^a	12–31 Oct 2020	Blood donor	0.86 (0.5–1.23)	44,254 (25,729–63,293)	14,733	3.0x (1.7–4.3)	
Canadian Blood Services, 2021a ^a	7–25 Nov 2020	Blood donor	1.51 (1.04–1.97)	77,701 (53,516–101,372)	29,086	2.7x (1.8,3.5)	
Canadian Blood Services, 2021b ^a	1–27 Jan 2021	Blood donor	1.48 (1.16–1.81)	76,265 (59,775–93,270)	65,719	1.2x (0.9–1.4)	
Statistics Canada, 2021c	Nov 2020–Apr 2021	Dried blood spot	1.6 (0.5–2.9)	82,449 (25,765–149,438)	129,482	0.6x (0.2–1.2)	
Alberta	Saeed et al., 2021 ^a	9 May–21 Jul 2020	Blood donor	0.48 (0.31–0.62)	21,255 (13,727–27,454)	9728	0.8x (0.5–1.0)
Canadian Blood Services, 2020 ^a	12–31 Oct 2020	Blood donor	0.76 (0.38–1.14)	33,653 (16,827–50,480)	28,245	0.7x (0.3–1.0)	
Canadian Blood Services, 2021a ^a	7–25 Nov 2020	Blood donor	1.79 (1.24–2.34)	79,263 (54,908–103,617)	50,801	1.6x (1.1–2.0)	
Canadian Blood Services, 2021b ^a	1–27 Jan 2021	Blood donor	3.41 (2.89–3.94)	151,276 (128,208–174,789)	122,360	1.2x (1.0–1.4)	
Statistics Canada, 2021c	Nov 2020–Apr 2021	Dried blood spot	4.0 (2.6–5.7)	177,450 (115,343–252,867)	190,734	0.9x (0.6–1.3)	
Saskatchewan	Canadian Blood Services, 2020 ^a	12–31 Oct 2020	Blood donor	0.17 (0–0.59)	2,002 (0–6,949)	3144	0.6x (0–2.2)
Canadian Blood Services, 2021a ^a	7–25 Nov 2020	Blood donor	4.17 (2.57–5.77)	49,114 (30,269–67,958)	7047	7.0x (4.3–9.6)	
Canadian Blood Services, 2021b ^a	1–27 Jan 2021	Blood donor	2.46 (1.59–3.33)	28,999 (18,743–39,255)	22,794	1.3x (0.8–1.7)	
Statistics Canada, 2021c	Nov 2020–Apr 2021	Dried blood spot	2.9 (1.6–4.3)	34,186 (18,861–50,690)	41,098	0.8x (0.5–1.2)	
Manitoba	Canadian Blood Services, 2020 ^a	12–31 Oct 2020	Blood donor	2.96 (1.7–2.43)	40,832 (23,451–58,352)	5723	7.1x (4.1–10.2)
Canadian Blood Services, 2021a ^a	7–25 Nov 2020	Blood donor	8.56 (6.51–10.62)	118,083 (89,803–146,500)	14,907	7.9x (6.0–9.8)	
Canadian Blood Services, 2021b ^a	1–27 Jan 2021	Blood donor	3.92 (2.92–4.93)	54,133 (40,323–68,080)	28,996	1.9x (1.4–2.3)	
Statistics Canada, 2021c	Nov 2020–Apr 2021	Dried blood spot	2.4 (1.2–3.6)	33,142 (16,571–49,714)	36,629	0.9x (0.5–1.4)	

^a References did not include data from Quebec (Saeed et al., 2021; Canadian Blood Services, 2020; Canadian Blood Services, 2021a; Canadian Blood Services, 2021b; Canadian Blood Services, 2021c)^b Reference only sampled 12/18 public health regions in the province (Héma-Québec, 2020).

2.4.3. Population-specific seroprevalence estimates

Assessments of population-specific seroprevalence were grouped into three categories: long-term care residents, healthcare workers, and children aged < 19 years. The highest seroprevalence estimates were observed in residents of two long-term care facilities (LTCFs) in Vancouver at 86.1% and 43.0% (Table S12A, see online supplementary material) following

facility-wide outbreaks in May 2020 before the licensure of vaccines (Vijh et al., 2021). Staff working in these two LTCFs on the same date had the highest reported seroprevalence amongst workers within healthcare institutions at 32.4% and 22.4% (Table S12B, see online supplementary material) (Vijh et al., 2021). Another study that compared the seroprevalence of intensive care workers in Montreal in July–September 2020 between high- and low-prevalence settings reported seropositivity of 14.0 and 3.1, respectively (Table S12B, see on-line supplementary material) (Brousseau et al., 2020). Seroprevalence estimates for children were obtained from different settings and recruitment methods, ranging from age-stratified population-based serosurveys to studies that only recruited children within hospital settings; as such, meaningful comparison was difficult. Seroprevalence estimates from a single study by Statistics Canada from November 2020 to April 2021 which used random national sampling reported higher prevalence in children aged < 19 years (3.3%) compared with adults aged 20–59 years (2.9%) or > 60 years (1.4%) (Table S13, see online supplementary material), and demonstrated an increase over time from 0% in March 2020 to 3.3% in April 2021 (Table S12C, see online supplementary material) (Statistics Canada, 2021c).

2.5. Discussion and Conclusion

Through April 2021, SARS-CoV-2 seroprevalence in Canada, and thereby the proportion of the population that had been infected by SARS-CoV-2, was low. The low seroprevalence mirrors the relatively low incidence of reported infections in Canada. While the Canadian serosurveys varied considerably in terms of their methods of recruitment, assays used and testing algorithms, limiting the ability to make direct comparisons between studies, some similarities could be observed. Across all studies, seroprevalence estimates increased over time, with a

peak in autumn 2020 followed by a plateau or decline by spring 2021 (Table 3 and Table S13, see online supplementary material). Correspondingly, there was a reduction in under-ascertainment ratios over time for most of the population-based serosurveys, with reported cases at parity with seroprevalence by April 2021. The downward trend observed for under-reporting multipliers over the course of the pandemic was consistent with a similar analysis conducted in the USA (Angulo et al., 2021). This is likely to be due to the initial SARS-CoV-2 testing capacity and protocols which restricted testing to symptomatic travellers, and likely led to substantial under-identification of infected individuals during the early part of the pandemic (Ontario Ministry of Health, 2021). As capacity improved and guidelines evolved to include testing of asymptomatic high-risk groups, an increased proportion of infected people were identified. Another explanation could involve the characteristics of the assays used in the studies, and the durability of immunity following natural infection. Anti-nucleocapsid antibody levels have been observed to wane as early as 4 months following natural infection, which has been known to lead to underestimation of cases by increasing the probability of false-negative results as time between natural infection and serology testing increases (Perez-Saez et al., 2021). This was demonstrated within the Ontario serosurvey when Public Health Ontario retested sera samples from their August 2020 samples using a reduced assay threshold to assess assay sensitivity. A 16% increase in seropositivity was detected, which they attributed to waning of anti-nucleocapsid antibodies as time from infection increased (Bolotin et al., 2021). The high seroprevalence in residents of LTCFs and healthcare workers reflects their higher frequency of exposure to the virus, particularly for LTCF residents who are vulnerable to poor health outcomes from SARS-CoV-2 infection. The widespread occurrence of LTCF out- breaks

during the first wave of the pandemic, and the high seroprevalence observed in LTCF staff, support the implementation of strict infection control policies to limit transmission in this health-care setting. As the pandemic progressed, the increasing seroprevalence observed in children and young adults raises concern about their contribution to community transmission of the virus within the community. Seroprevalence rates observed in Canada were lower than rates observed in other countries. Population-wide seroprevalence studies in the USA report approximately double the seroprevalence compared with that found in Canada during comparable time periods, with estimates up 10x higher in New York, Connecticut, Louisiana, and Florida (Angulo et al., 2021). National age-stratified seroprevalence estimates conducted by the CDC in April 2021 reported positivity of 27% in children aged < 17 years, 24% in adults aged 18–49 years, 20% in adults aged 50–64 years, and 13% in adults aged > 65 years, approximately 10x higher than Canadian national estimates by age group at that time (Center for Disease Control, 2021), when comparing assay results capturing natural, not vaccine-induced, immunity in both countries. A global seroprevalence review revealed population-wide seroprevalence estimates from areas in Eastern Europe, Russia and the Middle East to be substantially higher compared with Canada (13–16%), with an overall median seroprevalence rate of 4.5% (Bobrovitz et al., 2021). The average under-ascertainment ratio calculated within the global review was 18.1x higher than the reported incidence of COVID-19, which was higher than that observed in Canada, but demonstrates a similar issue with relying upon reported infections to monitor population exposure to SARS-CoV-2 (Bobrovitz et al., 2021). The difference observed between Canada and other jurisdictions may be due to Canada’s stringent public health response to the pandemic. Canada implemented extensive and prolonged lockdowns, which

included cessation of in-person education, primary healthcare service disruptions, closure of non-essential business, travel restrictions, and closure of US border crossing; these measures likely reduced community transmission from November 2020 to April 2021 (Canadian Institute for Health Information, 2021; Hale et al., 2021). Differences in recruitment, testing and study methods used in the Canadian seroprevalence surveys had advantages and disadvantages in evaluating the population-level exposure to SARS-CoV-2. The use of residual sera from healthcare services laboratories has the advantage of easy access to a large, geographically representative sample frame, as well as being a relatively fast and convenient specimen source, particularly within the conditions of a pandemic lockdown. However, this may disproportionately represent individuals with medical co-morbidities and under-represent children based upon medical-seeking behaviours and clinical standards for ordering specimen collection, particularly in children. Similarly, testing of residual sera from blood donor banks is a convenient and large specimen source. However, screening protocols for donating blood may lead to over-representation of healthier, urban populations (Atsma & de Vegt, 2011), and understandably would not provide any representation of children. Due to their advantages, study designs using residual sera and blood donors have been endorsed by the World Health Organization for SARS-CoV-2 seroprevalence surveys (World Health Organization, 2020). Prospective, randomized studies have the advantage of being more representative, but generally suffer from low response rates as subjects need to be motivated to comply with study activities and contribute specimen samples. The largest prospective seroprevalence survey in Canada recruited over 11,000 subjects, and collected specimens as well as conducting extensive surveys to assess the demographic and socioeconomic factors associated with SARS-CoV-2

exposure (Evans et al., 2022). The novel DBS assay used in this study provided some advantages in overcoming the need to travel to a laboratory for specimen collection, as subjects were able to self-administer the test at home and submit their samples by post. This may have facilitated participation of vulnerable populations, who may have been less likely to have access to primary care or to donate blood. This study described higher seropositivity in visible minorities, aboriginal populations and populations working in public-facing roles during the pandemic (Evans et al., 2022). The DBS assay also had the ability to test for three SARS-CoV-2 immune targets (N, S, RBD), which allows the distinction between naturally acquired immunity post infection and vaccine-mediated immunity; this has become an important factor as vaccines based upon the S protein became widely accessible in Spring 2021. COVID-19 vaccines were not widely available in Canada at the time of this analysis (April 2021). At that time, they were only available to healthcare workers and residents of LTCFs, so this review period primarily covers a period when the general population was unvaccinated. The seroprevalence of SARS-CoV-2 antibodies in the most recent survey was 2.6% for antibodies by natural infection and 1.0% for antibodies by vaccination, confirming low immunity from vaccine coverage (Statistics Canada, 2021c). Interestingly, this study also reported the highest population-wide seroprevalence in children aged 1–19 years at 3.3%, which was higher than other age groups at that time. It is likely that the random sampling method facilitated the recruitment of children and persons from geographically remote areas, who were underrepresented in previous studies using residual sera from healthcare laboratories and blood donor specimens (Statistics Canada, 2021c), which led to lower seroprevalence estimates in Canada. The DBS assay may improve the response rate by providing the convenience of using an at-home, less invasive specimen

collection method compared with drawing blood, removing a substantial barrier for study participation, and resulting in a more generalizable SARS-CoV-2 seroprevalence estimate for children. This may be a methodological recommendation for developing future seroprevalence surveys to improve study feasibility and reduce bias, particularly given the potential role of children in transmission dynamics. In conclusion, through April 2021, 6 months into the pandemic and 4 months after the introduction of COVID-19 vaccines for selected high-risk groups in Canada, a low proportion of the general population had been infected by SARS-CoV-2. However, a high proportion of residents in some LTCFs had been infected by SARS-CoV-2 by April 2021, which emphasizes the need for continued public health measures such as vaccination, social distancing measures and the use of face masks to protect against new, more transmissible strains that continue to circulate and cause infections, particularly within healthcare institutions and LTCFs. The new DBS assay in use in Canada is a promising tool to evaluate the ongoing seroprevalence of the Canadian population to monitor the persistence of immunity from both natural infection and vaccination. Loss of assay sensitivity over time due to waning of immunity is an important barrier to conducting accurate longitudinal assessments of seroprevalence.

3. Chapter 3: Study 2 - Estimating Incidence of LD in Manitoba using Administrative Data

3.1. Abstract

Introduction: LD is the most reported vector-borne disease in Canada, caused by infection with *Borrelia burgdorferi* and transmitted by ticks. While reported rates have been increasing in recent years, the incidence of LD in Canada is still substantially underestimated due to climate change factors and under-reporting. Manitoba reported peak incidence of 4.8 per 100,000 in 2019, the fourth highest rate in Canada behind Nova Scotia, Ontario, and Quebec. The purpose of our study is to estimate the incidence of LD in Manitoba, Canada, using administrative claims data.

Methods: A validated, LD-case finding algorithm, based on Lyme diagnostic codes and antibiotics previously used by the CDC, was adapted to estimate LD cases in Manitoba. We designed four algorithms to find LD cases from: emergency department (ED) visits, hospitalizations, primary-care visits; the fourth algorithm relied upon diagnostic serologic test results only. LD cases and demographic data (sex, age-group, Regional Health Authority (RHA), and neighbourhood income quintile) were extracted from the MPRDR for 2010-2021, under the stewardship of the Manitoba Centre for Health Policy (MCHP). Annual incidence rates were calculated using population estimates from Statistics Canada.

Results: Over the study period (2010-2021), 2,976 cases of LD were identified from primary care (80.1%), EDs or hospitalizations (6.3%), and by diagnostic serology (13.6%). The algorithm-derived incidence in Manitoba increased over the study period from 8.4 per 100,000 in 2010 to a peak of 28.5 per 100,000 in 2019. The algorithm identified between 5.1 to 11.0 times more cases than reported surveillance data from 2010 to 2021 and displayed less disparity in rates by sex compared to reported cases, which demonstrate a stronger male predominance.

Conclusion: Our study demonstrated that LD cases may be substantially under reported in Manitoba, Canada, with higher under-reporting rates observed in women and in regions with low reported incidence.

3.2. Introduction

LD is caused by an infection with the bacterium *Borrelia burgdorferi* (*B. burgdorferi*), transmitted to humans by tick bites, which was discovered by William Burgdorfer in 1982 (Burgdorfer et al., 1982). In Canada, LD is the most commonly reported vector-borne disease in Canada and is transmitted mainly by *Ixodes scapularis* (*I. scapularis*) or blacklegged tick in central and eastern Canada, and to a lesser extent by *Ixodes pacificus* (*I. pacificus*) or western blacklegged tick in British Columbia (Gasmi et al., 2022). Provinces and territories have surveillance programs to track the expansion of ticks and identify high risk areas for LD, but collection methods and geographic scope are inconsistent and therefore not a comprehensive assessment of risk (Robinson et al., 2023).

LD has been a notifiable disease in Canada since 2009 and provinces and territories (P/T) voluntarily reported cases to the PHAC through the CNDSS (Gasmi et al., 2022). Confirmed and probable LD cases may be reported to local public health units, using the most current case definition of LD developed in 2016 (Government of Canada, 2022). LD case reports in Canada have risen from 144 in 2009 to 3,147 in 2021, of which 95.6% were from Ontario, Québec, and Nova Scotia (Public Health Agency of Canada, 2023c), yet are believed to be substantially underreported (Lloyd & Hawkins, 2018; Ogden et al., 2024). Reasons for underreporting may include lack of awareness, misdiagnoses, failure to seek health care, lack of reporting to public health surveillance due to systemic issues around administration of reporting or indifference/perceived lack of importance, or health care system failures (Hill, 2012). The expansion of tick habitats of increased risk areas and accounting for under-reporting of cases is projected to drive the annual LD case count to between 120,000 and 500,000 in Canada by

2050, compared to the approximately 3,000 cases currently reported (Public Health Agency of Canada, 2023c; Ogden et al., 2024).

Studies conducted in the US by the CDC, using a clinically validated algorithm to identify LD cases from administrative claims data, identified approximately 6–8 times higher LD cases than reported through notifiable disease surveillance (Cocoros et al., 2023; Kugeler et al., 2021; Schwartz et al., 2021). While LD cases are believed to be under-reported in Canada, a similar study has not yet been conducted to estimate the degree of under-reporting. Due to the comprehensive administrative health record data holdings held by the MPRDR and made available for research purposes, this province was selected as an ideal setting to conduct the first study using the CDC algorithm in Canada. The objective of our study was to estimate the incidence of LD in Manitoba, Canada, using administrative claims data and the validated CDC algorithm.

3.3. Research Question

The primary objective of this study was to utilize data from the provincial healthcare administrative database to estimate the incidence of LD and describe the patient characteristics of medically attended LD in the province of Manitoba, Canada. Specifically, the study focuses on the incidence of medically attended LD stratified by patient characteristics: sex, age, and local residential area.

3.4. Methods

3.4.1. Study Design, Data Management and Case Definitions

This was a retrospective cohort study using administrative data to identify and evaluate characteristics of patients with medically attended LD in Manitoba, Canada. This study used the MPRDR, which consist of de-identified health data encompassing administrative health service records of any individuals who access the provincial publicly-funded healthcare system. MPRDR is a comprehensive collection of administrative, registry, survey, and other data on the residents of Manitoba. The MPRDR contains multiple healthcare datasets, that are linked through individual Personal Health Identification Numbers (PHIN). It includes data related to medical visits to hospitals, physicians, EDs and specialists, homecare, and pharmaceutical prescriptions.

Manitoba Centre for Health Policy (MCHP) is a steward of the MPRDR database and provided access to the data, in compliance with data management and data privacy policies, as per MPRDR internal protocols (Manitoba, 2024). All data outputs received were at an aggregate level, using pre-submitted table shells provided to MPRDR, with information suppressed for cell sizes between 1 and 5, inclusive. No individual-level data were provided. To protect patient privacy and potential de-identifying of data, any data cell values with a count of less than 6 patients were suppressed, along with the second smallest group to prevent back-calculation (i.e., double suppression). Where feasible, suppression rules were pre-specified by variable to collapse stratification of cells. No individual-level data were transferred outside of MPRDR data servers.

LD cases were identified from administrative databases housed at the MPRDR, Manitoba, using four LD case finding algorithms shown in Table 4 (Appendix B, S3-S5). Individuals were indexed into the study on the earliest date they were identified as a case by any of the LD case-finding algorithms during the selection period. Individuals were not reindexed if they met any of the case definitions again during the study period but were considered as a case of reinfection. Indexed LD cases were classified according to the algorithm definition they met when indexed into the study (e.g., primary algorithm-defined LD case). If an individual met more than one LD case definition on the same day, they were classified into one algorithm in the following order of precedence, to reflect the case severity: primary algorithm-defined LD (either hospital ED visit or inpatient admission), then the primary care-adapted algorithm-defined LD followed lastly by the serology-based algorithm-defined LD.

To identify LD cases from emergency room visits, LD-specific International Classification of Diseases (ICD)-10-CA codes were extracted from the National Ambulatory Care Reporting System (NACRS), with the requirement that a 7+ day course of antibiotics was dispensed within 30 days of the ICD-10-CA code, extracted from the Drug Program Information Network (DPIN). Consistent with the CDC algorithm, identification of hospitalized cases excluded the antibiotic criteria, as drug treatments are not coded in-hospital, but managed by hospital formularies (Schwartz et al., 2021). Hospitalized LD patients were identified by using LD-specific ICD-10-CA codes extracted from the Discharge Abstract Database (DAD) as the most responsible diagnosis. Hospitalized and emergency room cases were reported together. LD cases from primary care were identified using ICD-9 codes extracted from the Medical Claims-Medical Services (MC-MS) database, with the requirement that a 7+ day course of antibiotics was dispensed within 30

days of the ICD-9 code, extracted from the DPIN (Table 4). Prior to 2015, ICD-9 codes used a 3-digit code (i.e., 088) to identify LD cases, which was not specific to LD. MC-MS transitioned to full 5-digit codes in 2015, which did have a specific code for LD. To assess the validity of the 3-digit code to identify LD cases, University of Manitoba ran a sensitivity analysis on the 5-digit code distribution during 2015-2021, and 95.6% of the codes previously identified by the 3-digit codes were LD (Table 5). The coding algorithm developed for Manitoba was based upon Canadian LD case definition and adapted from the validated coding algorithm developed by the CDC in the US (Cocoros et al., 2023; Schwartz et al., 2021). An expert group was consulted on the 4th algorithm, which used diagnostic serology results from the Cadham Provincial Laboratory (CPL). Individuals who did not meet the criteria for the previous 3 algorithms but had a positive serology test result by western blot assay, were registered as a LD case.

The data used for this study were extracted by the MPRDR, under the supervision of the University of Manitoba. These data did not include personal identifiers and were provided in aggregate form, in pre-developed table shells that were given to the data custodian. This study was approved by Advarra's institutional review board (IRB#00000971) and the University of Waterloo's Office of Research Ethics (File# 45493).

Table 4: Operational Definitions for LD Algorithms

1. Primary LD Case Algorithm – Emergency Room Visits:	
<ul style="list-style-type: none"> • Having ≥1 LD ICD, Tenth Revision, Canada (ICD-10-CA) diagnosis code* at any position in ED/hospital; AND • Having prescription claim of ≥7 days of dispensed antibiotics* (e.g., prescription claim of doxycycline dispensed on 1 January 2012 for a duration of 7 days); AND • At least one course of antibiotics with a dispensing date within 30 days of the diagnosis code. 	
2. Primary LD Case Algorithm – Hospitalized Cases:	
<ul style="list-style-type: none"> • Having ≥1 LD ICD, Tenth Revision, Canada (ICD-10-CA) diagnosis code* at any position in ED/hospital. 	
3. Primary Care-Adapted LD Algorithm:	
<ul style="list-style-type: none"> • Having prescription claim of ≥7 days of dispensed antibiotics*; AND • Having ≥1 relevant LD ICD-9 code* in Manitoba primary care setting; AND • At least one course of antibiotics with a dispensing date within 30 days of the diagnosis code 	
4. Serology-Based Algorithm:	
Having a positive serology test result [†] by western blot assay ^{**}	
<p><i>*The earliest date of diagnosis code or antibiotic dispensing date occurring within 30 days of diagnosis code was defined as the index date.</i></p> <p><i>** The date of specimen collection is defined as the index date</i></p> <p><i>† A standard two-tiered algorithm comprised of first testing a specimen for total antibodies, followed by further testing for specific antibodies using western blot.</i></p>	

Table 5: Sensitivity Analysis for use of 3-Digit LD Pre-2015

Distribution of 088.xx codes during April 1, 2015 – December 31, 2021		
ICD-9 CM Code	Definition	Frequency
088.81	LD	4,136 (95.6%)
088.0	Bartonellosis	83 (1.9%)
088.82	Babesiosis	53 (1.2%)
088.9	Arthropod-borne disease, unspecified	47 (1.1%)
088.89	Other specified arthropod-borne diseases, other	9 (0.2%)

3.4.2. Study Time Periods

3.4.2.1. Selection Period

The selection period was defined to start on January 1, 2010, and end on December 31, 2021. During this period, individuals meeting the case definition and eligibility criteria were classified as index LD cases.

3.4.2.2. Index Date

The index date (Day 0) was defined as the date when an individual first met at least one of the LD case definitions (Table 4) during the selection period.

3.4.2.3. Index Period

The index period refers to a window of 61 days that starts on the Day -30 preceding index date and ends on Day +30 succeeding the index date (i.e., from Day -30 to Day +30). Further, the window of 30 days preceding the index date is referred to as the “pre-index period” (i.e., from Day -30 to Day -1); the window of 30 days succeeding the index date is referred as the “post-index period” (i.e., from Day +1 to Day +30).

3.4.2.4. Inclusion Criteria

Patients had to be identified as a LD case in the Manitoba database between January 1, 2010, to December 31, 2021, as defined in (Table 4) to be eligible for inclusion in the study.

3.4.2.5. Exclusion Criteria

Patients were excluded from the study if any of criteria 1 – 3 were met.

1. Patients without information on key demographics (e.g., sex, age).
2. Age \geq 105 years at index.
3. Death occurring at index.

3.4.3. Data Sources and Variables

Study variables were extracted from the Manitoba Population Research Data Repository (MPRDR) databases in Manitoba. All variables were selected based on availability in the administrative data sources and were finalized in consultation with the MPRDR analyst teams. Detailed information on the operational definitions of variables for which ICD-9 codes, ICD-10 codes, Drug Identification Numbers (DIN), Canadian classification of health interventions (CCI) codes, and Logical Observation Identifiers Names and Codes (LOINC) were used are provided within Appendix B, Table S2.

3.4.3.1. Demographic Variables

The demographic variables extracted for analysis were age, sex, local residential area, and neighbourhood income quintile. Age was defined by the difference (in years) between the date of birth and the index date. The calculated age at index was presented as a categorical variable with the following categories: ≤ 10 , 11 – 20, 21 – 30, 31 – 40, 41 – 50, 51 – 60, 61 – 70, 71 – 80, and ≥ 81 years. Sex was defined as a categorical variable (female/male) as reported in the data sources at index date.

Regional health authorities (RHAs) are Manitoba's independent governing bodies for healthcare delivery and regulation. RHAs have responsibility for the mandate, resources, and performance of the health authority, responding directly to the provincial Minister of Health, Seniors, and Active Living. The local residential area refers to 5 RHAs in Manitoba: Northern Regional Health Authority (NRHA), Interlake-Eastern Regional Health Authority (IERHA), Prairie Mountain Health (PMH), Winnipeg Regional Health Authority (WRHA), and Southern Health – Santé Sud (SHSS). In the event of small cell suppression, alternative groupings were considered

to collapse across local residential areas, at the discretion of the data custodian. For each LD case, the most recent record of RHA prior to the index date was used.

The neighborhood income quintile was derived by linkage of an individual's residence prior to the index date, based upon the relevant dissemination area, using the Statistics Canada Postal Code Conversion File. Dissemination areas are stable residential blocks, designed to provide a meaningful sub-population structure within which to analyze census data, such as median income. Each dissemination area contains 400 to 700 persons to avoid data suppression and respects census subdivisions. Cases were designated to a dissemination area, then median income was calculated for each neighborhood and an ordinal variable was created based on income quintiles, with quintile 1 the lowest 20% and quintile 5 the highest 20%. The most recent record of residence prior to the index date was used.

3.4.3.2. Clinical Characteristics

Clinical stage was assessed during the lookback period and the analysis period. LD cases were classified into one of 4 categories based on symptoms occurring within 90 days (i.e., 3 months) pre-index or post-index date: early localized stage, early disseminated stage, late disseminated stage, and undefined (LD cases that could not be mapped to one of the three clinical stages). To assess the clinical stage of LD cases at index, coding algorithms were developed matching the clinical symptoms associated with the three stages, early localized, early disseminated, and late disseminated, derived from an Ontario study that described clinical manifestations of reported cases (Johnson et al., 2018). Symptoms reported in ≥ 5 cases corresponding to LD clinical stages in Ontario case reports were included to build the coding algorithm for Manitoba per clinical stage (Appendix B; Tables S6 – S8). Cases were included

within a clinical stage if a binary variable (yes/no) indicating whether patients were diagnosed with at least one symptom related to LD, based on ICD-10-CA codes during the index period and/or the analysis period. Symptoms related to LD include rash, fever, fatigue, chills, myalgia, headache, pain in joint, cervicalgia, disturbance of skin sensation, and radiculopathy (Johnson et al., 2018).

Antibiotics dispensed were captured as a binary variable (yes/no) indicating whether a patient had ≥ 1 prescription claims for antibiotics dispensed during the index period. The antibiotics of interest are listed in Table S4 and were selected based upon Manitoba Health treatment guidelines for LD (Manitoba Health and Senior Care, 2021).

The duration of antibiotics was estimated using the number of days supply for the medication. For individuals who were dispensed antibiotics more than once, the duration, in days, was calculated by summing together each time interval and reported for the index period and/or the analysis period. If an individual was prescribed more than one antibiotic for LD concurrently, then the overlapping days of the time intervals were not double counted.

3.4.3.3. Time/Seasonality of LD

Season of LD index was based on the month of the index date and was categorized as Spring (Mar-May), Summer (Jun-Aug), Fall (Sep-Nov), or Winter (Dec-Feb). Year of LD index was based on the calendar year of the index date and was categorized annually from 2010 to 2021.

3.4.4. Data Analysis

The incidence analysis set includes patients with a defined index date who met the inclusion criterion, and who did not meet any of the exclusion criteria 1, 2, or 3, as defined in section 3.4.2.5. The frequency, proportion, and incidence per 100,000 population was

calculated from January 1 to December 31 for each calendar year between 2010 and 2021. LD case numbers were reported by qualifying case-finding algorithm, age, sex, RHA, and neighbourhood income quintile.

Incidence was defined as the number of LD cases divided by the total number of population at-risk in each year (annual incidence), expressed as the incidence per 100,000 population. The census population estimates for July 1st (mid-year) of Statistics Canada data were used to obtain the population at-risk for each year (Government of Canada SC, 2021). The incidence per 100,000 population of reported LD cases, using the incidence analysis set, was calculated from January 1 to December 31 for each calendar year between 2010 and 2021 using the following formula:

$$\text{Incidence} = \frac{\text{\# of LD}}{\text{Population at-risk}} \times 100,000 .$$

Comparison of the incidence analysis set was made to the cases of LD reported to public health surveillance, to estimate under-ascertainment of cases. Demographic and clinical variables were analysed for the longitudinal analysis set over the study period (i.e., the incidence analysis set, minus the 64 observations without 12 months of data following the index set). Where possible, analyses were stratified by age group, RHA, and sex. All calculation and analyses were conducted using Microsoft Excel, SAS version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or R, version 4.2.0 or later (The R Foundation for Statistical Computing, Vienna, Austria).

3.5. Results

3.5.1. Cohort Characteristics

Over the study period (2010-2021) the 4 Lyme algorithms identified 2,976 LD cases in the incidence analysis set, 46.7% female and 53.3% male, from the following algorithms: primary care (80.1%), EDs or hospitalizations (6.3%), and diagnostic serology (13.6%) (Appendix B; Table S11). While individuals in all income levels were identified with LD, the case distribution was skewed toward higher income strata (Appendix B; Table S12).

The incidence of algorithm-derived LD in Manitoba increased over the study period from a rate of 8.4 per 100,000 in 2010 to a peak of 28.5 in 2019, followed by a slight decline in 2020-21 (Figure 5). The seasonality of the cases were distributed as expected (Figure 6), based upon tick activity and human disease in Manitoba (Manitoba, 2020).

Figure 5: Case Counts and Incidence of Algorithm-Derived LD Cases (2010-2021)

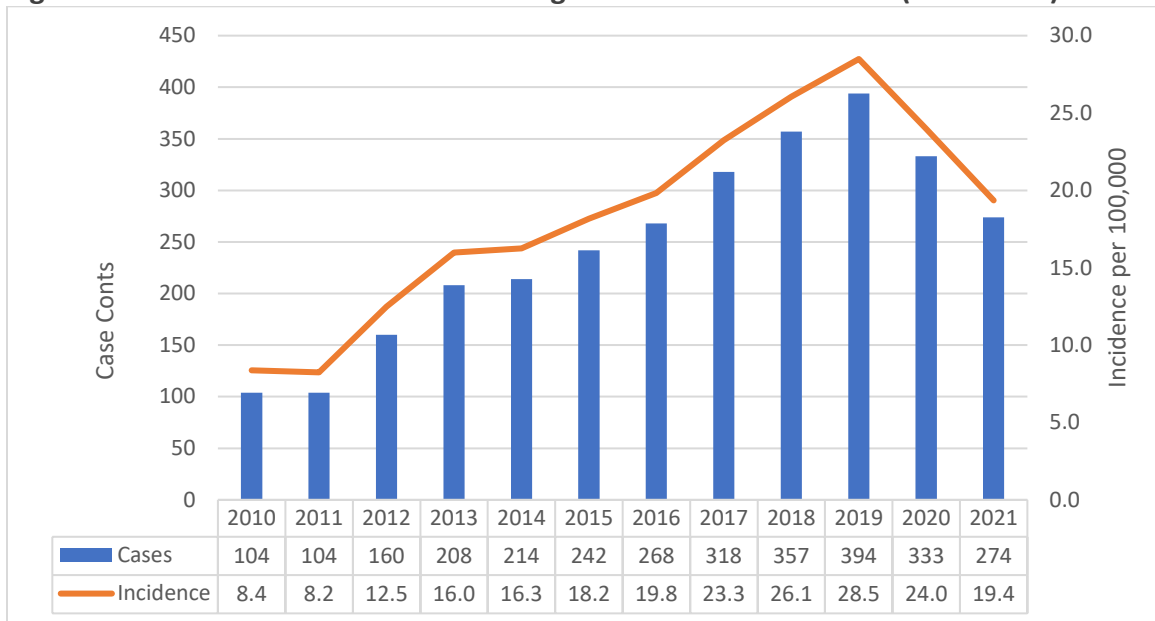
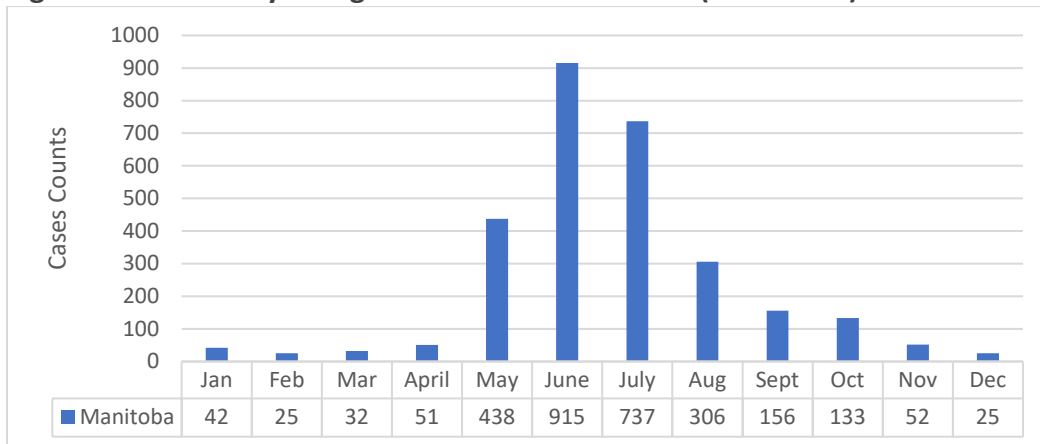


Figure 6: Seasonality of Algorithm-Derived LD Cases (2010-2021)



3.5.1.1. Age

The total cases of LD identified for the incidence analysis set, demonstrated a bimodal peak by age group, with the highest case counts in older adults aged 55-59 years and a lower peak in children aged 5-9 years (Figure 7). The mean (SD) age of cases was 46.18 (22.92), the median Interquartile Range (IQR) was 51.00 (29.50, 64.00), and the age range was 1 – 96 years (Appendix B; Table S12). The summary statistics were similar to those reported by Manitoba Health for the most recent regional LD report for 2013 – 2018, which also has a bimodal distribution (Manitoba, February 2020). The algorithm-derived incidence rates by age group were consistently highest for older age groups 61 – 70 years and 71 - 80 years (except for 2010 and 2011 when no cases were reported for the 71-80 age group). In most years, the incidence rates by age group demonstrated a bimodal distribution with small peaks in children < 10 years and larger peaks in adults over 60 years (Figure 8).

Figure 7: Algorithm-Derived Cases of LD, by Age Group (2010-2021)

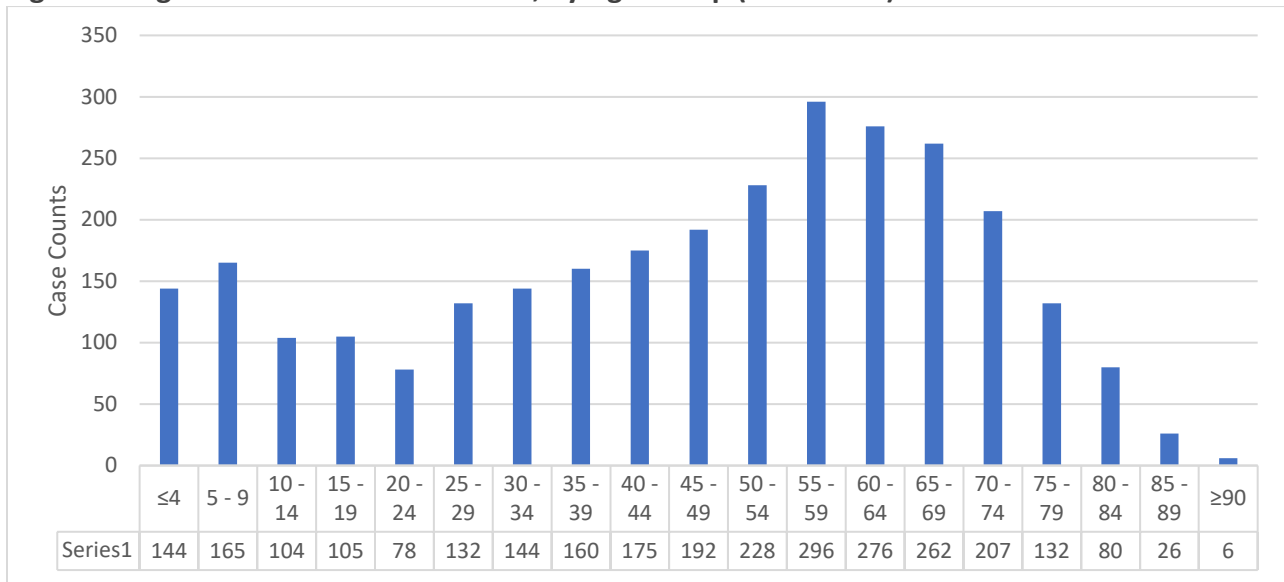
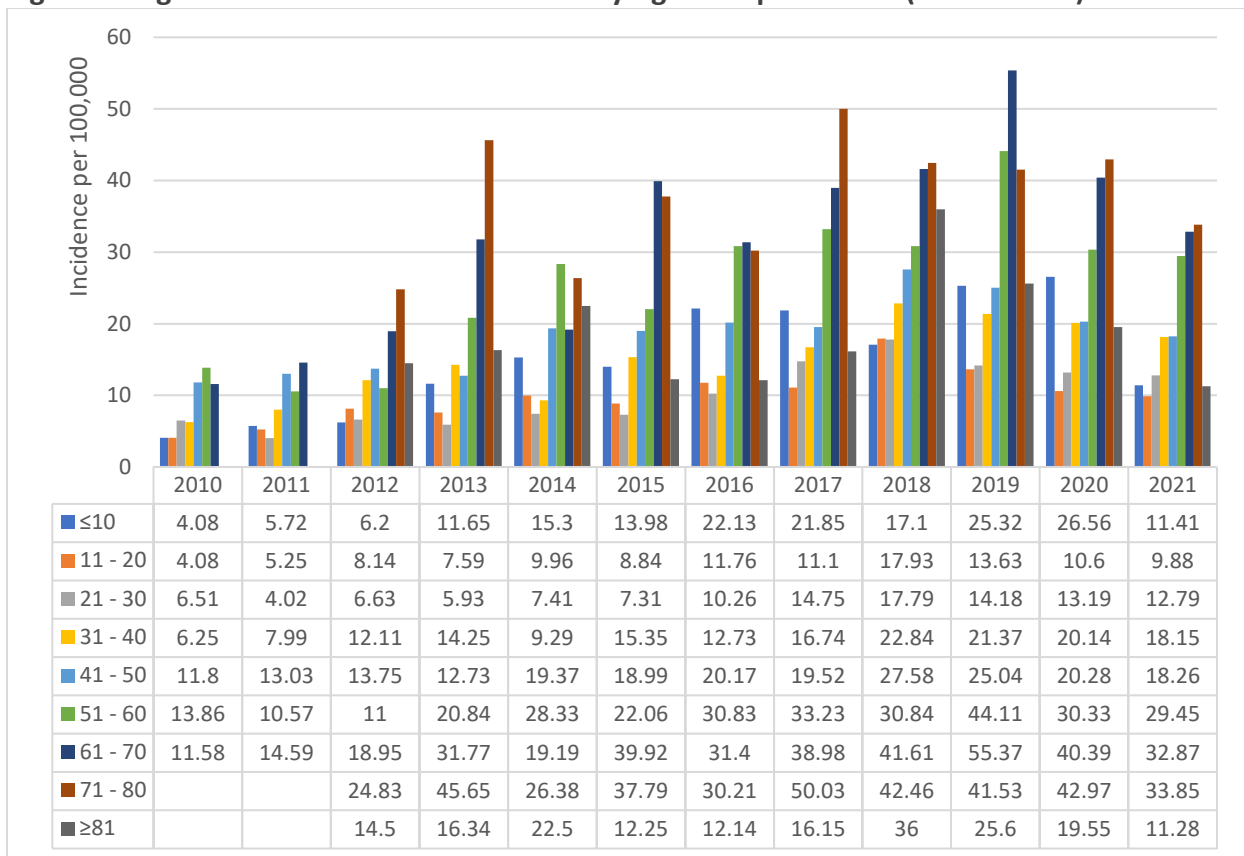


Figure 8: Algorithm-Derived Incidence of LD by Age Group and Year (2010 – 2021)

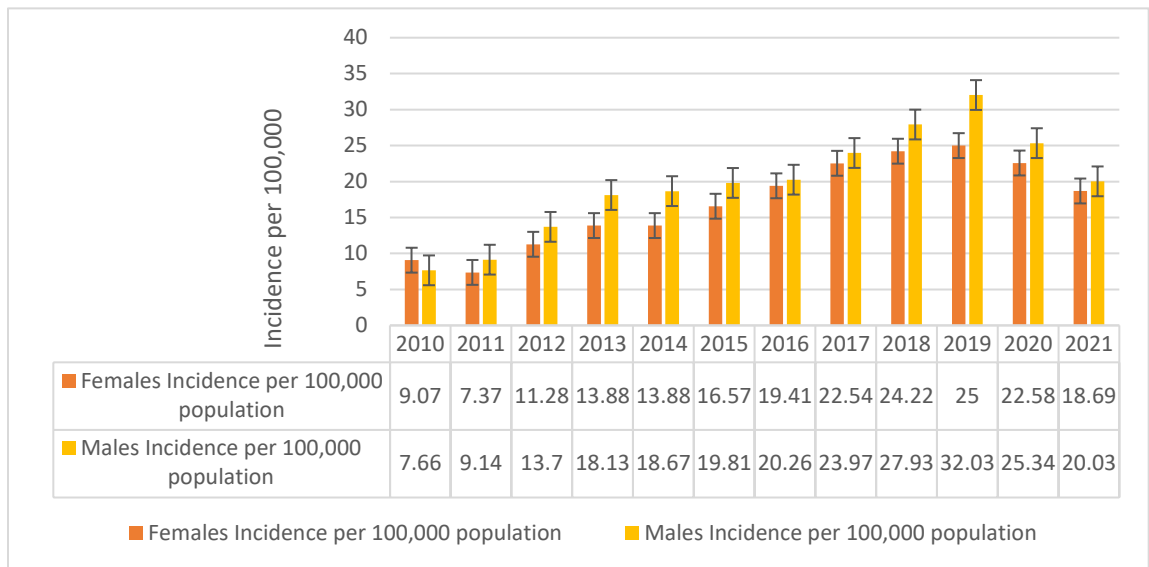


Blank cells = cell suppression (due to low incidence)

3.5.1.2. Sex

The algorithm-derived incidence estimates by sex were similar over the study period, with a higher incidence rate in males in years 2013, 2014, 2018, and 2019 (Figure 9).

Figure 9: Incidence of Algorithm-Derived LD Incidence by Sex (2010-2021)



3.5.1.3. Regional Health Authority

The local residential areas represent the RHA in Manitoba. Cases of algorithm-derived LD by RHA were distributed as follows: Northern Regional Health Authority (1%), Prairie Mountain Health (13%), Interlake-Eastern Regional Health Authority (15%), Southern Health – Santé Sud (31%), and Winnipeg Regional Health Authority (40%) (Figure 10). Over the study period, the Northern HA had no cases of LD, but the LD incidence in the remaining 4 RHAs was consistently high in recent years, with the exclusion of some missing data in PMH due to double-cell suppression caused by no cases in NHA (Figure 11).

Figure 10: LD Algorithm-Derived Case Counts by RHA (2010-2021)

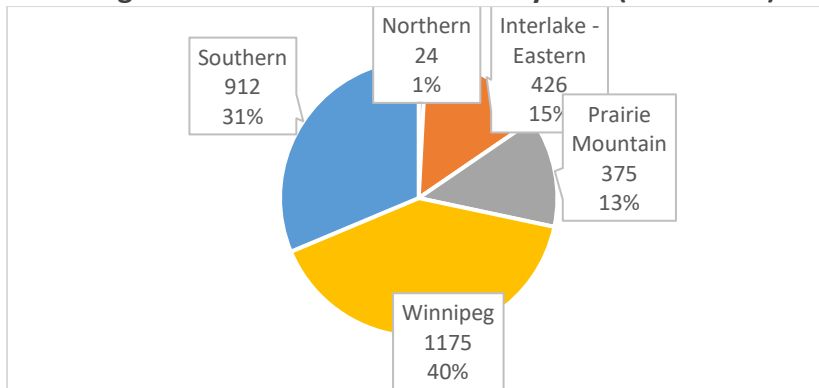
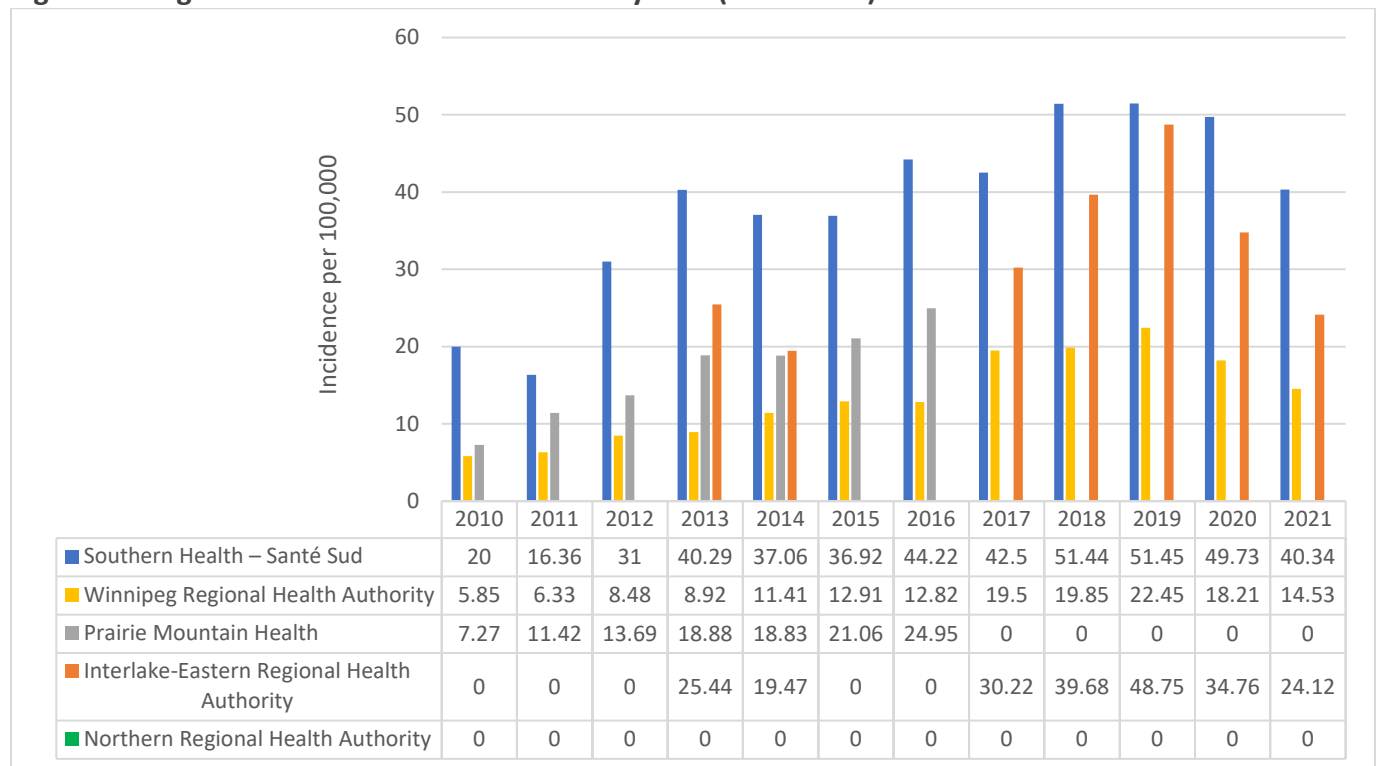


Figure 11: Algorithm-Derived Incidence of LD by RHA (2010-2021)



For cells from the algorithm-derived incidence data that were double-suppressed due to low numbers, a value of 0 was entered.

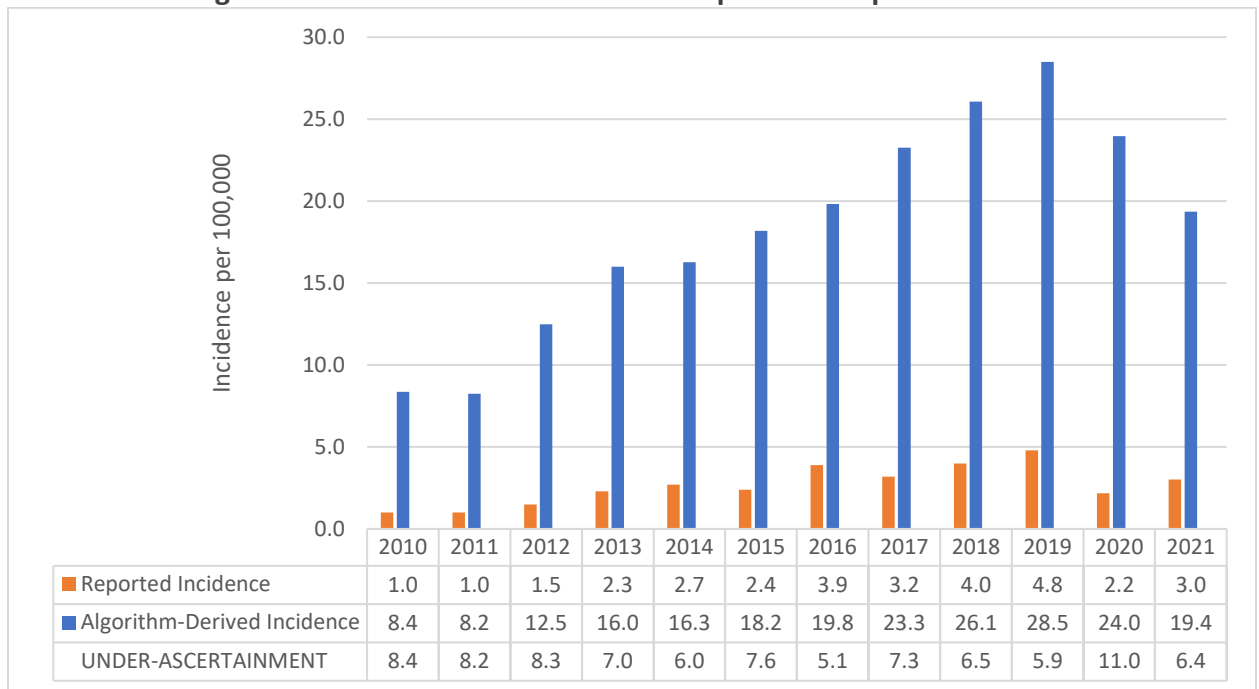
3.5.1.4. Clinical Staging

Between 90-100% of the LD cases identified could not be clinically staged using the algorithms defined in Tables S6-S8 and were categorized as “undefined”. Due to the small cell sizes, each year was subject to double cell suppression, except for 2010 which was 100% undefined and hence no analysis is presented here but is available in appendix B (Table S13).

3.5.2. Comparison of Algorithm-Derived LD to Surveillance Reports
3.5.2.1. Overall Incidence Rates

Annual LD incidence rates derived from administrative data were compared to incidence of LD reported to CNDSS during the study period (2010 – 2021) (Canada, 2023b, 2023c; Gasmi et al., 2022). The incidence analysis set identified between 5.1 to 11.0 times more cases than was reported to public health surveillance during the study period (Figure 12). There were no observable trends in under-ascertainment over time.

Figure 12: Manitoba Algorithm-Derived Incidence Rates Compared to Reported Incidence



3.5.2.2. Incidence Rates by RHA

Using regional LD incidence reports, comparisons were made between the regional incidence rates identified by the algorithm and the reported rates by region. Reported regional incidence rates were unavailable from 2019-2021, hence are not included in this analysis. Only average incidence rates were available from 2010 - 2014 (Government of Manitoba, 2016, 2017, 2019, 2020). The NRHA was excluded from the analysis here due to very low numbers of

cases and suppression of data cells. The algorithm-derived incidence identified a median (IQR): 9.32 (6.43, 9.80), 4.07 (4.85, 5.00), 19.03 (14.91, 27.10), and 13.78 (8.83,18.55) times more cases than those reported to surveillance in WRHA (Figure 13), SHSS (Figure 14), PMH (Figure 15), and IERHA (Figure 16), respectively, although low numbers in NA, caused many cells to be double suppressed, thereby creating data gaps making trends in IERHA difficult to interpret (Figure 16).

Figure 13: WRHA Algorithm-Derived Incidence Rates Compared to Reported Incidence

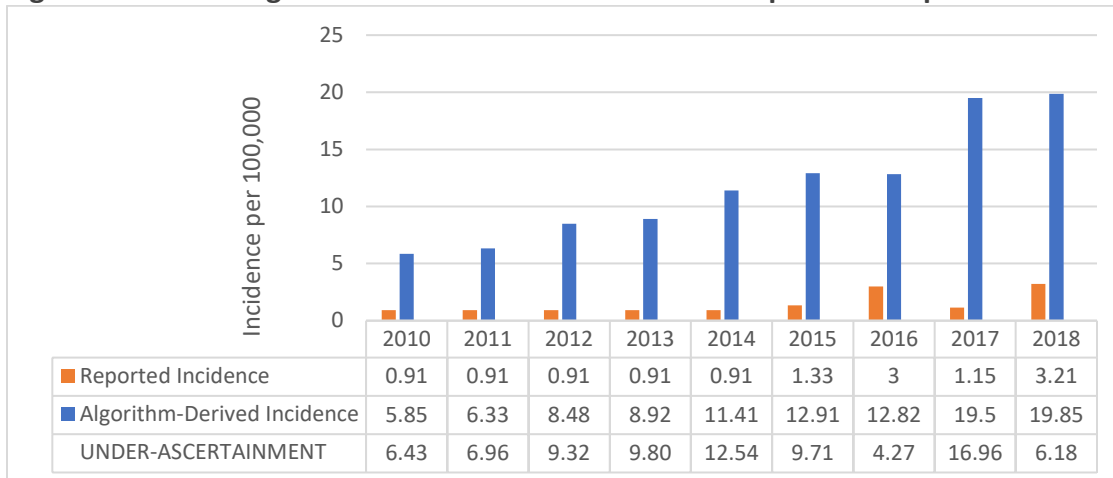


Figure 14: SHSS Algorithm-Derived Incidence Rates Compared to Reported Incidence

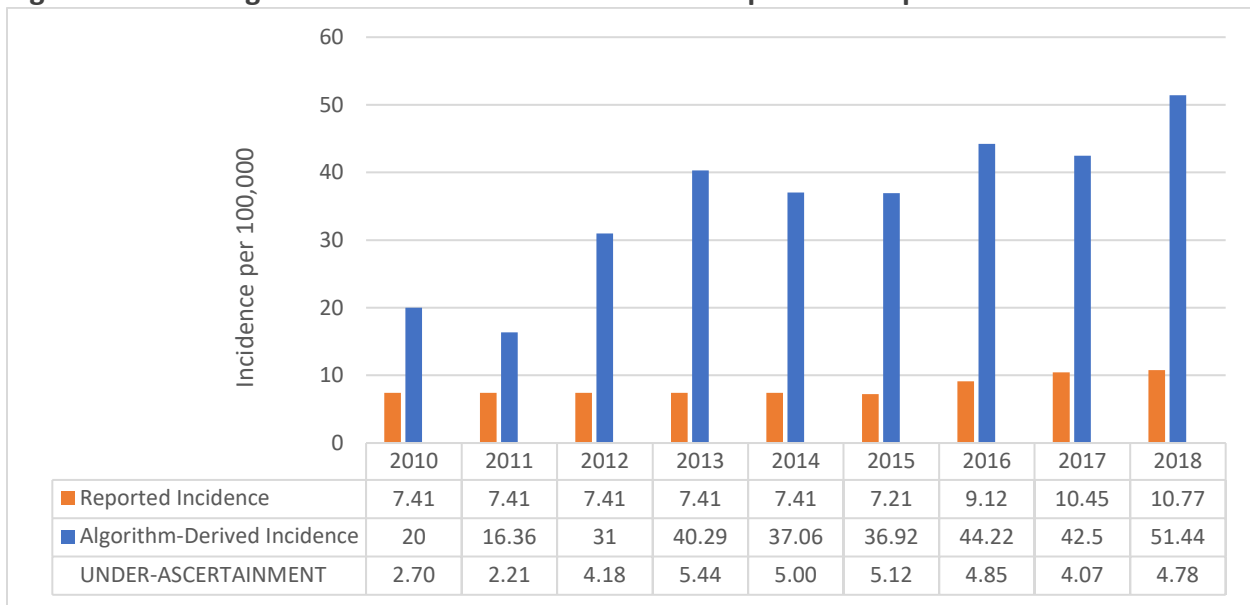


Figure 15: PMH Algorithm-Derived Incidence Rates Compared to Reported Incidence

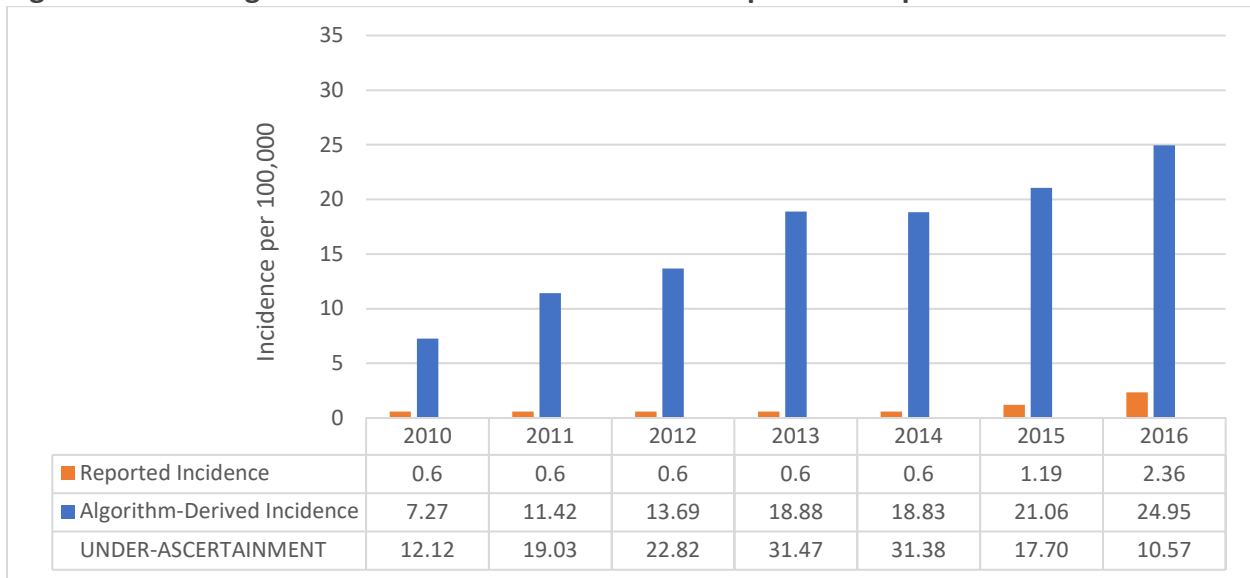
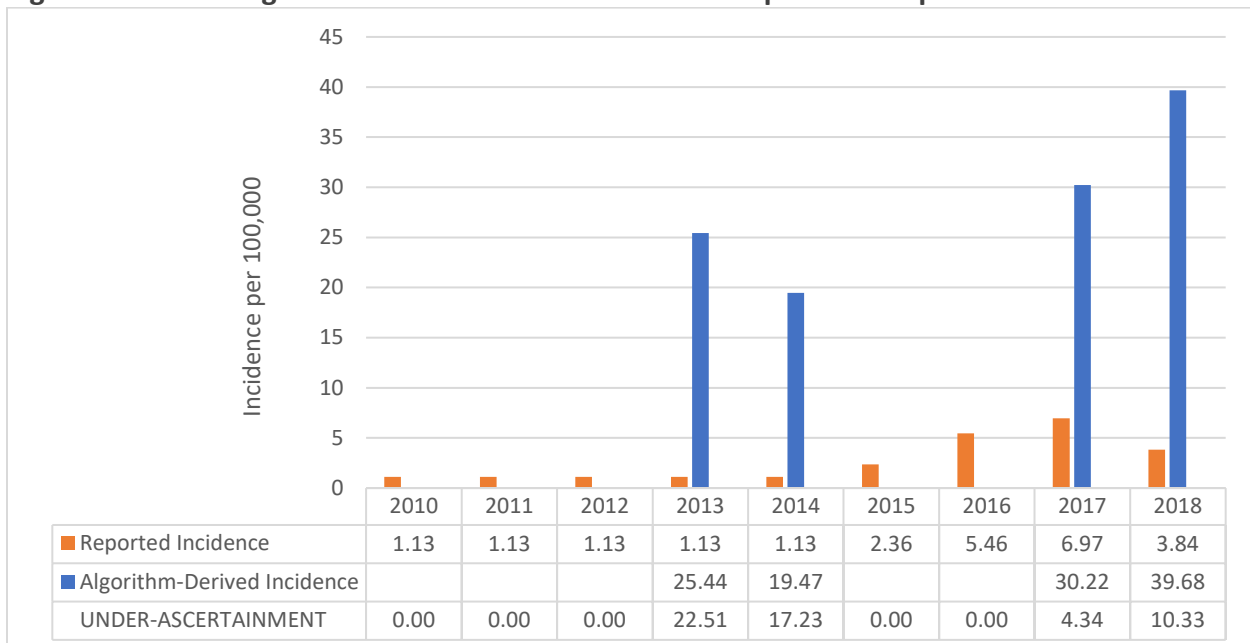


Figure 16: IERHA Algorithm-Derived Incidence Rates Compared to Reported Incidence



The empty cells from the algorithm-derived incidence data were double-suppressed due to case numbers < 5.

3.5.2.3. Incidence Rates by Sex

Algorithm-derived incidence rates by sex demonstrate that under-ascertainment of cases is higher for females than males. Under-ascertainment for females ranged from a low of 4.95x in 2011 to a high of 13.81x in 2015 (Figure 17). Under-ascertainment for males ranged from a low of 4.35x in 2011 to a high of 8.89x in 2014 (Figure 18). Reported incidence rates by sex were unavailable from 2019-2021, hence were not included in this analysis. Only average incidence rates by sex were reported from 2010-2014 (Government of Manitoba, 2016, 2017, 2019, 2020).

Figure 17: Female Algorithm-Derived Incidence Rates Compared to Reported Incidence

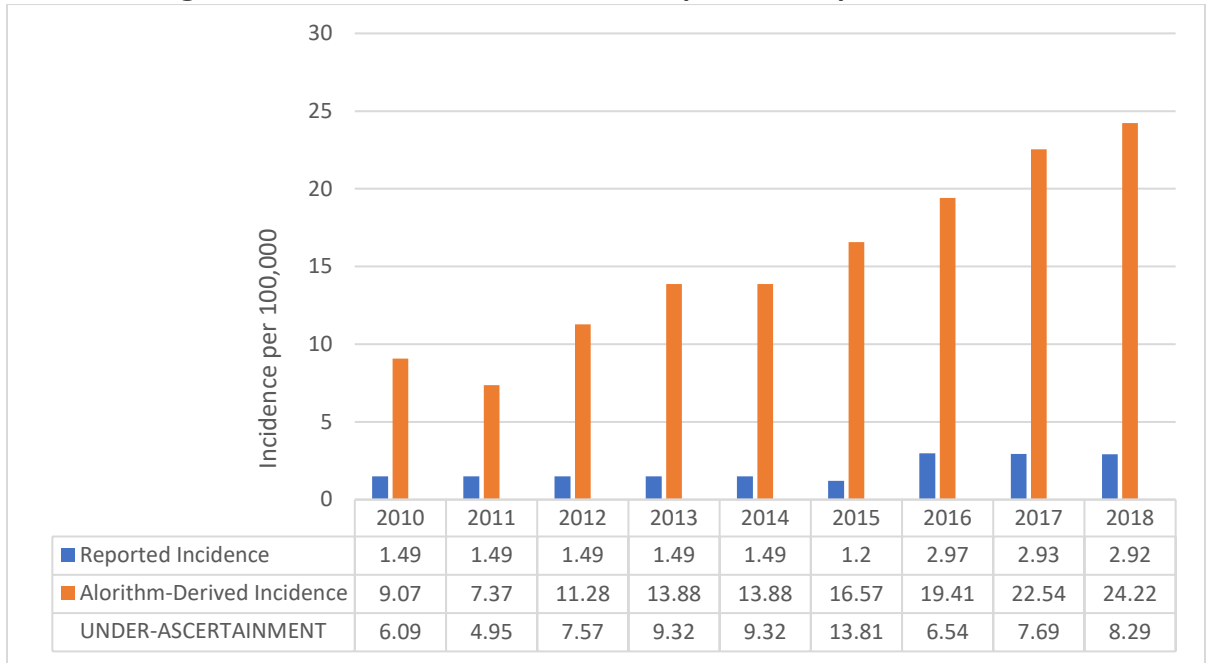
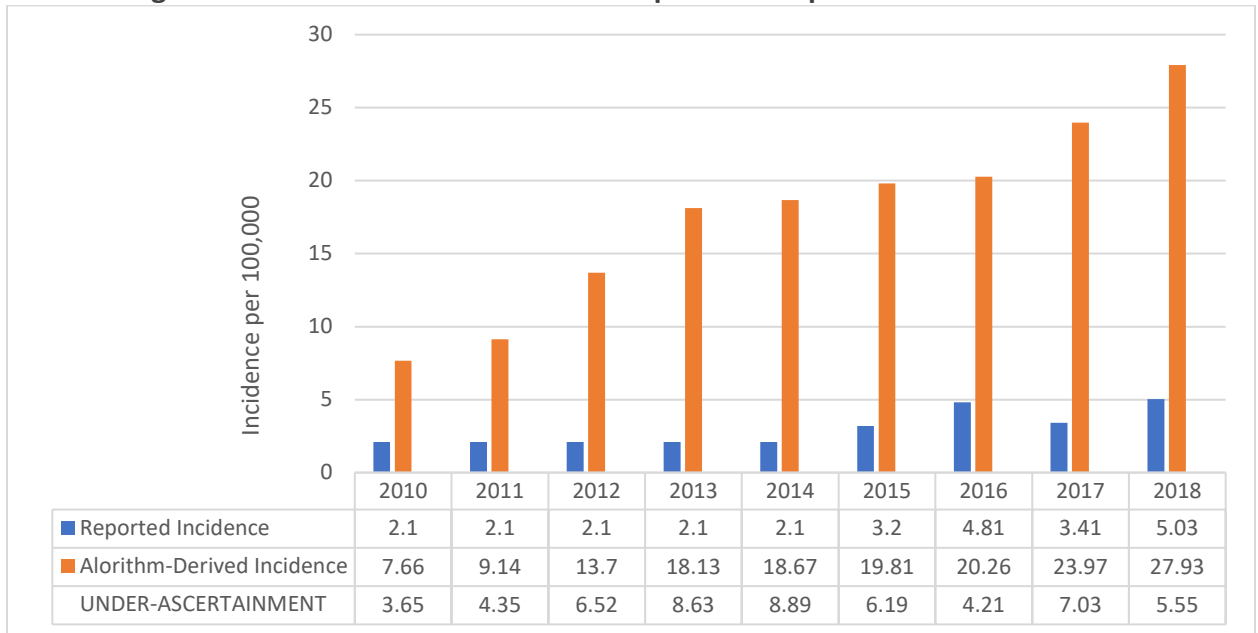


Figure 18: Male Algorithm-Derived Incidence Rates Compared to Reported Incidence



3.6. Discussion and Conclusion

Our study based upon administrative data provides valuable insights into under-ascertainment of LD in a low incidence province in Canada. Aside from using a validated algorithm, our data passes some validity checks. Over the 11-year study period, our cases were distributed in a seasonal pattern as would be expected for LD in Canada (Gasmi et al., 2022). We identified almost no cases in the Northern Region, which is also expected, as the Boreal Forest is known to be an unsuitable habitat for ticks (Ogden et al., 2021).

Cases of LD identified from the administrative claims database in Manitoba demonstrate substantial under-reporting of cases with claims data being 5.1 - 11.0 times higher than was reported to public health surveillance. Our findings were consistent with what was observed by the CDC, which used administrative data to estimate LD cases from high and low incidence states in the US, and reported a 6 – 8 times higher incidence than was reported to public health surveillance (Schwartz et al., 2021). The CDC observed higher under-ascertainment levels in low incidence states and lower under-ascertainment in high incidence states (Schwartz et al., 2021). Consistent with the CDC findings, the regional under-ascertainment ratios in this study were higher in health regions with lower reported surveillance rates. The Southern Health – Santé Sud Regional Health Authority had the highest reported rates and the lowest under-ascertainment ratios; the Prairie Mountain Regional Health Authority had the lowest reported rates and had the highest under-ascertainment ratios. Note that the Northern Regional Health Authority was excluded from this analysis due to cell suppression, due to very low rates. Areas of low incidence may have lower awareness of risk or consideration of LD as a diagnosis process of reporting cases to public health. The under-ascertainment of LD incidence in females was

consistently higher than males, which was also observed in the CDC study, possibly indicating a lack of consideration of LD as a diagnosis in females (Schwartz et al., 2021). Female cases in the CDC study were more likely to present outside of the Lyme season, indicating that they were missed early and may be diagnosed as a later clinical stage, which could lead to higher risk of sequelae and development of PTLDS (Murison et al., 2023; Steere et al., 1994). This trend was not observed in our study.

The algorithm-derived incidence of LD demonstrated a steady rise from 8.4 per 100,000 in 2010 to a peak in 2019 to 28.5 per 100,000, followed by a decline to 24.0 and 19.4 per 100,000 in 2020 and 2021, respectively, whereas the reported incidence during the study period peaked at 4.8 per 100,000 in 2019 (Gasmi et al., 2022). The CDC classifies a US jurisdiction as high incidence if it has an incidence of 10 per 100,000 per year, for 3 consecutive years (Centers for Disease Control, 2022). Based upon the reported rates of LD, Manitoba would be classified as a low incidence region, whereas the algorithm-derived rates may justify a re-classification of Manitoba as a high incidence region. The LD risk classification could also extend to the regional health authorities, as the LD cases identified by the algorithm were distributed unevenly throughout the province, with the southern region having the highest incidence and the northern region having almost no cases of reported or medically attended LD as identified by the algorithms. However, 4 of the 5 regional health authorities in Manitoba would meet the criteria for high incidence jurisdiction in Manitoba, using the algorithm-derived incidence rates.

Our study also demonstrated that 80% of Lyme cases were diagnosed by their primary care physician, since our algorithm was designed to identify the first diagnoses. The decline of algorithm-derived incidence observed during the SARS-CoV-2 pandemic may be accounted for by disruption in healthcare services during the lockdown. Provincial reports for LD were not available from 2019-2021, nor did the province report to LDES, which may have been due to the diversion of public health resources to manage the SARS-CoV-2 pandemic. The province did report LD cases to PHAC through CNDSS for 2019-2021, which indicates that they were reported by physicians, but were only reported to PHAC. These rates were used to compare rates of reported incidence to the algorithm-derived rates.

The incidence of reported LD by age group did not have a bimodal distribution, but it may have been obscured by the broad age grouping for children, which was <20 years (Manitoba, 2016, 2017, 2019, 2020). The algorithm-derived incidence of LD by age group demonstrated a bimodal distribution with a peak in children and larger peak in older adults. Due to the data being presented in different age groupings, a direct comparison was not conducted; however, the available data may indicate under-reporting in younger age groups. A Canadian Paediatric Surveillance study conducted from 2014 to 2017 reported that 58% of pediatric LD cases presented with arthritis, a symptom of the late disseminated stage of LD, indicating missed early diagnosis and treatment (Ogden et al., 2020). Data from the LDES also reported higher than expected incidence of late disseminated LD cases in all age groups in Ontario, which provides some insight into the clinical implications that result from delays in early detection and treatment, which is more typical in low incidence jurisdictions (Murison et al., 2023).

The study that validated the algorithm to identify LD cases had a very high PPV with the inclusion of suspected LD cases (Cocoros et al., 2023). Manitoba Health included case counts for suspected cases that were reported by physicians but did not meet the case definition for confirmed or probable cases in their regional summary reports. These were not included in our analysis (Manitoba, 2016, 2017, 2019, 2020). Inclusion of these additional cases (70 cases from 2013-2018) may have generated under-ascertainment values that were slightly lower than what we observed. However, one of the strengths of our study was the access to serologic test results used for diagnostic purposes, which were not available to the CDC in their study (Schwartz et al., 2021). This algorithm captured an additional 401 cases over the study period that did not register a Lyme code, which may have captured some of the suspected cases not reported to public health. This may indicate that there may be administrative barriers to reporting LD cases to public health, despite having ordered a diagnostic test and receiving a positive test result.

The recommended, two-tiered laboratory testing approach recommended in Canada is a conservative method of identifying LD cases. Depending upon clinical stage of disease, it has low sensitivity in detecting early infections and high sensitivity in detecting late-stage infections (TF & LR, 2020). This allowed us to be confident in the identification of positive cases flagged by serology, but not coded for LD. Another strength of our study was that due to the single-payer, publicly funded healthcare system, most of the population of Manitoba's healthcare visits were captured by the database, creating a population-level assessment that is less biased than a healthcare system with substantial private funding, as in the US.

There were several limitations of our study related to the use of administrative claims data. We were only able to identify medically attended cases for which LD was investigated as a potential diagnosis. Patients without access to healthcare or who may have been mis-diagnosed would not have been identified as a case in our study, which may make our findings a conservative estimate of LD under-ascertainment in Manitoba. The use of administrative claims data rather than medical charts creates the potential for cases to be misclassified. Finally, we did not have demographic data on race. Difficulty diagnosing LD and the clinical impact of late diagnoses in patients with darker skin colour has been studied in the US. In both adults and children, African Americans were less likely to be diagnosed with EM, and more likely to be diagnosed with Lyme-related arthritis than white comparator groups (Fix et al., 2000; Hunt et al., 2023). The evaluation of under-ascertainment rates by race was not possible using this method. Studies using other methods, such as electronic health records or active surveillance studies, should be conducted to evaluate the impact of race on diagnosis of LD in Canada.

The algorithms designed to identify clinical staging of cases at index failed, as most cases were categorized as “undefined”. These results indicate that most patients did not have billing codes that could describe the symptoms. The inability to categorize LD cases by clinical stage using administrative data was also identified as an issue in an Ontario study that was conducted to estimate costs associated by assessing the healthcare utilization of confirmed LD cases reported to surveillance (Mac et al., 2023). The purpose of administrative claims data is to manage payment to healthcare providers, yet it has been demonstrated to be reasonably good method of identifying LD cases (Cocoros et al., 2023; Schwartz et al., 2021). Further clinical characterization of LD cases should be conducted using studies with access to clinical data such

as electronic health records or enhanced surveillance data, as has been recently published by the LDES (Murison et al., 2023).

LD is an emerging public health threat in Canada, and it is expected to increase due to environmental factors that favour tick expansion and urbanization into forested areas, that increase opportunities for human-tick interaction. Low awareness of LD risk may exist in parts of Canada, which may be a factor for under-reporting of cases to surveillance. The clinical implications of missed or delayed diagnoses causes substantial health burden to individuals and the healthcare system. Our study demonstrated that administrative data is an effective tool to characterize the epidemiology of LD, as a supplement to public health surveillance data, and is the first to quantify the under-ascertainment of LD incidence in a Canadian jurisdiction.

As with all administrative studies, caution should be exercised when interpreting results. Our results may not be generalizable to other low incidence regions in Canada, due to the specific ecologic factors that favour conditions for tick habitats and risk of LD.

3.7. Suggestions for Future Study

Currently, seroprevalence studies for *B. burgdorferi* in Canada have focused on animal studies, from which human disease risk may be inferred, but lack specificity to generate public health policy (Evason et al., 2019; Neely et al., 2021). Future studies that employ the use of serosurveys within a sample frame that is representative of the population of interest would be informative in characterizing and mapping the population-level risk of LD exposure in Canada by using laboratory assays to identify the prevalence and distribution of individuals seropositive to *B. burgdorferi*. Blood donor sera could be used to generate seroprevalence estimates across

Canada in a relatively cost-effective manner (O'Brien et al., 2022). Seroprevalence data has been used to characterize the epidemiology of LD in Belgium, Germany, and Finland to supplement public health surveillance (Bohm et al., 2023; Lernout et al., 2019; Olsen et al., 2023).

4. Chapter 4: Study 3 – Modeling the impact of elevated LD incidence on population health in Manitoba, Canada

4.1. Abstract

Background: LD is an emerging and growing public health threat in Canada due to environmental factors such as climate change and urban sprawl, which are both responsible for the rapid expansion of *Borrelia burgdorferi*-infected ticks (*Ixodes scapularis*) into densely populated areas. Under-reporting delays early treatment, which can lead to serious and persistent sequelae. The objective of this study was to construct a cohort LD model to assess the impact of elevated incidence on health-related quality-of-life. We constructed a Markov state transition model for LD, to assess the difference in burden between the reported rate of LD and elevated incidence rates of LD in Manitoba from administrative data study that identified un-reported Lyme cases.

Methods: The Markov model was constructed with the following, mutually exclusive health states. Subjects started out healthy, in the “well” state. Then based upon the risk of disease, were diagnosed with LD in one of 3 clinical stages: early localized LD, early disseminated LD, late disseminated LD. Patients then either developed persistent sequelae, “PTLDS”, “died”, or “recovered”. The model had monthly cycles and ran for 120 cycles. Average costs were from the payer perspective; both costs and effects were discounted at 5%.

Results: The quality-of-life impact of LD in Manitoba over a 10-year period resulted in loss of 13.8 QALYs for the base case (reported incidence) and 73.4 QALYs for the elevated incidence scenario. Our model estimated average direct healthcare costs of \$210 for the base case and \$1,029 for the elevated incidence scenario. The model outcomes were highly sensitive to incidence, probability of acquisition, and time spent with persistent sequelae.

Interpretation: Our model demonstrates that elevated incidence rates that account for under-reporting of LD have a substantial impact on health-related quality-of-life and direct healthcare expenses.

4.2. Introduction

LD is an emerging public health threat in Canada, that is expected to rapidly grow due to climate change and ecological factors, such as urbanization into forested areas, that favour tick expansion into new and densely populated areas of Canada (Ogden et al., 2024). Despite the establishment of LD surveillance programs in Canada for both human cases and ticks, cases are substantially under-reported, thereby creating a gap in understanding the true burden of LD in Canada. Recent modeling studies of LD in Ontario assess costs and burden of disease, but have relied on administrative health data linked only to reported cases, despite the acknowledgment that incidence is under-ascertained (Mac et al., 2021; Mac et al., 2023; Shing et al., 2019).

Major et al (2024) estimated the incidence of LD in Manitoba, Canada, from 2010 – 2021, using a validated algorithm to detect cases from administrative billing claims (Cocoros et al., 2023; Schwartz et al., 2021). They found cases were between 5.1 to 11.0 times higher than those reported to public health surveillance (unpublished work, Major et al. UW Ph.D. Dissertation, Study 2). The objective of the present study was to estimate the impact of elevated incidence of LD in Manitoba on quality-adjusted life-years (QALYs).

4.3. Methods

4.3.1. Model Design and Structure

We developed a Markov state transition model for LD, to evaluate the health-related quality-of-life (HRQoL) difference between the reported rate of LD in Manitoba using incidence rates from 2019 (Gasmi et al., 2022) and the elevated LD incidence from Major et al. (2024). The model structure included the health states designated as well, early localized LD, early disseminated LD, late disseminated LD, PTLDS, dead, or recovered (Figure 19). The model used

monthly cycles which ran for 120 months (10 years), with incidence rates and probabilities converted to monthly values. All costs and effects were discounted at 5%, as per health economic guidelines for public health (Public Health Agency of Canada, 2023a). The model was constructed, and all analyses were performed, using heRo3 (Avalere Health Group©2019 Health Economics in R Online, LLC), a software package that uses R code. Access to this software was provided by the company through an academic license.

Individuals were assumed to be healthy upon entry to the model. The probability of an individual to contract LD was based upon the reported or the elevated incidence rate of LD in Manitoba for 2019, which was 4.8 or 28.5 per 100,000 per year, respectively (Gasmi et al., 2022; Mac et al., 2021; Mac et al., 2023). Individuals enter the LD disease states (early localized, early disseminated, or late disseminated) based upon the proportions reported in LDES (Murison et al., 2023). The probability of an individual having clinical manifestations (e.g. EM) or developing sequelae (e.g., Lyme carditis, Lyme arthritis, etc.) was estimated using recently published data from an enhanced LD surveillance report on clinical manifestations (Table 6) (Government of Canada, 2022; Murison et al., 2023). Cases of early disseminated LD were distributed to Bell's palsy and Lyme carditis and cases of late disseminated disease were distributed to Lyme arthritis and neurologic sequelae. Clinical stages were assumed to be progressive, with the probability of progression or recovery determined by the rates of treatment failure estimated from the literature (Table 6). Recovered individuals were assumed to be immune and did not re-enter the model. Individuals in the well state remained at risk for LD across the model cycles at the base case or elevated incidence rate. Individuals with early localized disease and early disseminated disease were estimated to have EM at 70% and 50%

respectively. Individuals who developed treatment resistant arthritis remained in that state for 2 years, while individuals with PTLDS remained in that clinical stage for 5 years (Logigian & Steere, 1992; Steere et al., 1994).

4.3.2. Data Sources and Outcomes

Reported incidence rates and clinical manifestations of LD in Manitoba were obtained from national and local surveillance reports published by the CNDSS, the LD Enhanced Surveillance (LDES) system of the PHAC, and the Government of Manitoba (Gasmi et al., 2022; Manitoba, 2020; Murison et al., 2023). Elevated incidence rates for LD were taken from an administrative claims study for Manitoba (Chapter 3, Major et al.). The probabilities used in the model were estimated from the literature (Table 6) and the costs were taken from an Ontario LD costing study (Mac et al., 2023) (Table 6). Ontario average costs were used as a placeholder until LD-related healthcare costing data from an ongoing study are received for Manitoba. The outcomes were from the publicly funded healthcare system perspective. A societal perspective was not evaluated.

Utility scores to estimate the severity and health-related quality-of-life impact of the clinical manifestations and sequelae from LD were taken from a study of LD patients living in Nantucket Island, Massachusetts, a high incidence area in the United States (Shadick et al., 2001). The model outcomes were QALYs and average costs, per 100,000 people.

4.3.3. **Assessing uncertainty**

Deterministic, one-way sensitivity analyses were performed for the reported incidence and elevated incidence scenario. All parameters were scaled up and down according to a pre-specified range (Table 6), to assess the robustness of the results and the reasonability of the Markov traces, with respect to the movement of individuals through the model health states. The model cycles of 120 months were selected based upon the literature, defining the timeframe needed to observe all relevant clinical manifestations and sequelae. Scenario analyses were conducted to compare the impact of LD incidence for the base case (Gasmi et al., 2022) and the elevated incidence rate, while all other parameters remained the same. We used the elevated incidence rate for the upper range of the reported incidence rate scenario analysis. A scenario analysis was assessed using the elevated incidence rates from Chapter 3, and a deterministic, one-way sensitivity analysis was performed using an upper incidence rate that estimated the impact of climate change on LD incidence, using data taken from a recent Canadian modeling study (Ogden et al., 2024). This scenario reflects estimates of elevated LD incidence from under-reported cases and from projections from climate change modeling.

4.4. Ethics Statement

We did not require ethics approval for this type of modeling study since we only used anonymized and summary data for this analysis.

4.5. Results

The quality-of-life impact of LD in Manitoba over a 10-year period resulted in loss of 13.8 QALYs for the base case and 74.4 QALYs for the elevated incidence scenario, per 100,000

people (Figure 20). Our model estimated average public healthcare costs of \$210 for the base case and \$1,029 for the elevated incidence scenario (Figure 21).

The deterministic, one-way sensitivity analyses demonstrate that the QALYs-lost and costs in the LD model are most sensitive to fluctuations in incidence (Figure 21, Figure 22, Figure 23, Figure 24). In the elevated incidence scenario, the model became increasingly more sensitive to the probability of acquiring arthritis and the efficacy of treating arthritis, a larger number of individuals acquired sequelae. The costs associated with treating arthritis were high, particularly for the elevated incidence scenario. After the 10-year period, for the base case, 62% had remained well (unexposed), 31% recovered, 3% developed PTLDS, 2% had Lyme arthritis and 1% developed neurologic sequelae. In the elevated incidence scenario, 83% were recovered (indicating a high LD exposure rate over 10 years), 9% developed PTLDS, 6% remained well (unexposed), 1% developed neurologic sequelae and 1% had arthritis.

4.6. Strengths and Limitations

Our results demonstrate that elevated incidence has a substantial impact on economic and patient quality-of-life measures. Our findings were consistent with a recent modeling assessment of health burden of LD in Ontario, Canada, based on reported rates of LD in Ontario (2.9-13.9 per 100,000), which resulted in 84.5 QALYs-lost using a lifetime horizon (Mac et al., 2021). A scenario analysis in that study estimated that a 1% increase in incidence over a 10-year period would generate 165.5 QALYs-lost, which may indicate our estimates are conservative (Mac et al., 2021). In Mac et al. 10% of individuals developed PTLDS over a lifetime, whereas in our model, in the elevated incidence scenario, 9% developed PTLDS over the 10-year timeframe

and 14% developed PTLDS over the 50-year time horizon, likely due to our assumption that patients would only remain in this stage for 5 years. In Mac et al. 22% of their population developed sequelae over a lifetime time horizon. In our model, between 6%-11% experienced sequelae over the 10-year period.

Some simplifying assumptions needed to be made due to the limitations of a Markov process, to ensure that each cycle equaled 1 over the 120 cycles. To run the sensitivity analysis, the amount of time individuals could remain in the arthritis state needed to be reduced to 6 months instead of 1 year, otherwise too many individuals accrued with sequelae over the 10-year period, bumping the cycles over 1. This likely means that our assessment of the impact of elevated incidence is likely underestimated, particularly the proportion of individuals who developed persistent sequelae. Using microsimulation rather than Markov modeling would be a way to correct for this issue.

A limitation to using a Markov modeling approach was the inability to track individual cases. LD is characterised by a bimodal distribution, with peaks in children and older adults, as well as clinical sequelae that afflict age groups at different rates (Murison et al., 2023). LD also has a distinct seasonality, with peak incidence in June through August and declines in the winter months, except for late detection of missed infections, which usually present in the late disseminated clinical stage (Murison et al., 2023). A Markov process assumes a constant rate across the population and over time, which does not allow for building this level of heterogeneity into the model.

There were limitations to using costing data derived from reported cases, as they may have been more likely to have received appropriate, early treatment, which reduces the likelihood of sequelae and PTLDS. Using costs from Ontario was also not ideal as there may be differences in healthcare costs. Data from an ongoing LD-related healthcare utilization study will be completed in future work and we will replace Ontario costs with Manitoba-specific, incremental costs. Another limitation was the use of utility scores taken from a study in Nantucket, Massachusetts (Shadick et al., 2001). There were very few Lyme-specific quality of life studies published and no studies that have researched LD utility scores that were conducted in Canada, although from a recently published protocol, there is a study ongoing that may fill this research gap (Loeb et al., 2023).

The policy implications for public health in Manitoba could include improving awareness campaigns for LD, so that individuals are aware of the risk and what they can do to prevent infection. In eastern provinces, tick removal kits are readily available in pharmacies at a very low cost, which can reduce one's risk of being infected. Education to healthcare providers could improve awareness of the probability of risk so that it could be considered in early diagnoses, and how to report cases to public health. Allocating public health resources to managing and creating awareness of LD is a priority. Simplifying the reporting process may improve both compliance and data collection for LD in Manitoba. Our study findings of elevated LD incidence in Manitoba data may not be generalizable to other provinces due to the ecological factors that create suitable habitats for the ticks that cause LD.

4.7. Conclusion

Based upon our model, elevated incidence rates that account for under-reporting of LD in Manitoba, Canada, represented a substantial quality-of-life burden when compared to reported incidence rates. The model was sensitive to increases in the rate of disease and to increases in the number and rate of individuals that develop persistent sequelae and PTLDS.

Figure 19: Model Structure

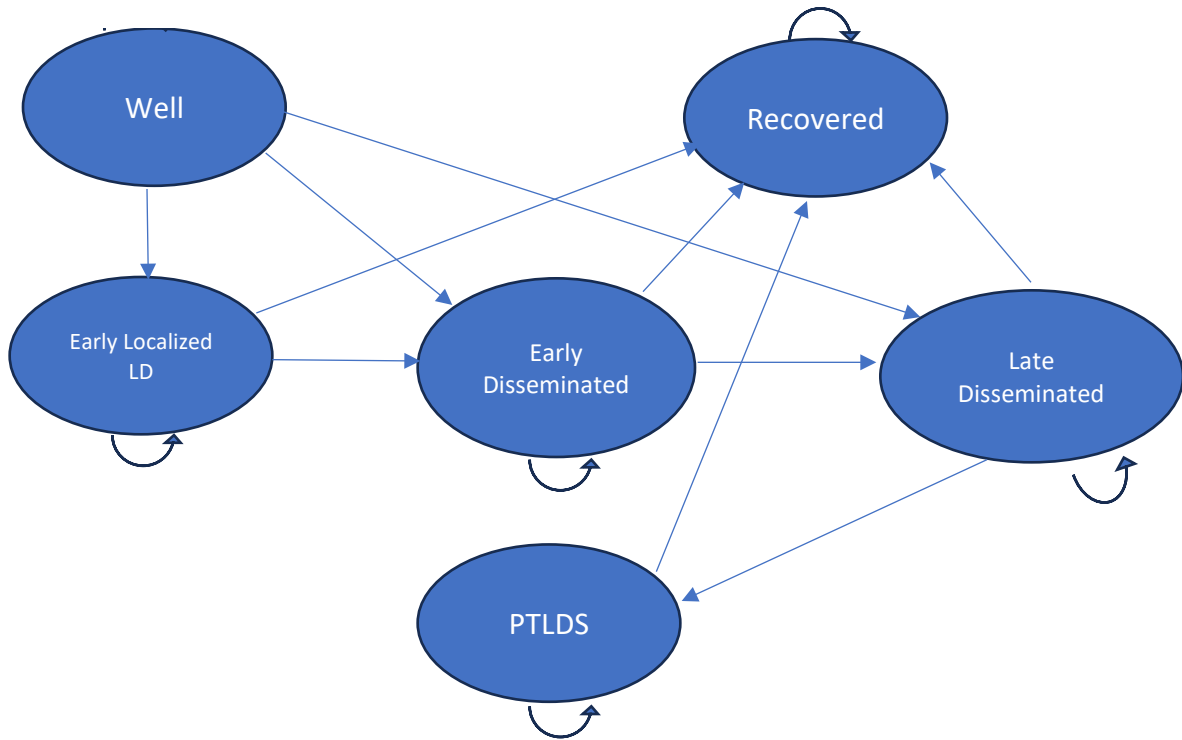


Table 6: Key parameters and data sources

Parameter	Base case	Source
Average reported LD incidence rate in 2019 (per 100,000)	4.8 (1.70-28.50)	(Gasmi et al., 2022; Manitoba, 2020)
Algorithm-derived LD Incidence rate in 2019 (per 100,000)	28.5 (4.80-49.88)	Unpublished data (study 2), Major et al.(Gasmi et al., 2022; Ogden et al., 2024)
Treatment efficacy		
EM	0.84 (0.80-0.88)	(Torbahn et al., 2018)
Arthritic sequelae	0.85 (0.40-0.80)	(Steere et al., 1994)
Cardiac sequelae	0.90 (0.80-1.00)	(Logigian & Steere, 1992; Steere et al., 1993)
Neurologic sequelae	0.90 (0.76-0.97)	(Logigian & Steere, 1992)
Clinical outcomes		
Single EM	0.758 (0.724-0.771)	(Murison et al., 2023)
Multiple EM	0.170 (0.140-0.204)	(Murison et al., 2023)
Bell's Palsy	0.08 (0.660-0.950)	(Murison et al., 2023)
Other neurologic manifestations	0.146 (0.127-0.165)	(Murison et al., 2023)
Lyme carditis	0.035 (0.260-0.460)	(Murison et al., 2023)
Lyme arthritis	0.358 (0.333-0.385)	(Murison et al., 2023)
Disease Stage		
Early localized	0.412 (0.321-0.510)	(Mac et al., 2021; Murison et al., 2023)
Early disseminated	0.167 (0.167-0.411)	(Mac et al., 2021; Murison et al., 2023)
Late disseminated	0.421 (0.189-0.421)	(Murison et al., 2023)
Key utility parameters		
Healthy	0.90 (0.38-0.98)	(Guertin et al., 2018)
<i>Erythema migrans</i>	0.80 (0.70–0.93)	(Shadick et al., 2001)
Arthritic sequelae	0.69 (0.51–0.86)	(Shadick et al., 2001)
Cardiac sequelae	0.61 (0.38-0.78)	(Shadick et al., 2001)
Cognitive sequelae	0.60 (0.37-0.73)	(Shadick et al., 2001)
Bell's palsy	0.61 (0.36-0.81)	(Shadick et al., 2001)
Meningitis/polyneuropathy	0.52 (0.27-0.73)	(Shadick et al., 2001)
PTLDS	0.54 (0.30-0.70)	(Shadick et al., 2001)
Healthcare costs		
Pre-diagnosis	\$209 (\$181, \$238)	(Mac et al., 2023)
Acute	\$1,084 (\$956, \$1,212)	(Mac et al., 2023)
Post-Acute	\$1,714 (\$1,499, \$1,927)	(Mac et al., 2023)

Figure 20: Total QALYs-Lost - Reported vs. Algorithm-Derived Incidence (120 Months)

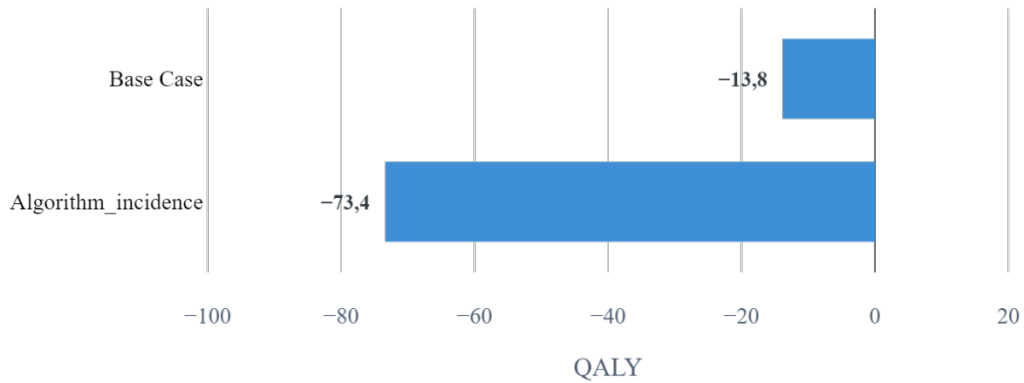


Figure 21: Total Average Costs - Reported vs. Algorithm-Derived Incidence (120 months)

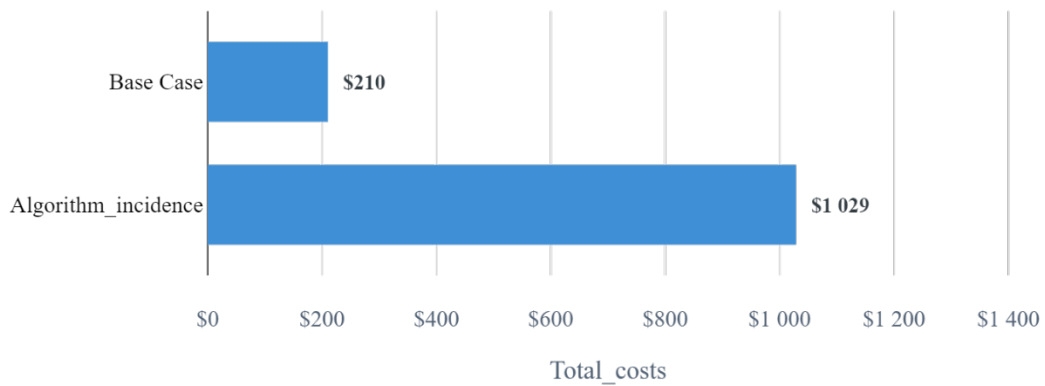


Figure 22: Deterministic Sensitivity Analysis for Reported Incidence Rates (QALYs)

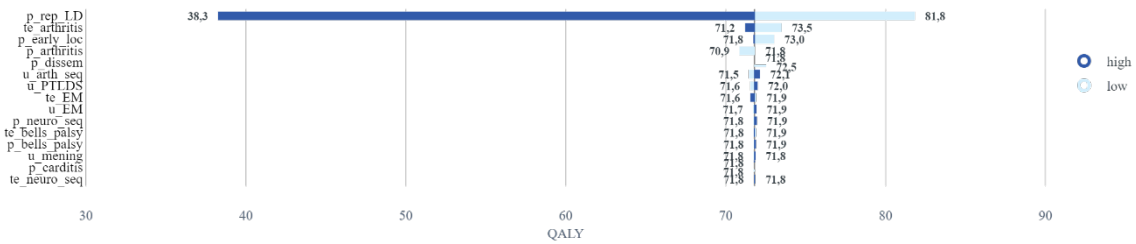


Figure 23: Deterministic Sensitivity Analysis for Reported Incidence Rates (Costs)

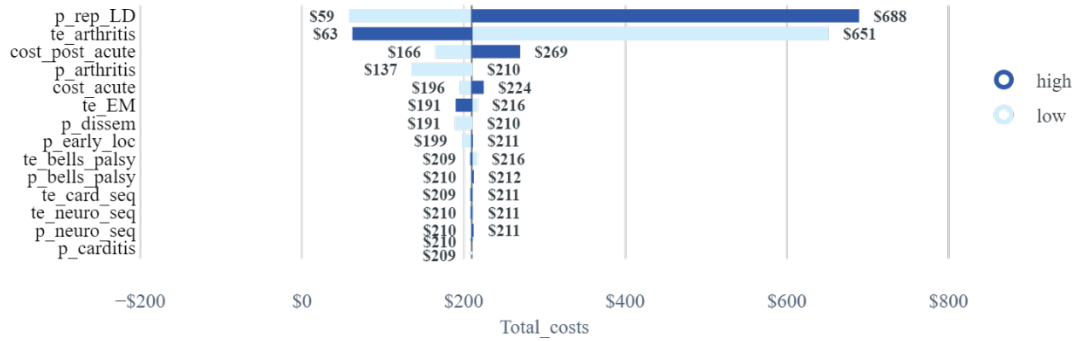


Figure 24: Deterministic Sensitivity Analysis for Algorithm-Derived Incidence Rates (QALYs)

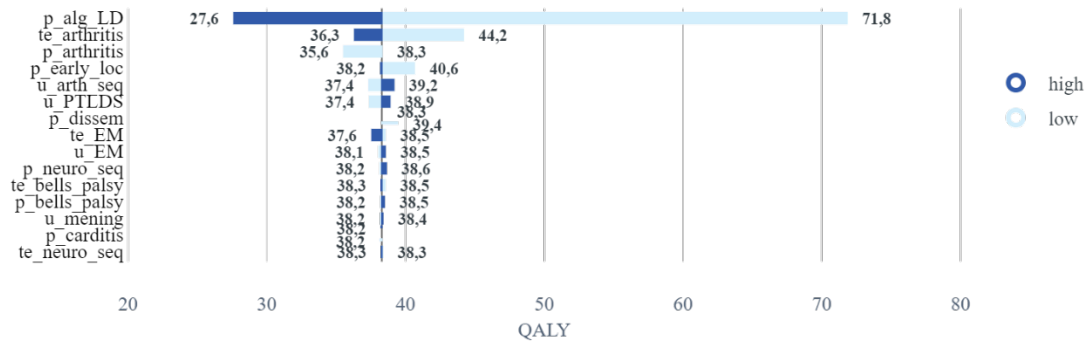
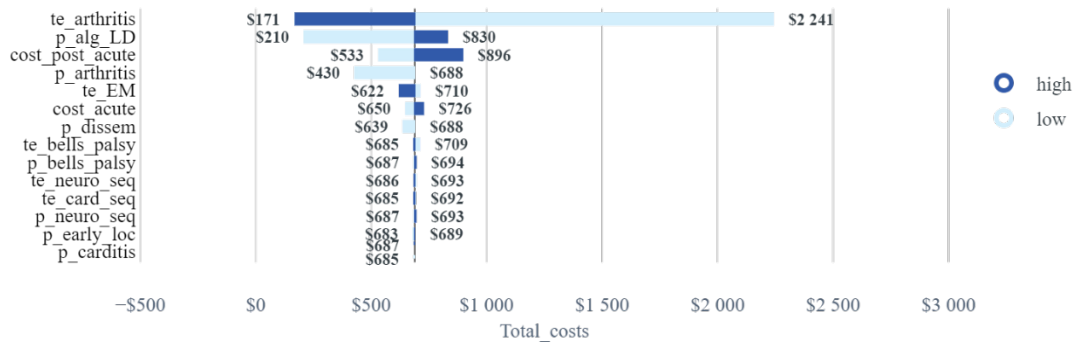


Figure 25: Deterministic Sensitivity Analysis for Algorithm-Derived Incidence Rates (Costs)



5. Chapter 5: General Discussion and Conclusion

5.1. Overview

Under-ascertainment of infectious diseases presents a challenge for public health efforts due to its potential to obscure the true burden of disease within a population and hinder effective disease control measures. This phenomenon occurs when cases of infectious diseases go undetected or unreported, leading to an incomplete understanding of disease incidence, prevalence, and transmission dynamics. Several factors contribute to under-ascertainment, including limitations in surveillance systems, such as passive reporting mechanisms that rely on healthcare providers or laboratories to voluntarily report cases. Additionally, inadequate access to healthcare, lack of awareness among healthcare professionals, and social determinants of health can all contribute to under-ascertainment. Furthermore, the asymptomatic or mild nature of some infectious diseases can result in cases being overlooked or misdiagnosed. Under-ascertainment not only undermines the ability to implement timely and targeted public health interventions, but also compromises efforts to monitor disease trends, detect outbreaks, and allocate resources effectively. Ultimately, addressing under-ascertainment requires strengthening surveillance systems, enhancing healthcare access, promoting awareness among healthcare providers and the public, and addressing underlying social and economic disparities that contribute to gaps in disease detection and reporting.

While the PHAC maintains an online list of nationally notifiable infectious diseases, the responsibility for reporting these diseases to public health surveillance falls under provincial jurisdiction (Government of Canada, 2024a). There is variability among provinces and territories regarding which diseases are considered high priority, leading to differences in the inclusion of

diseases on provincial notifiable lists compared to the national list. Most provinces offer online access to their surveillance data. Additionally, provinces voluntarily contribute disease data to the CNDSS, an interactive web-based tool facilitating the collection and dissemination of surveillance data from across the country to monitor trends in nationally notifiable infectious diseases. However, participation in reporting to CNDSS is voluntary, and discrepancies between provincial and national notifiable lists, along with reporting delays, can result in some nationally reportable diseases not being captured.

The decision to designate certain diseases as notifiable stems from various factors rooted in public health priorities and epidemiological considerations. Typically, diseases are classified as notifiable if they pose significant public health risks due to their contagious nature, severity, potential for outbreaks, or their impact on vulnerable populations. Diseases that are easily transmissible between individuals, have high mortality rates, or that can lead to widespread morbidity often receive priority status for notification (Government of Canada, 2024a). Additionally, diseases that have the potential to spread rapidly across borders or that require coordinated public health responses may also be included on notifiable lists. However, the decision ultimately depends on a combination of scientific evidence, public health expertise, and legislative mandates within each jurisdiction. Conversely, diseases that are less severe, rare, or not easily transmissible may not meet the criteria to be notifiable. As such, the designation of notifiable diseases reflects a balance between the need to monitor and control public health threats and the practical considerations of resource allocation and administrative capacity within public health systems.

For these reasons, public health researchers have employed alternative methods to gain greater clarity on infectious disease burden. Most health research in Canada that utilizes administrative data is typically initiated by individual researchers who employ a variety of data sources such as physician billing codes, diagnostic test codes, hospital discharge records, and pharmaceutical records for studies. For instance, a significant research endeavor led by Public Health Ontario (PHO) and the Institute for Clinical Evaluative Sciences (ICES) was undertaken to comprehensively evaluate infectious diseases in Ontario, known as The Ontario Burden of Infectious Disease Study (ONBOIDS) (Kwong et al., 2010). The aim was to utilize administrative data in conjunction with modeling techniques to estimate the true burden of infectious diseases in Ontario, categorized by pathogen and syndrome. A total of 51 infectious agents were evaluated based on their severity, incidence, notifiable status in Ontario, and relevance as emerging pathogens of interest. Similar global research initiatives include The Australian Burden of Disease Study (Government of Australia, 2024) and The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD, 2020), both of which include assessments of disability-adjusted life years (DALYs). Projects such as these are at the forefront of advanced surveillance methods that synthesize the best available evidence to prioritize health policy decisions, based upon overall impact to human health and economic burden.

5.2. Summary of Key Findings

5.2.1. Study 1: Systematic literature review of SARS-CoV-2 seroprevalence surveys in Canada through April 2021.

Our systematic review highlighted the benefits of using seroprevalence surveys to complement other epidemiological data. Early in the SARS-CoV-2 pandemic, the number of reported cases did not include all individuals infected with SARS-CoV-2 for several reasons.

Asymptomatic and mild infections were unlikely to be laboratory tested for SARS-CoV-2 due to reduced access and limited testing capacity required screening protocols which varied by jurisdiction, but generally prioritized access to symptomatic individuals (Hale et al., 2021). Laboratory-based surveillance relied on reporting of laboratory-confirmed cases to surveillance. For these and other reasons, public health case counts under-ascertained the number of individuals infected with SARS-CoV-2. Most patients infected with SARS-CoV-2 would generate a detectable immune response within a few weeks of infection (Charlton et al., 2021).

The systematic literature review identified 12 serosurveys with 210,321 specimens tested. While the Canadian serosurveys varied considerably in terms of their methods of recruitment, assays used and testing algorithms, limiting the ability to make direct comparisons between studies, some similarities could be observed. Across all studies, seroprevalence estimates increased over time, with a peak in autumn 2020 followed by a plateau or decline by spring 2021. There was a reduction in under-ascertainment ratios over time for most of the population-based serosurveys, with reported cases at parity with seroprevalence by April 2021.

The downward trend observed for under-reporting multipliers over the course of the pandemic was consistent with a similar analysis conducted in the USA (Angulo et al., 2021). This is likely to be due to the initial SARS-CoV-2 testing capacity and protocols which restricted testing to symptomatic travellers, and likely led to substantial under-identification of infected individuals during the early part of the pandemic (Ontario Ministry of Health, 2021). As capacity improved and guidelines evolved to include testing of asymptomatic high-risk groups, an increased proportion of infected people were identified. Another explanation could involve the characteristics of the assays used in the studies, and the limited durability of immunity

following natural infection. Anti-nucleocapsid antibody levels have been observed to wane as early as 4 months following natural infection. This was demonstrated within the Ontario serosurvey when Public Health Ontario retested sera samples from their August 2020 samples using a reduced assay threshold to assess assay sensitivity. A 16% increase in seropositivity was detected, which they attributed to waning of anti-nucleocapsid antibodies as time from infection increased (Bolotin et al., 2021).

Serosurveys are susceptible to selection bias based upon their sample frames, which may limit the generalizability to population estimates. Blood donors in Canada are known to be a healthier subset of the population and do not represent the immunity of children due to age restriction of donors (O'Brien et al., 2022). This may have implications for interpreting population immunity to a pathogen, given the role that children have in transmission dynamics.

The COVID-19 Immunity Taskforce (CITF) expanded the scope of the SARS-CoV-2 seroprevalence surveys from sourcing sera only from blood donors from Canadian Blood Services and Héma-Québec, to including specimens from anonymized discarded, or residual, blood samples from provincial laboratories and participants in CITF-funded research cohorts. While this creates a more generalizable sample frame, there remains heterogeneity in testing methods and assays used between the groups, which make it difficult to compare and combine the results (Swail et al., 2023). However, by building and maintaining the infrastructure to conduct seroepidemiologic research, many more questions could be researched. The pandemic taught us that you cannot ramp up capacity for surveillance quickly. Creating a national seroepidemiology research platform has research potential for surveillance of emerging diseases such as LD and other tick-borne diseases that are increasing in Canada.

In the early phases of the SARS-CoV-2 outbreak, there was limited understanding regarding natural immunity to this new pathogen and how exposure might confer protection against future infections. Monitoring population immunity became crucial for gaining insights into the effects of both natural and vaccine-induced immunity, enabling assessments of protection against subsequent infections. Despite the transition away from pandemic status, Canada Blood Services continues to update this work and is expanding their sources of sera for analysis against SARS-CoV-2.

The systematic review provided an important snapshot of all the Canadian research in this area, with attention to the how the methodologic approaches to conducting the serosurveys might impact the validity of results. Notably, many of the larger, longitudinal serosurveys, which were also the highest quality assessments, were conducted by public health entities and blood donation systems. Most of their data were not published in the peer reviewed literature but were posted on websites as interactive graphs or pdf formatted reports. We could realistically find ourselves in the future facing a new pandemic, without any record of this work or the lessons learned from it. Government reports are archived on a regular basis and websites can be taken down, particularly when the priorities change as is now happening with SARS-CoV-2. Some of the links in chapter 2 are no longer active.

Study 2: Estimating Incidence of LD in Manitoba using Administrative Data

LD is the most reported vector-borne disease in Canada, caused by infection with *Borrelia burgdorferi*, transmitted by ticks. While reported rates have been increasing in recent years, incidence of LD in Canada is still substantially underestimated due to climate change

ecological factors and under-reporting. The purpose of this study was to estimate the incidence of LD in Manitoba, Canada, using administrative claims data.

A validated, LD-case finding algorithm, based on Lyme diagnostic codes and antibiotics previously used by the Center for Disease Control (CDC), was adapted to estimate LD cases in Manitoba. LD cases and demographic data taken from the Manitoba Population Research Data Repository (MPRDR) for 2010-2021. Over the study period (2010-2021) 2,976 cases of LD were identified from: primary care (80.1%), EDs or hospitalizations (6.3%), and by diagnostic serology (13.6%). The algorithm-derived incidence in Manitoba increased over the study period from 8.4 per 100,000 in 2010 to a peak of 28.5 per 100,000 in 2019. The algorithm identified between 5.1 to 11.0 times more cases than reported to surveillance from 2010 to 2021 and displayed less disparity in rates by sex compared to reported cases, which demonstrate a stronger male predominance. This study demonstrated substantial under-reporting of LD in Manitoba, with 4 of the 5 regional health authorities meeting the US CDC criteria for high incidence, which is 10 per 100,000 per year, for 3 consecutive years (Centers for Disease Control, 2022).

Other key findings when the algorithm-derived rates were compared to the reported rates were that under-ascertainment levels were higher in low incidence states and lower in high incidence states. Women consistently had higher under-ascertainment rates than men and often presented outside of the typical Lyme season, indicating that their diagnosis and treatment were delayed. Delayed diagnosis has implications for the clinical course of LD, leading to sequelae and possibly PTLDS (Murison et al., 2023).

Our study demonstrated that the reported rates are dramatically underestimating the burden of LD in Manitoba and likely elsewhere in Canada. The differences in reporting by sex

are not well understood, but there may be some indication from the CDC data, that women are being diagnosed later than men and for some reason this is leading to reduced reporting to public health surveillance (Schwartz et al., 2021). Administrative database studies are not adequate for clinically staging diseases, as was discovered in our study. Our exploratory algorithm to clinically stage the LD cases failed, due to the low specificity of billing codes. Other administrative studies have had the same issues with clinically staging LD cases (Mac et al., 2023). This makes it difficult to assess, from our study, what the clinical implications are for this under-reporting of cases in women relative to men. However, the modeling assessment indicates that under-reporting of LD has substantial implications for patient quality of life and costs of treating persistent sequelae.

Manitoba was an excellent pilot for our administrative data study. The quality of the linked datasets and the availability of pharmaceutical data and serology lab results provide confidence in our ability to identify LD cases. Manitoba is not among one the high-risk areas of Canada, which makes our findings interesting.

Study 3 – Modeling the impact of elevated LD incidence on population health in Manitoba, Canada

The objective of the third study was to construct a cohort LD model to assess the impact of elevated incidence on patient quality-of-life. A Markov state transition model for LD was developed to evaluate the difference between the reported rate of LD and elevated incidence rates of LD in Manitoba from an administrative data study that identified un-reported Lyme cases. The model health states were well, early localized LD, early disseminated LD, late disseminated LD, PTLDS, dead, or recovered, with transitions to clinical manifestations and

sequelae. The model had monthly cycles and ran for 120 cycles, to reflect the time it takes for individuals to develop persistent clinical manifestations and sequelae of LD.

The quality-of-life impact of LD in Manitoba over a 10-year period resulted in a loss of 16 QALYs for the base case and 84.3 QALYs for the elevated incidence scenario. Our model estimated average costs of \$314 for the base case and \$1531 for the elevated incidence scenario. The model was most sensitive to variation in incidence rates and the probability of acquiring and time spent with persistent sequelae. Our model demonstrates that elevated incidence rates accounting for under-reporting of LD in Manitoba have a substantial impact on quality-of-life.

Modeling is an important way to understand the impact of infectious diseases, particularly when disease incidence estimates are uncertain. Most people who contract LD will recover. LD is also characterized by a constellation of clinical manifestations that have different disease paths and age-specific risks. Without employing methods of quantitative analysis, it would be difficult to map out how individuals move through the disease course and evaluate the impact of the burden.

5.3. Implications for Public Health Policy: Serosurveys

Serological surveys gauge the prevalence of pathogen-specific antibodies in blood samples from participants by examining serum samples. Serological surveillance entails periodic sampling, ideally using consistent testing methods, within a particular population. The presence of antibodies indicates past or current infection, irrespective of symptom manifestation, or previous vaccination. Thus, serosurveys offer valuable insights into quantifying the prevalence of past or ongoing infections (or vaccinations) at a given time. Public health applications of

serosurveys encompass assessing exposure to new pathogens (i.e., infection rates), forecasting disease attack rates and potential pandemic wave impacts, monitoring susceptibility to vaccine-preventable diseases, and assessing the efficacy of vaccine programs and vaccine durability (Bolotin et al., 2023). Common sources of specimens for serosurveys include residual sera from provincial diagnostic laboratories or blood donations, although samples may also be collected prospectively for specific serosurvey studies.

At a workshop held in Toronto, Canada, on November 18th-19th, 2019, invited international experts shared their research and insights into the public health management of infectious diseases (Bolotin et al., 2023). Deficiencies in immunity to rubella and measles were identified both in Canada and globally, aiding in the formulation of vaccine programs, and workshop participants emphasized the necessity and value of establishing a national center for seroepidemiological research (Bolotin et al., 2023).

Following the onset of the SARS-CoV-2 pandemic in Canada in March 2020, the theoretical discussions held during prior meetings swiftly transformed into urgent priorities as the nation grappled with the emergence of this novel pathogen. Almost immediately, a number of seroprevalence studies were launched across the country, employing diverse specimen sources, laboratory testing assays, and sampling methodologies (Major et al., 2022). This led to an expansion in using serosurveys (Bolotin et al., 2021; Saeed et al., 2021; Swail et al., 2023). By employing assays capable of detecting both anti-nucleocapsid and anti-spike antibodies, these studies enabled the separate assessment of vaccine-induced immunity and infection-induced immunity, a crucial distinction particularly following the introduction of COVID vaccines in January 2021 (Murphy et al., 2023).

Setting up broader programmatic serosurveillance on a national scale would be expensive, in part due to the laboratory requirements. Lab assays used for diagnostic purposes are not adequate for the purposes of surveillance because they provide qualitative results (immune, non-immune), rather than antibody levels. Population immunity is dynamic and specific antibody levels are important to evaluate trends in susceptibility (Bolotin et al., 2023).

Lessons learned from serosurveys include that cross-sectional serology data, without accounting for waning antibodies, led to an underestimation of the cumulative incidence of SARS-CoV-2 infection which can be partially mitigated by lowering the antibody threshold level (Bolotin et al., 2021). Modeling methods were developed to quantify this underestimation and to adjust estimates accordingly by considering waning antibodies (Shioda et al., 2020).

The findings in chapter 2 pointed out the benefits of using serology data at the beginning of a pandemic to a novel pathogen (Angulo et al., 2021; Major et al., 2022; O'Brien et al., 2022). Serology becomes less useful when disease become endemic where most people have acquired some form of hybrid immunity, after exposure to both vaccination and infection. Having an ongoing national serosurvey platform is therefore important as new diseases emerge.

5.4. Implications for Public Health: Administrative Database Research

The Canada Health Act 1984 ensures publicly funded healthcare is provided to all, yet constitutionally preserves the rights of the provinces and territories (P/T) to administer the systems independently, which has led to some inconsistencies in the administrative processes used to fund healthcare across the country (Government of Canada, 1984). In Canada, both data custodian and data stewardship models play crucial roles in managing administrative

health databases, but they have distinct responsibilities and approaches. Some provinces adopt data custodian models, where an organization or entity is designated as the custodian of the data and has legal ownership and control over the data within the administrative health database (Katz et al., 2018). The data custodian is primarily responsible for safeguarding the data, ensuring compliance with privacy regulations and policies, and managing access to the data. In contrast, the data stewardship model emphasizes collaboration and governance among multiple stakeholders involved in the management of the data. Data stewardship involves a broader range of responsibilities beyond mere custody, including data quality assurance, metadata management, data governance, and promoting data sharing and interoperability. Data stewards often work closely with data users, researchers, policymakers, and other stakeholders to understand their needs and ensure that the data are used effectively and ethically (Katz et al., 2018). Enhanced privacy protocols have generally resulted in a relaxation of restrictions, researchers still face obstacles in accessing administrative data due to prolonged application procedures and extraction wait times, as highlighted in Katz et al. (2018). Lack of harmonization makes it difficult to compare results across provinces.

Administrative datasets in each province have inconsistent access to pharmaceutical data. In-hospital, ED, and specialty clinics do not use administrative billing codes for pharmaceuticals because those costs are managed internally within the hospital formulary budget. Therefore, no record exists of treatments provided, except for when the mode of delivery is billed, such as for intravenous drugs. Inconsistencies also exist in outpatient pharmaceutical data by jurisdiction. Some provinces such as British Columbia, Alberta, and Manitoba, have comprehensive databases of patient-level pharmaceutical treatments

prescribed and dispensed, whereas Ontario only collects data for pharmaceuticals administered by the publicly funded drug plan. When treatment forms an important component of algorithms to identify cases of infectious diseases, this gap may reduce the specificity of an administrative study to identify cases. In this scenario, cases may need to be validated by use of EHRs or conducting chart reviews, which are often not included in the data holdings that are available for health research.

Differences in coding practices and linked datasets by jurisdiction make comparisons across jurisdictions challenging to conduct and interpret. In fact, research agreements with data custodians often limit the right to make or publish comparisons with extracted data with similar data from another province. Our LD study team attempted to conduct a similar study to estimate LD cases in Ontario. We were not able to successfully extract Lyme cases, due to the lack of specificity of Ontario Health Insurance Plan (OHIP) billing codes used in primary care. In the Manitoba LD study, 80% of the LD cases were identified by their primary care provider. We needed the ICD-9 or ICD-10 codes that have specificity to identify LD cases from administrative billing claims databases (Chapter 3). This explains the why it would be difficult to use administrative data to identify LD cases in Ontario.

Administrative database studies which use ICD-9/ICD-10 billing codes in addition to other linked datasets, can be used to conduct research on medically attended cases of disease. While this method may provide a more accurate sense of the clinically relevant cases, it is susceptible to under-reporting of cases that are improperly diagnosed, improperly coded or “under-coded” due to guidelines on using most responsible diagnoses. Another important factor to using administrative data as a research tool is the specificity of the billing codes used.

While standard of practice uses ICD-10 codes, jurisdictions such as Ontario use OHIP billing codes in primary care, which are less specific than ICD-9 codes in terms of identifying diseases. This is a major limitation for conducting administrative studies in Ontario.

Electronic health records are valuable sources of healthcare information which allows better access to clinical and symptom-level patient data, which can be used to validate findings from administrative database studies. Supplementing disease surveillance with additional study can provide a more accurate characterization of the burden to inform health policies and economic analyses.

5.5. Methodological Reflections and Future Research

The methods used to characterize infectious disease burden are highly dependent upon the microbe, disease state, and diagnostic laboratory testing sensitivity and specificity to produce valid results that have meaningful interpretation to human disease risk. This thesis contributed to the literature by demonstrating the benefits of serosurveys, administrative data, and lab-based surveillance for two different emerging pathogens and provide some policy conclusions with a more general application for other infectious diseases.

Seroprevalence studies provide a snapshot of population-level immunity to a pathogen but are susceptible to bias based upon sampling method and sensitivity of assay thresholds to detect antibody thresholds. Sources for serum can include blood donors, residual specimens from public health laboratories, or prospective samples drawn for study. Seroprevalence surveys capture all infections, including asymptomatic infections, which can be important in characterising the base of the epidemiologic pyramid. This could be useful for an emerging

disease such as LD, if cases are unreported and tick surveillance is not a comprehensive tool to assess risk.

Administrative data represents about 95% of the Canadian population due to universal healthcare coverage. Health research method that makes use of administrative healthcare claims data, holds a lot of promise in terms of producing population-level estimates of disease rates and healthcare utilization. An important health policy change could include improving the harmonization of billing codes of certain jurisdictions, consistent with current coding guidelines, to improve their specificity, as well as uniform access to pharmaceutical data.

5.6. Conclusion

Unreported disease can become invisible to policymakers if credible, quantitative, and qualitative research methods are not used characterize disease burden. The importance of integrative methods to generate meaningful comparisons between diseases is an important scientific approach to help drive health policy decisions, based upon the true burden of disease. This thesis has employed many of these methods to generate insights into the burden of two infections diseases of public health importance.

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Appendices

Appendix A: Supplemental Material for Study 1

Table S1 | PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	PROSPERO 2021 CRD42021246958
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3, Lines 26-45
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 4-5 Lines 47-89 Figure 1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5-6, Lines 90-94
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pages 6-7 Lines 108-116 Lines 129-134 Tables S7, S11-S13
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6 Lines 101-107
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	PROSPERO Tables S2-S6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7 Lines 117-124
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7 Lines 121-125
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7 Lines 126-128

Section and Topic	Item #	Checklist item	Location where item is reported
			Table S8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 7 Lines 126-128 Table S8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7-8 Lines 135-140 Table S9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 8 Lines 142-147
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 8 Lines 143-147
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8 Lines 166-169
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 8 Lines 148-150
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n/a
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 8 Lines 152-165
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8 Lines 152-165
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9 Lines 172-173 Figure 2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9 Lines 173-176 Table S12
Study characteristics	17	Cite each included study and present its characteristics.	Page 10 Lines 184-198 Tables 1-3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 10 Lines 199-202

Section and Topic	Item #	Checklist item	Location where item is reported
			Figure 3 and S10
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 3 Figures 4A-G
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 10 Lines 199-202 Figure 3 and S10 Table 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 11 Lines 204-239 Table 2 Figures 4A-G
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Table 3, S11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n/a
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Figure 4A-G
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 12-14 Lines 241-273
	23b	Discuss any limitations of the evidence included in the review.	Page 14 Lines 274-289 Lines 302-306
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	Page 15-16 Lines 307-340
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	PROSPERO
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	PROSPERO
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	Affiliation
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplement PROSPERO Registration

Search Strategies

Table S2| Published Academic Work – Scopus

Category	Search Terms
Canada	(TITLE-ABS-KEY (canad* OR ontario OR quebec OR montreal OR british columbia OR vancouver))
Serology	(TITLE-ABS-KEY ("Immunoglobulins" OR antibody OR "anti-body" OR "antibodies" OR "anti-bodies" OR "Serologic Tests" OR "Immunoassay" OR "Serology" OR resurvey OR "resurvey"))
COVID-19 ¹	((KEY (coronavirus OR coronavirus OR "coronavirus infections") AND KEY ("disease outbreaks" OR epidemics OR pandemics)) OR (TITLE-ABS-KEY (ncov* OR 2019ncov OR 19ncov OR covid19* OR cvid OR sars-cov-2 OR sars-cov2 OR sarscov-2 OR sarcoma OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "Severe Acute Respiratory Syndrome Corona Virus 2")) OR (TITLE-ABS-KEY ((new W/3 coronavirus*) OR (new W/3 "corona virus*") OR (new W/3 betacoronavirus*) OR (new W/3 cov) OR (new W/3 hcov) OR (novel W/3 coronavirus*) OR (novel W/3 "corona virus*") OR (novel W/3 betacoronavirus*) OR (novel W/3 cov) OR (novel W/3 hcov) OR (19 W/3 coronavirus*) OR (19 W/3 "corona virus*") OR (19 W/3 betacoronavirus*) OR (19 W/3 cov) OR (19 W/3 hcov) OR (2019 W/3 coronavirus*) OR (2019 W/3 "corona virus*") OR (2019 W/3 betacoronavirus*) OR (2019 W/3 cov) OR (2019 W/3 hcov) OR (wuhan W/3 coronavirus*) OR (wuhan W/3 "corona virus*") OR (wuhan W/3 betacoronavirus*) OR (wuhan W/3 cov) OR (wuhan W/3 hcov) OR (hubei W/3 coronavirus*) OR (hubei W/3 "corona virus*") OR (hubei W/3 betacoronavirus*) OR (hubei W/3 cov) OR (hubei W/3 hcov) OR (china W/3 coronavirus*) OR (china W/3 "corona virus*") OR (china W/3 betacoronavirus*) OR (china W/3 cov) OR (china W/3 hcov) OR (chinese W/3 coronavirus*) OR (chinese W/3 "corona virus*") OR (chinese W/3 betacoronavirus*) OR (chinese W/3 cov) OR (chinese W/3 hcov))) OR (TITLE-ABS-KEY ((coronavirus* W/3 pandemic*) OR (coronavirus* W/3 epidemic*) OR (coronavirus* W/3 outbreak*) OR (coronavirus* W/3 crisis) OR ("corona virus*" W/3 pandemic*) OR ("corona virus*" W/3 epidemic*) OR ("corona virus*" W/3 outbreak*) OR ("corona virus*" W/3 crisis) OR (betacoronavirus* W/3 pandemic*) OR (betacoronavirus* W/3 epidemic*) OR (betacoronavirus* W/3 outbreak*) OR (betacoronavirus* W/3 crisis))) OR (TITLE-ABS-KEY ((wuhan W/5 pneumonia) OR (hubei W/5 pneumonia))))
Limits	(PUBYEAR > 2018) English

CADTH COVID-19 Pandemic. [Website] CADTH COVID-19 Search Strings for Scopus (Updated July 10, 2020; Accessed Jan 30, 2021) Available at: <https://covid.cadth.ca/literature-searching-tools/cadth-covid-19-search-strings/>

Table S3 | Published Academic Work – PubMed

Category	Search Terms
Canada	"canada"[MeSH Terms] OR "canad*"[Title/Abstract] OR "ontario"[Title/Abstract] OR "quebec"[Title/Abstract] OR "British columbia"[MeSH Terms] OR "canada"[All Fields] OR "canada s"[All Fields] OR "canadas"[All Fields]
Serology	"Immunoglobulins"[MeSH Terms] OR "antibodie"[All Fields] OR "antibodies"[MeSH Terms] OR "antibodies"[All Fields] OR "antibody s"[All Fields] OR "antibodys"[All Fields] OR "Immunoglobulins"[MeSH Terms] OR "Immunoglobulins"[All Fields] OR "antibody"[All Fields] OR "anti-body"[All Fields] OR "antibodies"[All Fields] OR "anti-bodies"[All Fields] OR "Serologic Tests"[MeSH Terms] OR "Immunoassay"[MeSH Terms] OR "Serology"[MeSH Terms] OR "serosurvey"[All Fields] OR "serosurveys"[All Fields] OR "serosurvey"[All Fields]
COVID-19*	((Coronavirus[mh:noexp] OR Betacoronavirus[mh:noexp] OR Coronavirus Infections[mh:noexp]) AND (Disease Outbreaks[mh:noexp] OR Epidemics[mh:noexp] OR Pandemics[mh])) OR COVID-19 drug treatment [Supplementary Concept] OR COVID-19 serotherapy [Supplementary Concept] OR spike glycoprotein, COVID-19 virus [Supplementary Concept] OR COVID-19 [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 [Supplementary Concept] OR nCoV[tiab] OR nCoV[tt] OR 2019nCoV[tiab] OR 2019nCoV[tt] OR COVID19*[tiab] OR COVID19*[tt] OR COVID[tiab] OR COVID[tt] OR SARS-CoV-2[tiab] OR SARS-CoV-2[tt] OR SARSCOV-2[tiab] OR SARSCOV-2[tt] OR SARSCOV2[tiab] OR SARSCOV2[tt] OR Severe Acute Respiratory Syndrome Coronavirus 2[tiab] OR Severe Acute Respiratory Syndrome Coronavirus 2[tt] OR ((severe acute respiratory syndrome[tiab] OR severe acute respiratory syndrome[tt]) AND (corona virus 2[tiab] OR corona virus 2[tt])) OR new coronavirus[tiab] OR (new[tt] AND coronavirus[tt]) OR novel coronavirus[tiab] OR novel coronavirus[tt] OR novel corona virus[tiab] OR (novel[tt] AND corona virus[tt]) OR novel CoV[tiab] OR (novel[tt] AND CoV[tt]) OR novel HCoV[tiab] OR (novel[tt] AND HCoV[tt]) OR ("19"[tiab] OR "19"[tt] OR "2019"[tiab] OR "2019"[tt] OR Wuhan[tiab] OR Wuhan[tt] OR Hubei[tiab] OR Hubei[tt]) AND (coronavirus*[tiab] OR coronavirus*[tt] OR corona virus*[tiab] OR corona virus*[tt] OR CoV[tiab] OR CoV[tt] OR HCoV[tiab] OR HCoV[tt])) OR ((coronavirus*[tiab] OR coronavirus*[tt] OR corona virus*[tiab] OR corona virus*[tt] OR betacoronavirus*[tiab] OR betacoronavirus*[tt]) AND (outbreak*[tiab] OR outbreak*[tt] OR epidemic*[tiab] OR epidemic*[tt] OR pandemic*[tiab] OR pandemic*[tt] OR crisis[tiab] OR crisis[tt])) OR ((Wuhan[tiab] OR Wuhan[tt] OR Hubei[tiab] OR Hubei[tt]) AND (pneumonia[tiab] OR pneumonia[tt]))
Limits	Publication type: not review; Publication dates: 2019/11/01 to present; Species: Humans; Languages: English; Sorted by: Most Recent

*CADTH COVID-19 Pandemic. [Website] CADTH COVID-19 Search Strings for PubMed (Updated April 15, 2020; Accessed Jan 30, 2021) Available at: <https://covid.cadth.ca/literature-searching-tools/cadth-covid-19-search-strings/>

Source: Campbell, Sandy. Hedge to Retrieve Studies Related to Canada and Canadian Provinces from Most Databases. John W. Scott Health Sciences Library, University of Alberta. Rev. March 09, 2020 https://docs.google.com/document/d/1VbD1BgOB69pBDWt1CGj2tQ4_RQdAFvEqV_P73IJRbtw/edit

Table S4 | Unpublished Academic Work - BioRxiv and MedRXIV

Category	Search Terms
Canada	Canada AND Ontario
Serology	seroprevalence OR immunoglobulin
COVID-19	COVID-19
Limits	Date Posted: 2019-11-01 to 2021-01-30; Include articles: bioRxiv AND MedRxiv

Source: <https://www.medrxiv.org/search>

Table S5 | Unpublished Academic Work – COVID-19 Data Repositories

Organization	Sources
COVID-19 Immunity Task Force (CITF)	https://www.covid19immunitytaskforce.ca/
SeroTracker	https://serotracker.com/en/Explore
Public Health Ontario	https://www.publichealthontario.ca/en/diseases-and-conditions/infectious-diseases/respiratory-diseases/novel-coronavirus
World Health Organization (WHO) COVID-19 Global literature on coronavirus disease	https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/ Search Terms: tw:(tw:(seroprevalence) AND mj:("Antibodies, Viral" OR "Antibodies, Neutralizing") AND type_of_study:(("prevalence_studies") AND la:("en"))

Table S6 | Press Releases – Google

Category	Search Terms – under “any of these words”
Serology	seroprevalence
COVID-19	Coronavirus; COVID-19; SARS-CoV-2
Filters	Language: English; Region: Canada; Last update: past year

Source: Google Advanced Search: https://www.google.com/advanced_search

Table S7 | Inclusion and Exclusion Criteria

Characteristics	Criteria for Inclusion	Criteria for Exclusion
Population	Human – any age	Non-human, animal, in vitro
Condition	Previous SARS-CoV-2 infection, COVID-19 disease	<ul style="list-style-type: none"> • Active SARS-CoV-2 infection • Other infections
Intervention	Validated serological assay that can detect the presence of SARS-CoV-2 antibodies (IgG, IgM, IgA).	<ul style="list-style-type: none"> • Unvalidated serologic assays for SARS-CoV-2 • SARS-CoV-2 immunologic assays that do not measure antibodies (cell-mediated immunity).
Types of Evidence	Published or unpublished academic literature, grey literature, media reports, or press releases	Reports that cannot be sourced to a credible public health or research group.
Study Design	Cross-sectional or Cohort Studies	Any other study design, case reports, case-control studies
Outcome Measures	<ul style="list-style-type: none"> • Seroprevalence estimates expressed as a percent or proportion. • Reports number of positive tests as a proportion of the total screened population for a defined period during the pandemic. 	<ul style="list-style-type: none"> • Data related to SARS-CoV-2 immunity but without reported seroprevalence estimates. • SARS-CoV-2 serologic assay validation studies.
Language	English or French	Non-English, Non-French
Geographical Region	Study conducted within Canada or any defined jurisdiction within Canada	Any study conducted outside of Canada
Time Frame	During SARS-CoV-2 pandemic (after 2019)	

Table S8 | Data Extraction Items

Publication Level Information	Publication source, organization conducting survey, jurisdiction, testing interval (start date, end date)
Assay/Testing Characteristics	Name and manufacturer of test, immune target (N, S, RBD), isotype (IgG, IgM, IgA), test sensitivity (95% CI), test specificity (95% CI), assay positivity threshold and testing algorithm or criteria for positivity
Study Characteristics	Study design, sample size, sample frame, sampling method, sampling interval
Outcome Level Information	Seroprevalence estimates with confidence intervals (CI), seroprevalence estimates stratified by location, sex, and age-group (if reported). Adjusted seroprevalence estimates corrected for testing sensitivity and specificity were used when reported.

Table S9 | Critical Appraisal Checklist and Decision Criteria

Item 1: Was the sample frame appropriate to address the target population?	
Yes	Target sample frame described and representative of target population.
No	Target sample frame described but not representative of target population.
Unclear	Target sample frame not described.
Item 2: Were study participants sampled in an appropriate way?	
Yes	Probability sampling method.
No	Non-probability sampling method.
Unclear	Sampling method not described.
Item 3: Was the sample size adequate?	
Yes	A sample size calculation was conducted to ensure adequacy or sample size was very large.
No	A sample size calculation was not conducted, and sample size was very small.
Unclear	Sample size calculation was not conducted, yet sample size is not small.
Item 4: Were the study subjects and the setting described in detail?	
Yes	Study subjects were described by age and sex.
No	Study subjects were not described by age and sex.
Item 5: Was the data analysis conducted with sufficient coverage of the identified sample?	
Yes	The sample is representative of the target population by age, sex, geographic distribution.
No	The sample is not representative of the target population by age, sex, geographic distribution.
Unclear	The representativeness of the sample is not described and/or cannot be evaluated based upon the information provided.
Item 6: Were valid methods used for the identification of the condition?	
Yes	The assay met Health Canada standards of at least 95% sensitivity and 99.5% specificity. ¹
No	The assay did not meet Health Canada standards of at least 95% sensitivity and 99.5% specificity.
Unclear	Sensitivity and Specificity were not reported.

Item 7: Was the condition measured in a standard, reliable way for all participants?	
Yes	Use of orthogonal testing algorithm to determine seropositivity of SARS-CoV-2, as per public health recommendations. ¹
No	Use of orthogonal testing algorithm to determine seropositivity of SARS-CoV-2, as per public health recommendations.
Unclear	Testing algorithm not reported.
Item 8: Was there appropriate statistical analysis?	
Yes	All the following: study sample is representative or adjusted if non-probability sample; adjustments made for testing characteristics; outcome clearly reported with numerator, denominator, and confidence intervals.
No	Study sample is not representative, nor adjustments made to correct.No corrections made for testing characteristics. Missing data reporting numerator, denominator, or confidence intervals.
Item 9: Was the response rate adequate, and if not, was the low response rate managed appropriately?	
Yes	Was there a low non-response rate and the sample demographics matched the target population.
No	Was there a high non-response rate and the sample demographics did not match the target population.
Unclear	The response rate was not reported.
Item 10: Overall Risk of Bias	
Low	All criteria assessed for risk for bias were met and the seroprevalence estimate is likely accurate for the target population.
Moderate	Most of the criteria assessed for risk for bias were met and the seroprevalence estimate may be accurate for the target population.
High	Most of the criteria assessed for risk for bias were not met and the seroprevalence estimate is likely not accurate for the target population.

Table S10 | Assessment of Bias by Decision Criteria

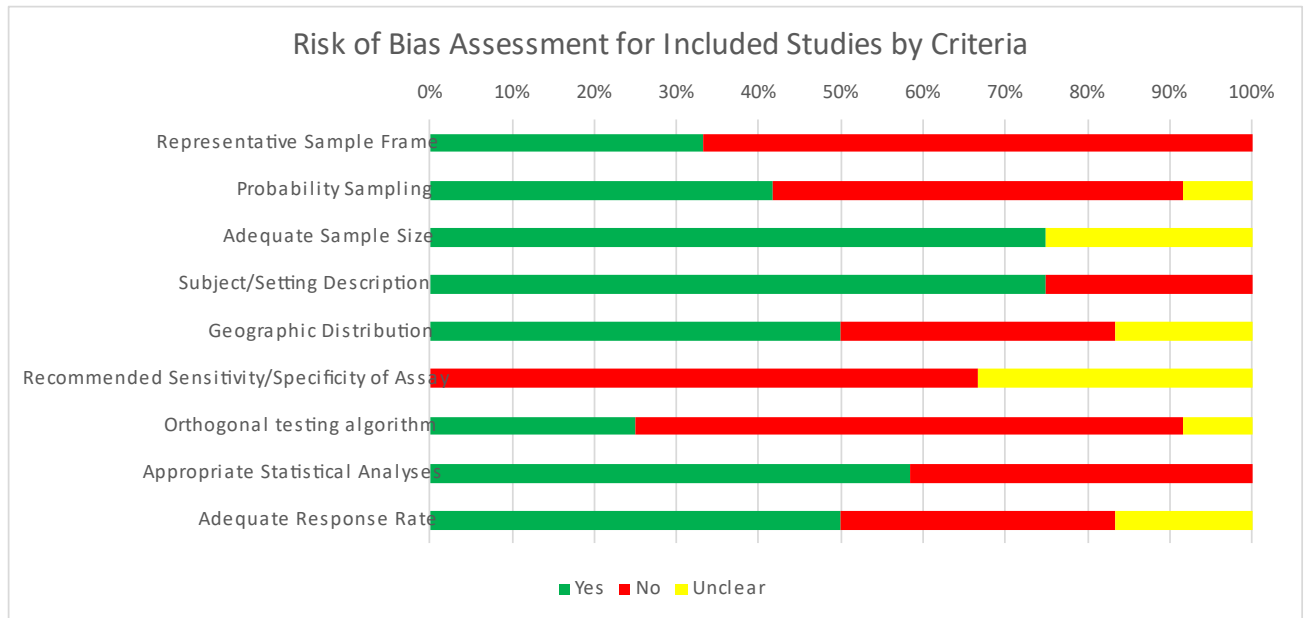


Table S11 | Summary of Data Extraction from Included Studies

Study #	Articles	Jurisdiction	Test Characteristics [name (assay type), isotype (immune target)]	Sensitivity (95% CI) /Specificity (95%CI)	Sampling Method (Sample Frame)	Sampling Interval	Number (N)	Seroprevalence % (95%CI)	
1	Saeed, 2021 ²	Canada	Abbott Architect (CMIA), IgG (N)	92.7% (90.2- 94.8%)/99.9% (99.4-100%)	Non-probability (Blood donors)	May 9-July 21, 2020	74642	0.7 (0.63-0.76)	
	Oct 12-31, 2020					16811	0.88 (0.73-1.04)		
	Nov 7-25,2020					17049	1.51 (1.31-1.71)		
	Jan 1-27, 2021					34921	1.99 (1.84-2.15)		
2	Tang, 2021 ⁶	Canada	Dried Blood Spot (ELISA), IgG (N, S, RBD)	94% (NR)/99% (NR)	Probability (Angus Reid) Representative	May-July, 2020	7068	1.7 (NR)	
						Aug-Sept, 2020	1899	2.54 (NR)	
3	Public Health Ontario, 2020 ⁷⁻¹⁰	Ontario	Abbott Architect (CMIA), IgG (N)/ Ortho VITROS (CLIA), IgG (S)	90.4% (NR)/100% (NR)	Non-Probability (Residual specimens, public health laboratory)	Mar 27-Apr 30, 2020	827	0.4 (0.1-1.1)	
						May 24- 31, 2020	1061	1.4 (0.7-2.1)	
						June 5- 30, 2020	7023	1.1 (0.9-1.4)	
						July 4-31, 2020	7001	1 (0.8-1.2)	
						August 1-31, 2020	5764	1.1 (0.8-1.4)	
						Sept 3-30, 2020	4901	0.7 (0.4-0.9)	
Oct 1 – 30, 2020	7107	1.2 [0.9; 1.4]							
4	Ferreira, 2021 ¹¹	Toronto, ON	Abbott Architect (CMIA), IgG (N)/ Euroimmun (ELISA), IgG (S)	100% (NR)/99.6% (NR)	Non-probability (asymptomatic healthcare workers)	April 17-29, 2020	996	1.4 (NR)/ 1.2 (NR)	
5	Skowronski, 2021 ¹²	Vancouver, BC	Ortho VITROS (CLIA), Total Ab (S)/ Abbott Architect (CMIA), IgG (N)	85% (76.5- 91.4%)/99.5% (98.2- 99.9%),92.7% (85.6-97%)/100 (99.1-100%)	Non-Probability (Residual specimens, outpatient laboratory network)	March 5-13, 2020	870/869	0.8 (0.32-1.65)/ 0.46 (0.13-1.17)	
						May 15-27, 2020	889/885	0.67 (0.25-1.46)/ 0.79 (0.32-1.62)	
6	Vijh, 2021 ¹³	Vancouver, BC	DiaSorin Liaison (CLIA) IgG (S1/S2)/Ortho VITROS (CLIA), Total Ab(S)/ Ortho VITROS (CLIA), IgG (S)/ Abbott Architect (CMIA), IgG (N)/ Siemens Centaur (CLIA) Total Ab (RBD)	NR/NR	Non-Probability (Long term care residents – facility A)	May 4-14, 2020	36	86.1 (NR)	
							Non-Probability (Long term care residents – facility B)	71	32.4 (NR)
							Non-Probability (Long term care staff-facility A)	86	43.0 (NR)
							Non-Probability (Long term care staff-facility B)	98	22.4 (NR)
7	Majdoubi, 2021 ¹⁴	Vancouver, BC	Ortho VITROS (CLIA), Total Ab (S)	NR/NR	Non-Probability (Adults)	May 17-June 20, 2020	276	0.6 (0.00-2.71)	
8	Institut National de Santé	Quebec	DiaSorin Liaison (CLIA) IgG (S1/S2)	88.4% (83- 92.6%)/NR	Non-Probability (Healthcare workers; Intensive care unit; high prevalence)	July 6-Sept 24, 2020	1630	14 (NR)	

	Publique du Quebec, 2020 ¹⁵				Non-Probability (HCW ICU low prevalence)		426	3.1 (NR)
9	Héma-Quebec, 2020 ¹⁶	Quebec	In-house laboratory assay (ELISA), IgG (RBD)	98.9%(NR)/98.5%(NR)	Non-Probability (Blood donor)	May 25-July 20, 2020	7691	2.25 (1.93-2.61)
10	Bardai, 2020 ¹⁷	Montreal, QC	Mologic-Omega Diagnostics (ELISA) IgG (N, S1)	NR/97%(NR)	Non-Probability (Children)	June 10-July 27, 2020	39 (children)	8 (NR)
					Non-Probability (Caregivers)		61 (caregiver)	12(NR)
					Non-Probability (Hospital staff)		99 (staff)	12 (NR)
11	Manny, 2021 ¹⁸	Edmonton, AB	Abbott Architect (CMIA), IgG (N)	100%(NR)/NR	Non-Probability (Children)	Aug-Oct, 2020	565	1.6 (NR)
12	Statistics Canada, 2021 ¹⁹	Canada	Dried Blood Spot (ELISA), IgG (N, S, RBD)	NR/NR	Probability (Representative)	Nov 2020-Apr 2021	11,000	2.6 (1.6-3.2)

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Appendix B: Supplemental Material for Study 2

Table S1: Description of Manitoba Population Research Data Repository (MPRDR) Databases

MPRDR Databases	Description
MC-MS	Claims for visits to physicians/primary care providers in offices, hospitals, and outpatient departments; fee-for-service components for tests such as lab tests.
DAD	hospital forms/computerized records containing summaries of demographic and clinical information (e.g., gender, postal code, diagnoses, and procedure codes) completed at the point of discharge from the hospital.
NACRS	Hospital-based and community-based ambulatory care at a national level: day surgery, outpatient clinics, and EDs.
Drug Program Information Network (DPIN)	prescription drug claims from all pharmacies for all Manitoba residents, including Registered First Nations, regardless of insurance coverage or final payer. Excludes hospitals, wards, cancer care
Manitoba Health Insurance Registry (MHIR)	Demographic data
Cadham Provincial Laboratory (CPL)	Laboratory values
National Rehabilitation Reporting System (NRS)	Demographic, administrative, and clinical information pertaining to physical rehabilitation.
Long Term Care (LTC) Utilization	Long Term Care (LTC) Utilization data is maintained by Manitoba Health and consists of records of chronic and rehabilitative services provided by long term care institutions in Manitoba, including hospital patients awaiting placement

Source: [Manitoba Population Research Data Repository Data List](#) | [MCHP Concept Dictionary and Glossary for Population-Based Research](#) | [Max Rady College of Medicine](#) | [University of Manitoba \(umanitoba.ca\)](#)

Table S2: Description of Variables

Variable	Time Period	Data Source	Definition
Demographics:			
Age	Index date	MHIR	Continuous
Sex	Index date	MHIR	Categorical
Local residential area	Index date	MHIR	Categorical
Neighborhood income quintile	Index date	MHIR	Ordinal
Clinical Characteristics:			
Clinical stage	Lookback period, Analysis period	MC-MS	Categorical
Season of LD diagnosis <i>Spring (Mar-May), Summer (Jun-Aug), Fall (Sep-Nov), Winter (Dec-Feb)</i>	Index date	MC-MS	Categorical
Year of LD diagnosis	Index date	MC-MS	Categorical
Charlson Comorbidity Index (CCI) <i>Mild (CCI 1-2), Moderate (CCI 3-4), Severe (CCI ≥5)</i>	Lookback period	DAD; MC-MS	Categorical
Symptoms related to LD	Index period	DAD; NACRS; MC-MS	Binary
Co-infection <i>Anaplasma phagocytophilum, Babesia microti</i>	Index period	DAD; NACRS; MC-MS	Binary
LD diagnostic codes	Index period	DAD; NACRS; MC-MS	Binary
Lab test			
Serology test for LD	Index period	CPL	Binary
Treatment:			
Antibiotics dispensed	Index period	DPIN	Categorical
Duration of antibiotics treatment, days	Index period	DPIN	Continuous

Table S3: Coding Algorithm Used to Identify Lyme Cases

	ICD-10-CA	ICD-9-CM	DIN	LOINC
LD	A69.2, M01.2*	08881		
Antibiotics			See Table S4	
Laboratory test				See Table S5

Table S4: Drug Identification Numbers for Antibiotic Treatment

Antibiotic	Drug Identification Number (DIN)
Doxycycline	740713, 874256, 887064, 2375885, 860751, 2512645, 2351234, 2351242, 725250, 2158574, 2247104
Amoxicillin	2477726, 2237154, 2352710, 2352729, 2352753, 2352788, 2401509, 2401541, 2434709, 2434717, 2241826, 2241827, 2525348, 2525356, 2243224, 2243225, 2514648, 2514656, 2514664, 2514672, 2388073, 2388081, 2458586, 2458594, 2230615, 2230616, 2230617, 2230618, 2433060, 2433079, 2230244, 2532042, 2532050, 2495856, 2495864, 406716, 406724, 452130, 628115, 628123, 628131, 628158, 644315, 644331, 1934163, 2036355, 2492210, 2493381, 2535793, 2535815
Cefuroxime axetil	2244393, 2244394, 2344823, 2344831, 2212307
Azithromycin	2480700, 2415542, 2482363, 2482371, 2330881, 2442434, 2523825, 2524449, 2483890, 2465604, 2452308, 2502038, 2479680, 2261634, 2261642, 2310600, 2275309, 2265826, 2332388, 2332396, 2267845, 2212021, 2223724, 2223716, 2239952
Penicillin G	2220261, 2220288, 2220296
Cefotaxime	2434091, 2434105
Clarithromycin	2403196, 2274744, 2274752, 2413345, 2146908, 2244641, 1984853, 2126710, 2324482, 2324490, 2408988, 2408996, 2442469, 2442485, 2466120, 2466139, 2471388, 2471396, 2247573, 2247574, 2346532, 2266539, 2266547, 2361426, 2361434, 2390442, 2390450
Erythromycin	873454, 682268, 682276, 2326663, 1912755, 2225271
IV Ceftriaxone	2409968, 2499711, 2499738, 2287633, 2287668, 2250276, 2250292, 2292262, 2292270, 2292289, 2292297, 2325594, 2325616, 2325624, 2325632

Table S5: Laboratory Codes for LD Diagnostic Assays

Assay	LOINC
VlsE1/pepC10 Borrelia (Lyme) IgM/IgG Enzyme-linked immunoassay (ELISA)	100711-1, 16478-0, 16480-6, 20449-5, 31155-5, 38173-1, 40612-4, 43842-4, 44455-4, 46248-1, 5060-9, 5062-5, 5064-1, 51742-5, 51743-3, 51744-1, 51747-4, 83081-0, 98205-8
Western blot assay (IgG/IgM)	12781-1, 12873-6, 12874-4, 12877-7, 12878-5, 12879-3, 12890-0, 12891-8, 12892-6, 12896-7, 13502-0, 13503-8, 18201-4, 18203-0, 21116-9, 21117-7, 27982-8, 27985-1, 27986-9, 28002-4, 29898-4, 32666-0, 42238-6, 44452-1, 44946-2, 44947-0, 44948-8, 44949-6, 49977-2, 49979-8, 49981-4, 49983-0, 49992-1, 49994-7, 49996-2, 49997-0, 51745-8, 51746-6, 60342-3, 60343-1, 62342-1, 6320-6, 6321-4, 9587-7, 9588-5, 9589-3, 9590-1, 9591-9, 9592-7, 9593-5, 9594-3, 9595-0, 9596-8, 9597-6, 9598-4, 9599-2, 96429-6, 96430-4, 96431-2, 96432-0, 98204-1, 98206-6, 94476-9, 94477-7

Table S6: Clinical Staging Code Algorithm for Early Localized Disease

For a patient to be assigned as EARLY LOCALIZED STAGE, the following criteria must be met:

Criteria: Mutual Exclusivity Component							
Patients must not be assigned as LATE DISSEMINATE STAGE							
Patients must not be assigned as EARLY DISSEMINATE STAGE							
AND							
Criteria: Symptom & Time Component							
Patients must meet at least ONE of the the following sub-criteria ±90 days from index date:							
OR	Subcriteria 2a: Patients must have the following combination of codes on the same hospitalization abstract at least ONCE in the follow-up period:						
	Conditions	ICD-10-CA codes	ICD-9-CM codes	AND, any of:	Conditions	ICD-10-CA codes	ICD-9-CM codes
	LD	A69.2	08881		Erythema	L54*, L50*, L53.8, L53.9	06950, 07080, 69589, 06959
					Swelling, localized	R22*	07822
					Cellulitis	L03*	68100
					Rash	R21*	07821
					Fatigue, Weak, Lethargy, Malaise	R53*	78079
					Headache	R51*	07840
					Myalgia	M79.1	07291
					Chills	R50.8, R68.8	07806, 07999
					Back pain	M54.5, M54.0*	07242, 07236
					Body, generalized aches	R52*	78096
					Fever	R50.8, R50.9	07806
Subcriteria 2b: Patients must have the following code in their follow-up period:							
ICD-10-CA: A26.0/ ICD-9-CM: 00271	<i>Erythema migrans</i>						

Table S7: Clinical Staging Code Algorithm Criteria for Early Disseminated Disease

For a patient to be assigned as EARLY DISSEMINATED STAGE, the following criteria must be met:

Criteria: Mutual Exclusivity Component		
Patients must not be assigned as LATE DISSEMINATE STAGE		
AND		
Criteria: Symptom & Time Component		
Patients must have at least TWO* of any of the following conditions occurring within ±90 days from index date:		
Conditions	ICD-10-CA codes	ICD-9-CM codes
Bell's palsy/other cranial neuritis	G51.0, M79.28, M79.29, G52*, G53.1*, G53.2*	03510, 07292, 07292, 03520, 03529, 03526
Neck pain/neck, stiff	M54.2	07231
Paresthesia	R20.2	07820
Cognitive impairment/mood disturbance	F07.9, F06.3, F38*, F39*, F60.3*	03109, 29383, 29660, 29690, 03013
Visual symptoms	R44.1	36816
Auditory symptoms	R44.0	07801
Dizziness	R42*	07804
Lymphocytic meningitis/encephalitis/encephalomyelitis	A87.2, G04*, G05*	00490, 03235, 03234
Radiculoneuropathy	M54.1*	07244
Palpitations/arrhythmia	R00.2, I49*	07851, 42741
Chest pain	R07.3, R07.4, R07.1, I20.9	78659, 78650, 78652, 04139
A-V heart block [second or third degree]	I44.1, I44.2, I44.3	42612, 04260, 42610

Table S8: Clinical Staging Code Algorithm Criteria for Late Disseminated Disease

Criteria: Symptom & Time Component		
Patients must have at least ONE of any of the following conditions occurring within ±90 days from index date:		
Conditions	ICD-10-CA codes	ICD-9-CM codes
Arthralgia	M25.5*	71949
Joint inflammation	M01.2*, M01.3*, M01.8*, M02.8*, M03.2*, M03.6*, M13*, M14.8*, M00.8, M00.9	71189, 71149, 71189, 71689, 71149, 71182, 71650, 07138, 71109, 71109

Table S9: Clinical Symptom Variables and Codes

Clinical Characteristics	Symptom	ICD-10 Codes	ICD-9 Codes
Symptoms related to LD	Rash	R21*	07821
	Fever	R50.8, R50.9	07806
	Fatigue	R53*	78079
	Chills	R50.8, R68.8	07999
	Myalgia	M79.1	78096, 07291
	Headache	R51*	07840
	Pain in joint	M25.5*	71949
	Cervicalgia	M54.2	07231
	Disturbance of skin sensation	R20*	07820
	Radiculopathy	M54.1	07244
Musculoskeletal manifestations	Arthritis due to LD	M01.2*	71100-9, 71190-9
	Arthralgia	M25.5*	71140-9, 71180-9
	Joint inflammation	M01.3*, M01.8*	8070-9
Nervous system manifestations	Lymphocytic meningitis	G00.8, G00.9, G01*, G02.8*, G03*	03209, 03207 03218, 03220
	Cranial neuritis	M79.28, M79.29, G52*, G53.1*, G53.2*	07292, 03520, 03526, 03529
	Radiculoneuropathy	M54.1*	07244
	Encephalomyelitis	G04*, G05*	03234-5
	Bell's palsy	G51.0	03510
Cardiovascular manifestations	Atrioventricular conduction defects - complete heart block, third degree heart block, high-grade atrioventricular block	I44.1, I44.2, I44.3	42612, 04260, 42610
	Myocarditis	I51.4, I40*, I41.0*, I41.2*	04290, 42292, 04220
Ocular manifestations	Conjunctivitis	H10.0, H10.1, H10.2, H10.3, H10.8, H10.9	37200, 37203, 37205, 37239
	Keratitis	H16.3	37050
	Uveitis	H20.0, H22.0	36400, 36403
	Papillitis	H46	37730
	Episcleritis	H15.1, H19.0	37900, 37909
Persistent symptoms	Fatigue	R53*	78079
	Headache	R51*	07840
	Stiff neck or neck pain	M54.2	07236
	Arthralgia	M25.5*	71949
	Myalgia	M79.1	07291, 78096
	Radiculopathy	M54.1*	07244
	Problems with cognition or memory	F04*, F05.8, F05.9, F06.7, R41*	02940, 29389, 02930, 03101, 02989

* all sub-codes under this code are included.

Table S10: Treatment Table Codes

Class	Treatment or Procedure	DIN
Oral Antibiotics	Doxycycline	740713, 874256, 887064, 2375885, 860751, 2512645, 2351234, 2351242, 725250, 2158574, 2247104
	Amoxicillin	2477726, 2237154, 2352710, 2352729, 2352753, 2352788, 2401509, 2401541, 2434709, 2434717, 2241826, 2241827, 2525348, 2525356, 2243224, 2243225, 2514648, 2514656, 2514664, 2514672, 2388073, 2388081, 2458586, 2458594, 2230615, 2230616, 2230617, 2230618, 2433060, 2433079, 2230244, 2532042, 2532050, 2495856, 2495864, 406716, 406724, 452130, 628115, 628123, 628131, 628158, 644315, 644331, 1934163, 2036355, 2492210, 2493381, 2535793, 2535815
	Penicillin G	2220261, 2220288, 2220296
	Cefotaxime	2434091, 2434105
	Clarithromycin	2403196, 2274744, 2274752, 2413345, 2146908, 2244641, 1984853, 2126710, 2324482, 2324490, 2408988, 2408996, 2442469, 2442485, 2466120, 2466139, 2471388, 2471396, 2247573, 2247574, 2346532, 2266539, 2266547, 2361426, 2361434, 2390442, 2390450
	Erythromycin	873454, 682268, 682276, 2326663, 1912755, 2225271
	Cefuroxime axetil	2244393, 2244394, 2344823, 2344831, 2212307
	Azithromycin	2480700, 2415542, 2482363, 2482371, 2330881, 2442434, 2523825, 2524449, 2483890, 2465604, 2452308, 2502038, 2479680, 2261634, 2261642, 2310600, 2275309, 2265826, 2332388, 2332396, 2267845, 2212021, 2223724, 2223716, 2239952
Intravenous antibiotics	Ceftriaxone	2409968, 2499711, 2499738, 2287633, 2287668, 2250276, 2250292, 2292262, 2292270, 2292289, 2292297, 2325594, 2325616, 2325624, 2325632

Table S11: Cohort Selection Criteria

Step	Cohort Selection Criteria Inclusion Criteria	N Excluded	N Remaining	% Remaining
1	Total patients identified as a LD case in the Manitoba databases between January 1, 2010, to December 31, 2021, by any of the case finding algorithms*		2976	100%
	LD case finding algorithms			
A	Primary algorithm [hospitalized and ED patients]			
	Patients in Manitoba with ≥ 1 LD ICD-10-CA diagnosis code; AND		176	
	Patients with ≥ 7 days of dispensed antibiotics within 30 days of LD diagnosis code (ED SETTING)	21	155	
	Patients in Manitoba with ≥ 1 LD ICD-10-CA diagnosis code (INPATIENT SETTING)		61	
	Patients who met the primary algorithm		216	
	Patients indexed on the primary algorithm	29	187	
B	Primary care adapted algorithm			
	Patients in Manitoba with relevant LD MC-MS code; AND		4024	
	Patients with ≥ 7 days of dispensed antibiotics within ± 30 days of LD diagnosis code	1426	2598	
	Patients who met the primary care adapted algorithm		2598	
	Patients indexed on the primary care adapted algorithm	215	2383	
C	Serology-based algorithm			
	<i>Patients have relevant LD positive reactive laboratory tests</i>		520	
	Patients who met the serology algorithm		520	
	Patients indexed on the serology algorithm	114	406	
	Exclusion Criteria			
1	Patients without information on key demographics (e.g., sex, age)	0	2976	100%
2	Patient aged ≥ 105 years at index	0	2976	100%
3	Death occurring at index	0	2976	100%
	Incidence Analysis Set		2976	100%
*Individuals were indexed on the earliest date they were identified as a case by any of the LD case finding algorithms between January 1, 2010, and December 31, 2021. Individuals were not re-indexed if they met the definitions of case finding algorithms more than once during the selection period (i.e., N is the sum of n1, n2, and n3).				

Table S12 Demographic Characteristics at Index Date

	Category	Total (%)
	Number of patients	2912 (100%)
Sex	Females	1364 (46.84 %)
	Males	1548 (53.16 %)
Age Group (years)	≤4	144 (4.95 %)
	5 - 9	165 (5.67 %)
	10 - 14	104 (3.57 %)
	15 - 19	105 (3.61 %)
	20 - 24	78 (2.68 %)
	25 - 29	132 (4.53 %)
	30 - 34	144 (4.95 %)
	35 - 39	160 (5.49 %)
	40 - 44	175 (6.01 %)
	45 - 49	192 (6.59 %)
	50 - 54	228 (7.83 %)
	55 - 59	296 (10.16 %)
	60 - 64	276 (9.48 %)
	65 - 69	262 (9.00 %)
	70 - 74	207 (7.11 %)
	75 - 79	132 (4.53 %)
	80 - 84	80 (2.75 %)
	85 - 89	26 (0.89 %)
	≥90	6 (0.21 %)
		Mean (SD)
	Median (Q1, Q3)	51.00 (29.50, 64.00)
	Range (Min - Max)	(1.00 - 96.00)
Local residential area	Northern	24 (0.82 %)
	Interlake - Eastern	426 (14.63 %)
	Prairie Mountain	375 (12.88 %)
	Winnipeg	1175 (40.35 %)
	Southern	912 (31.32 %)
Neighborhood income quintile	1 (lowest)	431 (14.80 %)
	2	487 (16.72 %)
	3	630 (21.63 %)
	4	644 (22.12 %)
	5 (highest)	714 (24.52 %)
	Unavailable	6 (0.21 %)

Table S13: LD Cases by Clinical Stage and Year (2010-2021)

Year	Outcome	Early localized	Early disseminated	Late Disseminated	Undefined
2010	Cases (N)	0	0	0	104
	Incidence per 100,000	0	0	0	8.37
2011	Cases (N)	0	0	*1-5 (S)	*99-103(S)
	Incidence per 100,000	0	0	*(S)	*(S)
2012	Cases (N)	0	0	*1-5 (S)	*155-159(S)
	Incidence per 100,000	0	0	*(S)	*(S)
2013	Cases (N)	*1-5 (S)	0	*1-5 (S)	*198-206(S)
	Incidence per 100,000	*(S)	0	*(S)	*(S)
2014	Cases (N)	*1-5 (S)	0	*1-5 (S)	*204-212(S)
	Incidence per 100,000	*(S)	0	*(S)	*(S)
2015	Cases (N)	*1-5 (S)	*1-5 (S)	*1-5 (S)	*227-239(S)
	Incidence per 100,000	*(S)	*(S)	*(S)	*(S)
2016	Cases (N)	*1-5 (S)	*1-5 (S)	*1-5 (S)	*253-265(S)
	Incidence per 100,000	*(S)	*(S)	*(S)	*(S)
2017	Cases (N)	8	*1-5 (S)	*1-5 (S)	*300-308(S)
	Incidence per 100,000	0.58	*(S)	*(S)	*(S)
2018	Cases (N)	*1-5 (S)	*1-5 (S)	*1-5 (S)	*342-354(S)
	Incidence per 100,000	*(S)	*(S)	*(S)	*(S)
2019	Cases (N)	*1-5 (S)	6	6	*380-384(S)
	Incidence per 100,000	*(S)	0.43	0.43	*(S)
2020	Cases (N)	*1-5 (S)	6	*1-5 (S)	*318-326(S)
	Incidence per 100,000	*(S)	0.43	*(S)	*(S)
2021	Cases (N)	7	6	*1-5 (S)	*255-260(S)
	Incidence per 100,000	0.49	0.42	*(S)	*(S)

*Indicates suppressed cell due to low numbers

S = suppression

UNIVERSITY OF WATERLOO

Notification of Ethics Clearance to Conduct Research with Human Participants

Principal Investigator: Susan Horton

Student investigator: Maria Major

Co-Investigator: Mark Loeb (McMaster University)

Co-Investigator: Fred Angulo (Pfizer)

Co-Investigator: Kate Halsby (Pfizer)

Co-Investigator: Sarah Willis (Pfizer)

Co-Investigator: James Stark (Pfizer)

Study coordinator: Natalie Nightingale (IQVIA Canada)

Co-Investigator: Calum Neish (IQVIA Canada)

Data analyst: Irene Wang (IQVIA Canada)

Data analyst: Saranya Nair (IQVIA Canada)

File #: 45493

Title: An observational study of Lyme disease in Ontario, Canada: Incidence and Healthcare Resource Utilization

The Human Research Ethics Board is pleased to inform you this study has been reviewed and given ethics clearance.

Initial Approval Date: 06/23/23 (m/d/y)

University of Waterloo Research Ethics Boards are composed in accordance with, and carry out their functions and operate in a manner consistent with, the institution's guidelines for research with human participants, the Tri-Council Policy Statement for the Ethical Conduct for Research Involving Humans (TCPS, 2nd edition), International Conference on Harmonization: Good Clinical Practice (ICH-GCP), the Ontario Personal Health Information Protection Act (PHIPA), the applicable laws and regulations of the province of Ontario. Both Boards are registered with the U.S. Department of Health and Human Services under the Federal Wide Assurance, FWA00021410, and IRB registration number IRB00002419 (HREB) and IRB00007409 (CREB).

This study is to be conducted in accordance with the submitted application and the most recently approved versions of all supporting materials.

Expiry Date: 06/24/24 (m/d/y)

Multi-year research must be renewed at least once every 12 months unless a more frequent review has otherwise been specified. Studies will only be renewed if the renewal report is received and approved before the expiry date. Failure to submit renewal reports will result in the investigators being notified ethics clearance has been suspended and Research Finance being notified the ethics clearance is no longer valid.

Level of review: Delegated Review

Signed on behalf of the Human Research Ethics Board



Joanna Eidse, Research Ethics Officer, jeidse@uwaterloo.ca, 519-888-4567, ext. 47163

This above named study is to be conducted in accordance with the submitted application and the most recently approved versions of all supporting materials.

Documents reviewed and received ethics clearance for use in the study and/or received for information:

file: 2916273_Pfizer Lyme disease_protocol_FINAL_v1.0_5May2023.docx

file: Nightingale Protocol Initial Approval Notice May1523.pdf

file: Pfizer Lyme disease_study definitions_v1.0_4May2023.xlsx

file: ICES DAS Agreement_P2022-119_IQVIA Lyme Disease_28Apr2023_FE.pdf

Approved Protocol Version 1 in Research Ethics System

This is an official document. Retain for your files.

You are responsible for obtaining any additional institutional approvals that might be required to complete this study.