The epidemiology and healthcare costs of pregnancy-related listeriosis in British Columbia, Canada, 2005-2014

by

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A thesis

presented to the University of Waterloo

in fulfillment of the

thesis requirement for the degree of

Master of Science

in

Public Health Sciences

Waterloo, Ontario, Canada, 2023

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

With the exception of the content noted below, the work of this thesis consists of content that I authored.

I used existing data provided by Population Data BC. Access to data provided by the Data Steward(s) is subject to approval, but can be requested for research projects through the Data Steward(s) or their designated service providers. All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not reflect the opinions or policies of the Data Steward(s).

I wrote this thesis with input from Dr. Shannon Majowicz. I also received feedback on the methodology and results from my thesis committee, Dr. Dimitra Panagiotoglou and Dr. Zahid Butt; and from members of the CIHR grant that my research was part of, Dr. Eleni Galanis and Marsha Taylor.

Abstract

Introduction: Listeriosis, a disease caused by the bacteria *Listeria monocytogenes*, remains relatively rare in Canada. However, the case-fatality rate from listeriosis is high at 20-30%. Listeriosis in pregnancy is of special concern, as the pathogen can be transmitted to the fetus or neonate and cause neonatal infection, spontaneous abortion, stillbirth, and death. This thesis aimed to describe the epidemiologic characteristics, pregnancy outcomes, and direct healthcare costs of pregnancy-related listeriosis in British Columbia, Canada, during 2005-2014.

Methods: This secondary data analysis leveraged administrative health and surveillance data from eight databases provided by Population Data BC. The first part of the analysis used descriptive epidemiologic methodology to describe all cases of listeriosis that occurred in pregnant women and neonates during the 10 years. This included the demographic and clinical features of the pregnancy-related listeriosis cases, the proportion of pregnancies that resulted in stillbirth, and the fraction of all stillbirths in British Columbia that can be attributed to listeriosis. The second part of the analysis used a matched cohort design to compare the direct healthcare costs for pregnant women and neonates with and without listeriosis. Healthcare utilization and unadjusted costs per type of healthcare use were summarized descriptively. A generalized linear model with a gamma distribution and log-link was also used to model highly skewed cost data, adjusted for several variables.

Results: There were 10 lab-confirmed and an additional 1-5 potential cases of listeriosis in pregnant women. There were 1-5 lab-confirmed and an additional 1-5 potential cases of neonatal listeriosis. Pregnant women with confirmed listeriosis had a median gestational age at listeriosis onset of 31 weeks and on average, gave birth pre-term (median of 34 weeks). Neonates with listeriosis had a median birthweight of 2,915g, which was lower than the average birthweight in

British Columbia, and experienced complications at birth such as meningitis and sepsis. Between 10-50% of confirmed pregnant women with listeriosis had a stillbirth and the fraction of stillbirths that can be attributed to listeriosis was between 0.048% and 0.239%. Pregnant women and neonates with listeriosis had significantly more hospital visits, days in hospital, and physician visits on average than those without listeriosis. Pregnant women with confirmed listeriosis on average had 2.48 times higher mean total healthcare costs than those without listeriosis, adjusted for age, health authority, and income quintile ($p<.0001$). Neonates with confirmed listeriosis on average had 14.48 times higher mean total healthcare costs than neonates without listeriosis, adjusted for sex, income quintile, and presence of a congenital abnormality ($p<.0001$).

Conclusion: Between 2005 to 2014, pregnancy-related listeriosis in British Columbia was rare. Some pregnant women did experience stillbirth but no neonates died. All maternal cases experienced pregnancy complications and all neonatal cases experienced birth complications. Pre-term delivery among pregnant women and low birth weight among neonates were common. Furthermore, compared to pregnant women and neonates without listeriosis, healthcare costs were on average significantly higher for pregnant women and neonates with listeriosis. This study has highlighted important information for public health specialists, clinicians, and policy makers.

Acknowledgments

First and foremost, I would like to thank my supervisor Dr. Shannon Majowicz for her endless support, guidance, and mentorship. She has provided me with so many tools to excel in my research, inspired me to take on challenges, and cared for my well-being along the way. I am immensely grateful for the transformative impact she has had on my academic journey and my career.

I would also like to thank my committee members, Dr. Dimitra Panagiotoglou and Dr. Zahid Butt for their feedback and support during this process. Their advice has made this work better and I have learned so much from them. I also wish to thank Dr. Eleni Galanis and Marsha Taylor for generously sharing their clinical and epidemiological expertise with me. I am grateful to the folks at Population Data BC, not only for providing the data access, but for all of the kind email support I have received from them as well. Thank you to the Canadian Institutes of Health Research (CIHR) for funding this work and my stipend under the Project Grant program, grant number 156385. Without this support, this work would not have been possible.

Thank you to the Foodborne Disease Epidemiology Group for enriching my grad school experience. A special thank you to Bryn Crandles for being the best person to share an office with. Being around her kindness and good energy made doing this work easier. Not to mention for answering all of my coding and statistics questions. A thank you to Ben Chen and Dr. Mahmood Gohari for helping me navigate the SRE when I started this project. Having access to their code was also instrumental in me learning SAS. Finally, thank you to my family, friends, and especially Duncan for their support and for listening to me talk about Listeria for 2 years. To my late dad, thank you for encouraging me in my love for learning.

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List of Abbreviations

ACOG: American College of Obstetricians and Gynecologists
BC: British Columbia
BCCDC: British Columbia Centre for Disease Control
CAD: Canadian dollar
CDC: Centers for Disease Control and Prevention
CIHI: Canadian Institute for Health Information
CIHR: Canadian Institutes of Health Research
CMG+: Case Mix Groups Plus
CSHS: Cost of standard hospital stay
DAD: Discharge Abstracts Database
DALY: Disability adjusted life-years
ICD: International Classification of Diseases
LHA: Local health area
MSP: Medical Services Plan
PAF: Population attributable fraction
PHAC: Public Health Agency of Canada
PHN: Personal health number
RIW: Resource intensity weight
RTE: Ready-to-eat
US: United States
USD: United States dollar
VS: Vital statistics

1. Introduction

Foodborne infections pose a significant threat to public health, causing a multitude of illnesses and deaths globally. One in eight Canadians experience a domestically acquired foodborne infection each year (Thomas et al., 2013). These infections occur when individuals consume contaminated food and beverages, leading to a range of symptoms that can vary from mild discomfort to severe sickness and even long-term adverse health outcomes (World Health Organization, 2015).

One particular foodborne pathogen that has received increased attention in research and public health in recent decades is *Listeria monocytogenes* (*L. monocytogenes*). This bacterium is responsible for causing a serious illness called listeriosis, which primarily affects individuals with weakened immune systems, pregnant women, newborns, and the elderly (Lamont et al., 2011). *Listeria* infections are of significant concern due to their potentially severe consequences and the challenges involved in controlling and preventing their spread (Allerberger & Wagner, 2010; Silk et al., 2012). Globally, it was estimated that in 2010, listeriosis caused 23,150 illnesses, 5,463 deaths, and 172,823 disability-adjusted life years (DALY) (Maertens de Noordhout et al., 2014). The health consequences of listeriosis in pregnancy are especially dangerous, with the potential for transmission to the fetus and risk of pregnancy loss and severe illness in neonates (Lamont et al., 2011).

More Canadian data on the epidemiology, outcomes, and economic costs of listeriosis, tailored to high-risk groups such as pregnant women, are needed to inform policy, clinical decisions, and public health initiatives.

2. Literature review

2.1 *L. monocytogenes* and listeriosis

L. monocytogenes is a gram-positive, facultative coccobacillus that causes the disease listeriosis (Vazquez-Boland et al., 2001). The pathogen is principally transmitted to humans via food. However, non-foodborne routes of transmission for humans also include direct contact with animals infected with *L. monocytogenes*, transmission from mother to fetus, and cross-infection in hospital (Low & Donachie, 1997; McLauchlin, 1996). While there are other species of *Listeria*, such as *L. ivanovii* and *L. seeligeri*, these species are not known to cause illness in humans (Borcan et al., 2014). Thus, throughout this thesis, when *Listeria* is mentioned, it refers to *L. monocytogenes* specifically unless otherwise indicated.

2.1.1 Listeria in food and food production

In food, *Listeria* is most commonly found on ready-to-eat (RTE) foods, soft cheeses, deli meats, and seafood (Havalaar et al., 2010). *Listeria* can survive and multiply at refrigeration temperatures, which presents a challenge to the prevention of listeriosis. While safe food handling is important at the level of the consumer, some consumer food safety guidelines, such as keeping meat in the refrigerator, will not necessarily prevent growth of this bacterium (Low & Donachie, 1997; Havalaar et al., 2010). Therefore, prevention at the level of food processing environments is vital (Tompkin et al., 2002). In RTE food processing facilities, contamination of food with *Listeria* can occur through several routes: contamination of raw materials, poor sanitation, cross-contamination from other areas of the facility, and the ability of the bacteria to form biofilms which make it resistant to cleaning products (Alvarez-Ordóñez et al., 2018; Spanu & Jordan, 2020). There is a body of research focused on listeriosis prevention at the food

processing level and interventions to make food safer before it reaches consumers, but this is outside the scope of this review.

Furthermore, many studies have been done to estimate the prevalence of *L. monocytogenes* on food and in food production facilities. These studies have generally found a relatively low but consistent presence of *L. monocytogenes*. For example, a 2019 systematic review looking at the global prevalence of *L. monocytogenes* in select ready-to-eat foods, including deli meats, soft cheeses, and packaged salads, found the prevalence of *Listeria* to be 3.5% in deli meats, 3.6% in soft cheeses, and 0.5% in packaged salads (Churchill et al., 2019). A study done in B.C., Canada (the setting of interest for this thesis) looked at the presence of several *Listeria* species, including *L. monocytogenes* in RTE foods and food facilities throughout B.C. The authors found *L. monocytogenes* to be present in 6% of 250 RTE food samples tested (Kovacevic et al., 2012). Food categories were split into fish, meat, and dairy and *L. monocytogenes* was only found in RTE fish products. Further, *L. monocytogenes* was detected in the food production facilities for all three categories (fish, meat, dairy). They also noted inadequate sanitation procedures and frequent surface contamination in some of these facilities (Kovacevic et al., 2012). This illustrates the complexity of *Listeria* prevention and the ongoing importance of *Listeria* control strategies in food processing facilities.

2.1.2 Presentation and pathogenesis of listeriosis

While it is not rare for *Listeria* to be present in food processing facilities leading to contaminated food reaching the homes of consumers, the development of listeriosis in healthy individuals is very rare (Goulet et al., 2012). Those considered high risk for listeriosis are those who are immunocompromised, elderly, pregnant, and infants. Further, listeriosis can be non-invasive or invasive. Non-invasive listeriosis, or febrile listerial gastroenteritis, presents more

mildly with symptoms such as diarrhea and fever (Allerberger & Wagner, 2010). Non-invasive listeriosis can typically be found in the individuals who are not considered high risk for serious listeriosis infection (Allerberger & Wagner, 2010). Non-invasive listeriosis is also difficult to detect and is often not tested for unless there is an outbreak investigation (CDC, 2022). For this reason, typically only invasive listeriosis is reported to public health surveillance systems, which is the case in Canada (Government of Canada, 2016). Invasive listeriosis occurs when the bacteria goes beyond the intestines and into the blood or central nervous system, where it can cause symptoms such as septicemia and meningitis, especially in high-risk groups (Allerberger & Wagner, 2010). The incubation period, which is the time between exposure to the pathogen and the onset of symptoms, for listeriosis, can vary greatly. It is much shorter in cases of non-invasive listeriosis (median of 24 hours), and around 20 to 30 days in cases of invasive listeriosis (Vasquez-Boland et al., 2001; Goulet et al., 2013). Among invasive cases, incubation time has also been reported to be longer in pregnancy-related cases (median of 27.5 days) than for central nervous system and bacteremia cases, with medians of nine and two days, respectively (Goulet et al., 2013).

The pathogenesis of how *L. monocytogenes* enters a human host and leads to listeriosis can be described, in simple terms, as such: *L. monocytogenes* enters the host through contaminated food and reaches the intestines. From the intestines, the bacteria invade the epithelial and then host cells, which can cause gastroenteritis (Osek et al., 2022). The ability for *L. monocytogenes* to colonize the gastrointestinal tract is in part due to the bacteria's capability to persist in acidic environments. *L. monocytogenes* can also cross the intestinal barrier, enter the blood, and reach target organs such as the liver and spleen, from which it could then also reach secondary organs such as the uterus or brain (Osek et al., 2022).

2.1.3 Diagnosis and treatment of listeriosis

Invasive listeriosis is diagnosed by isolating a bacterial culture of *L. monocytogenes* from the blood, cerebrospinal fluid, or the placenta (Lamont et al., 2011). However, listeriosis, like many foodborne infections, is understood to be underdiagnosed. In a Canadian study assessing under-reporting of infectious gastrointestinal illnesses from all causes in provincial disease statistics in British Columbia, the authors found only 8.2% of infectious gastrointestinal illness cases identified were reported to public health authorities (MacDougall, 2008). Looking at listeriosis specifically, a retrospective cohort study in Israel found that 117 pregnant women were admitted with suspected listeriosis and were treated as such; yet only 7 women, of which none were admitted with suspected listeriosis, received a culture-confirmed diagnosis of listeriosis (Fouks, 2018). After comparing these groups, the authors concluded that diagnosis based on clinical symptoms was a poor diagnostic indicator for listeriosis and that relying on this leads to both under-reporting of confirmed cases and over-treatment of suspected cases (Fouks, 2018). Therefore, estimates of the incidence of listeriosis are often underestimates.

Listeriosis is treated with antibiotics. The first-line antibiotic recommended for invasive listeriosis treatment is intravenous ampicillin, typically coupled with gentamicin and administered for 14-21 days (American College of Obstetricians and Gynecologists [ACOG], 2014). Other antibiotics such as penicillin and amoxicillin are sometimes recommended instead (ACOG, 2014). For individuals with allergies to these antibiotics, trimethoprim-sulfamethoxazole is recommended. Individuals exposed to *Listeria* but who have mild, afebrile symptoms may be prescribed an oral ampicillin or amoxicillin while they await a positive diagnostic test for *Listeria* (Centers for Disease Control and Prevention [CDC], 2021). However, some experts suggest withholding antibiotics until *Listeria* is confirmed. The CDC does not

recommend treatment for those exposed to *Listeria*, but who are asymptomatic (CDC, 2021). However, there is very little evidence available to inform treatment of listeriosis in high-risk groups, such as pregnant women and thus, treatment regimens can vary greatly for such populations (ACOG, 2014). In general, more research on listeriosis treatment is needed.

2.2 Listeriosis in Canada

This thesis is set in British Columbia, Canada. Thus, it important to understand the general landscape of listeriosis in Canada as well the province of British Columbia specifically. Invasive listeriosis is a notifiable disease at the national and provincial levels in Canada (Government of Canada, 2016). While illness from *Listeria* is rare compared to other foodborne pathogens like norovirus, *Salmonella*, and *Campylobacter*, *Listeria* is the leading cause of deaths related to foodborne illness each year in Canada (Government of Canada, 2016). The Government of Canada estimates that there are 178 illnesses, 150 hospitalizations, and 35 deaths due to *Listeria* each year (Government of Canada, 2016). In a study that aimed to account for under-reporting of foodborne illnesses in Canada, the authors estimated that the mean number of annual hospitalizations due to listeriosis was 190 and the mean annual number of deaths was 44 (Thomas et al., 2015).

Listeriosis has also been at the center of foodborne illness outbreaks in Canada. In fact, the first foodborne listeriosis outbreak on record globally took place in Nova Scotia, Canada in 1981, where there were 41 cases, among which there were 6 infant deaths (Todd, 1987). This outbreak was traced to coleslaw. The more recent major outbreak in Canada was in 2008, where there were 57 cases of reported listeriosis across 7 provinces in Canada, which were traced to a deli meat contamination and resulted in 22 deaths (Currie et al., 2015). This outbreak predominantly affected older adults in long-term care facilities and hospitals (Currie et al., 2015).

In recent years, smaller outbreaks of listeriosis across the country have also occurred between 2015-2019, with implicated food sources including, cooked chicken, pre-packaged salad, and pre-packaged caramel apples (PHAC, 2015; PHAC 2016; PHAC 2019).

In British Columbia specifically, there were an average of 12 cases of listeriosis reported to the British Columbia Centre for Disease Control (BCCDC) per year between 2001 and 2010 (BCCDC, 2023). In 2002, British Columbia was the province at the center of two separate listeriosis outbreaks of a combined 130 illnesses (McIntyre, 2015). Only a small number of these illnesses were invasive listeriosis, with the vast majority being febrile gastroenteritis with a positive stool sample for *Listeria*. Nevertheless, these outbreaks notably lead to the discovery of new environmental transmission pathways for *Listeria* in the cheese post-pasteurization process and the implementation of new prevention programs for cheese plants in British Columbia (McIntyre et al., 2015).

2.3 Economic costs of listeriosis and cost of illness analysis

Studies looking at the economic costs of listeriosis in Canada are rare. One such study by Thomas et al., (2015) estimated the economic costs associated with the 2008 listeriosis outbreak across Canada. The authors included healthcare costs of cases, cost of deaths, costs of the federal outbreak response, and implicated meat processing facility costs in their analysis and estimated the total costs to have been $242 million. The estimated direct cost of illness for the 57 cases alone was estimated at $778,934 total or $13,666 per case (Thomas, 2015). There have been studies conducted in the US to estimate cost of illness for listeriosis. For example, the US Department of Agriculture (2020) had conducted cost estimates for all listeriosis cases in 2013. They estimated that in 2013, the total mean economic cost of listeriosis was $2.8 billion, which included all medical costs, costs associated with deaths, and productivity loss costs (USDA,

2020). There were 196 hospitalized maternal cases alone, for which the total mean cost was estimated at $6.8 million (USDA, 2020).

The goal of cost of illness analysis is to assess the economic burden of a particular disease or condition in order to inform decisions related to prevention, treatment, and resource allocation. Cost of illness analysis commonly involves estimating the direct and indirect costs of an illness, but the definitions of 'direct' and 'indirect' differ across studies (Akobundu et al., 2006). Typically, direct costs include but are not limited to: diagnostic costs, treatment costs, physician office visit costs, hospital services costs, and community services costs (Akobundu et al., 2006). Many studies also consider direct costs to include non-healthcare expenditure costs incurred by the individual, such as lawyer fees, transportation costs, and childcare. Indirect costs typically refer to productivity costs due to morbidity and mortality (Akobundo 2006). Further, there are various accepted methodologies used in the cost of illness literature to estimate direct costs, each with their own strengths, but this does it make it difficult to compare costs for the same illnesses across studies. Some examples of cost of illness methodologies include the top-down approach, the bottom-up approach, and the econometric approach (Jo, 2014). Briefly, the top-down approach uses aggregated cost data along with a population attributable fraction for the illness of interest to calculate attributable costs (Jo, 2014). The bottom-up approach estimates direct costs by calculating the average cost of treatment for the illness and multiplying this by the prevalence of the illness (Jo, 2014). Finally, the econometric approach estimates direct costs due to an illness by comparing the costs in a cohort with the illness to costs in a cohort without the illness. In the econometric approach, the cost difference can be estimated through a means differences approach or a multiple-stage regression (Jo, 2014).

2.4 Risk factors for listeriosis

As mentioned, population groups considered high risk for the development of listeriosis are pregnant women, infants, older adults, and people with weakened immune systems. However, there are also more specific risk factors for listeriosis, both related and unrelated to these high-risk groups, such as ethnicity, food safety knowledge/attitudes/behaviors, and the presence of a comorbidity.

According to CDC, pregnant women in general are 10 times more likely than the average population to be infected with *Listeria*, whereas Hispanic pregnant women are 24 times more likely to be infected (CDC, 2022A). Indeed, several studies have demonstrated a link between ethnicity and incidence of listeriosis. Looking at differences in the incidence of listeriosis in the United States (US) over a period of eight years, Pohl et al. (2019) reported a higher incidence among Hispanic, non-Hispanic Black, and non-Hispanic Asian individuals, compared to non-Hispanic White individuals. This effect was observed to be even larger for Hispanic and non-Hispanic Asian females of child-bearing age. Jackson et al. (2010) also found pregnant women with listeriosis in the US had over three times the odds of reporting Hispanic ethnicity and over two times the odds of reporting consumption of Mexican-style cheese, compared to the average woman giving birth in the US A study in New Zealand spanning 15 years found that among pregnant women and children, the incidence of listeriosis was highest in people of Pacific and Asian ethnicities (Jeffs et al., 2020).

Another factor impacting the risk of listeriosis is food safety knowledge, attitudes, and behaviors. For example, a U.K. study by Evans & Redmond (2016) found that although most of the older adults in their study knew of *Listeria*, more than half were unaware of which foods are most commonly associated with *Listeria*. Many participants also identified pregnant women as being at the greatest risk of listeriosis, but none identified themselves (as older adults) to be at

risk. Further, participants reported consuming foods commonly associated with listeriosis past the expiration date, such as cured meat, pâté, and pre-packaged salads (Evans & Richmond, 2016). Another study conducted in China found that among pregnant women, the separation of raw and cooked foods significantly decreased risk of listeriosis by 95% (Niu et al., 2022).

The presence of certain comorbidities has also been reported to increase the risk for listeriosis as well as mortality related to listeriosis. Such comorbidities include those related to having a weakened immune system, such as ongoing immunosuppressive treatment and cancer, but also other conditions such as severe cardiovascular disease and renal disease (Maertens De Noordhout et al., 2016; Huang et al., 2023). An epidemiologic study in England and Wales calculated the risk for listeriosis by concurrent condition and found malignancies, liver disease, kidney disease, diabetes, and alcoholism to be associated with an increased risk for listeriosis in non-pregnant cases (Mook et al., 2011). Some other risk factors reported in the literature include male sex, seasonality (with incidence being highest during the summer months in Canada), and the health of the gut microbiota (Friesema et al., 2015; John et al., 2022; Alam et al., 2021).

2.5 Listeriosis in pregnancy

Studies have shown that pregnant women have a 10-24 times greater risk of infection with *Listeria*, compared to the general population (Southwick & Purich, 1996; Lamont et al., 2011; CDC, 2022A). Based on studies that have estimated the incidence of listeriosis among the entire population, pregnant women also make up 9-17% of all listeriosis cases (Goulet et al., 2012; Silk et al., 2012; Charlier et al., 2017; Choi et al., 2018). Thus, it is important to understand the unique impact of listeriosis in pregnant women.

Biologically, listeriosis is understood to affect pregnant women differently than the average population due to changes in immunity during pregnancy. During pregnancy, and

particularly starting at 26-30 weeks of gestation, there is a suppression of T-cells that occurs (Weinberg, 1984; Vasquez-Boland et al., 2017). Once a pregnant individual is infected with *Listeria*, there is risk of vertical transmission to the fetus via crossing the placental barrier (Bakardjiev et al., 2005). Transmission during birth is also possible through the presence of the bacteria in the birth canal (Schuchat et al., 1991). Another reason why there could be more diagnosis of *Listeria* in pregnant women compared to the general population is that complications with the fetus or neonate leads to the testing for *Listeria* in the pregnant woman. For example, a US study found that more than 50% of pregnant listeriosis cases were also linked to a neonatal listeriosis case, which may suggest a bias in the recognition of listeriosis in this population (Silk et al., 2012).

The most common symptoms experienced by pregnant women with listeriosis are fever and flu-like symptoms, although many cases experience no symptoms at all (Sapuan et al., 2017). Further, listeriosis is most commonly diagnosed in the third trimester of pregnancy. This may be again due to the timing of immune suppression, however, some studies also posit that there is hesitancy among physicians to culture the placenta following a spontaneous abortion in early pregnancy, which is an outcome associated with listeriosis in pregnancy (Lamont et al., 2011; Mylonakis et al., 2002). While listeriosis often presents with mild symptoms in pregnant women, there are serious risks to the fetus or newborn, including acute illness (neonatal listeriosis), spontaneous abortion, stillbirth, and death of live-born infants (Charlier et al., 2020).

Neonatal listeriosis is an outcome of listeriosis in pregnancy and can be classified into early-onset and late-onset neonatal listeriosis. Early-onset neonatal listeriosis is passed down *in utero* via the placenta, and is defined by symptom onset occurring at seven or less days after birth (Swaminathan & Gerner-Smidt, 2007). Late-onset neonatal listeriosis is transmitted through

the birth canal, or is acquired after birth, and is defined by onset occurring after day seven (Shuchat, 1991). In both cases, symptoms include respiratory distress, meningitis, and septicemia (Mateus, 2013). The case-fatality rate for neonatal listeriosis can be between 20-50% (Sapuan, 2017). *Listeria* infection in pregnancy can also cause stillbirth or spontaneous abortion. Stillbirth is defined as the loss of an infant at or after the 20th week of pregnancy (CDC, 2020). Spontaneous abortion is defined as the loss of a fetus before the 20th week of pregnancy (CDC, 2020).

Due to these serious risks related to fetal transmission, pregnant women should be advised on their risk of listeriosis during pregnancy. However, in Canada, studies looking at food safety knowledge among pregnant women, as well as advising practices among healthcare providers, have shown a lack of knowledge and dissemination of information about listeriosis in pregnancy. For example, a qualitative study assessing food safety knowledge and behaviors around listeriosis in British Columbia found that pregnant women in the study thought of food safety during pregnancy to be important but had limited knowledge of high-risk foods. They also found that there were barriers to getting this information from healthcare providers and therefore did their own research on food safety (Taylor et al., 2012). A survey of healthcare providers who counsel pregnant women in Canada also found that only one third of respondents were aware of listeriosis being more common in pregnancy, and even fewer were aware of the incubation period for listeriosis and trimester of pregnancy where risk is highest (Cook et al., 2018). These healthcare providers attributed this to having a lack of information about listeriosis in pregnancy. These studies demonstrate the importance of having good quality information on listeriosis in pregnancy and ensuring this information is reaching healthcare providers and those at risk.

2.6 Epidemiologic studies on listeriosis in pregnancy

Globally, several epidemiologic studies looking at pregnancy-related listeriosis have been conducted. These studies were focused on populations in the US, Israel, the United Kingdom, New Zealand, France, China, Spain, Denmark, and South Korea (see Appendix A for full list with citations). In the Canadian context, a recent study by Abu-Raya et al., (2021) looked at surveillance data in Canada and Switzerland to determine epidemiological and clinical features of listeriosis in infancy. However, because this study looked at listeriosis in infants up to six months old, this included infants old enough to no longer be pregnancy-related. This study also did not include pregnant individuals. Thus, to date, there have not been any epidemiologic studies focused on pregnancy-related listeriosis in the Canadian population. Nonetheless, the existing international studies provide valuable epidemiologic information about listeriosis infection in pregnancy and neonates, such as incidence, clinical features, and outcomes.

2.6.1 Incidence

Across epidemiological studies looking at rates of pregnancy-related listeriosis, the reported incidence rates ranged from 3.4/100,000 live births from a study in the UK, to 16.7/100,000 deliveries from a study in China (Sapuan et al., 2017; Ke et al., 2022). The highest incidence rates were reported in studies done in China, Israel, and New Zealand (Ke et al., 2022; Elinav et al., 2014; Jeffs et al., 2022). Further when calculated separately, neonatal listeriosis rates were typically higher than maternal listeriosis rates. For example, Qu et al., (2022) found an incidence rate of 5.0/100,000 for maternal cases and 10.4/100,000 for neonatal cases. Overall, the incidence of listeriosis remains relatively low across studies.

2.6.2 Clinical features

Listeriosis in pregnant women and neonates can present with a range of clinical features, but there have been clear similarities found in the epidemiologic literature. In pregnant women,

presentation of listeriosis was typically related to the pregnancy or delivery itself, such as with decreased fetal movement and pre-term delivery (Jackson et al., 2010; Vergnano et al., 2021; Kuang et al., 2022). Relatively high proportions of C-sections were also reported in these studies. Across the epidemiologic studies included in this literature review, the median gestational age of these deliveries ranged from 33 to 36 weeks (Vergnano et al., 2021; Jackson et al., 2010; Charlier et al., 2022). Other symptoms reported in pregnant women across these studies were fever, abdominal pain, and sepsis. However, some pregnant women did not experience any symptoms at all. The presenting clinical features were much more severe in neonates. For example, in Canada and Switzerland, Abu-Raya et al., (2021) found that all 12 infants in the study exhibited signs of sepsis. Clinical manifestations in newborns, as described by Jackson et al., (2021) encompassed bacteremia (36.5% of cases), meningitis (32.9% of cases), pneumonia (5.9% of cases), and other unidentified symptoms (15.3% of cases). Chalier et al., (2022) found that 70% of neonates had abnormal clinical status at birth, including acute respiratory distress, neurological symptoms, and meningitis. In the prospective surveillance study conducted by Vergnano et al., (2021), it was found that confirmed sepsis was the most common presentation in young infants, followed by probable sepsis, and confirmed meningitis. Further, these studies have observed lower birthweights among neonates with listeriosis, likely associated with the high proportion of pre-term births among pregnancy-related listeriosis cases (Vergnano et al., 2021; Charlier et al., 2022; Qu et al., 2022). Overall, while pregnant women often experienced non-specific symptoms or no symptoms at all, these studies did show some common symptoms that healthcare professionals should look for in pregnancy. Clinical presentation in pregnant women also became more evident through delivery complications and a high proportion of neonates experienced the serious manifestations commonly associated with listeriosis.

2.6.2 Sequelae

With fetal loss being a major sequela of concern with pregnancy-related listeriosis, epidemiologic studies have unsurprisingly reported spontaneous abortion and stillbirth as outcomes. For example, a study examining all cases of pregnancy-related listeriosis in England and Wales over a 20-year period found 21.8% (n=101) of pregnant cases resulted in spontaneous abortion or stillbirth (Awofisayo et al., 2015). A national prospective cohort study in France enrolled 107 maternal-neonatal listeriosis cases and found that 24% of pregnant women experienced pregnancy loss (Charlier et al., 2017). In an examination of *Listeria* infections in the US for 2004-2007, of the 128 pregnant cases, 20.3% experienced pregnancy loss (Jackson et al., 2010). In a retrospective review of perinatal listeriosis patients in Beijing, China over a five-year period, 12 perinatal patients were identified and 5 of these cases experienced pregnancy loss (Li et al., 2020). These studies demonstrate a continued challenge in preventing fetal loss among those with listeriosis in pregnancy.

Death is also a sequela of concern for listeriosis in high risk groups, with the case fatality rate for invasive listeriosis being high. For pregnant women specifically, the risk of death following listeriosis is low compared to other high-risk groups such as newborns, older adults, and those who are immunocompromised (Goulet et al., 2012; Chalier et al., 2017). Of the epidemiologic studies included in this review, only Jeffs et al. (2020) reported death in two pregnant women following *Listeria* infection. In neonates however, these studies did find expectedly high proportions of death following *Listeria* infection. For instance, Sapuan et al. (2017) and Awofisayo et al. (2015) found a case-fatality rate of 21% from neonatal listeriosis based on their respective studies and Qu et al., (2022) reported a rate of 33%. In addition, some studies also estimated predictors for survival among neonates. Such findings included that early-

onset neonatal listeriosis (compared to late-onset), greater gestational age, and maternal treatment with antibiotics one day before delivery were associated with increased odds of infant survival (Awofisayo et al., 2015; Charlier et al., 2022). However, these factors are difficult to control and death among neonates continues to be an important concern in pregnancy-related listeriosis.

2.6.3 Healthcare use

Hospitalization rates, hospital length of stay, and antibiotic treatment for cases of pregnancy-related listeriosis have also been described in some of these studies. In Canada and Switzerland, Abu-Raya et al. (2021) reported that a significant number of infants were admitted to the intensive care unit, with some requiring assisted ventilation for varying durations. All infants received ampicillin or amoxicillin via intravenous route. Among studies in the US, Silk et al. (2012) found that 97% of pregnancy-associated cases were hospitalized from 2004-2009 in the US Jackson et al. (2010) found that almost half of the affected women were hospitalized, with a median hospitalization length of four nights. Similarly, Craig et al. (2022) compared *Listeria* deliveries to non-*Listeria* deliveries and found average length of stay to stay to be 4 days for *Listeria* deliveries, compared to 2.3 days for non-*Listeria* deliveries. In France, Charlier et al. (2022) discovered that neonates with listeriosis spent a median of 16 days in the hospital, and 50% of them were admitted to the intensive care unit. A high percentage of neonates received IV amoxicillin, but some were not treated at all. Only a small portion of pregnant women were prescribed anti-*Listeria* antibiotics before birth. In the UK and Ireland, Vergnano et al. (2021) found only a few pregnant women received penicillin before delivery, likely due to the challenges in diagnosing listeriosis in pregnant women. However, most infants received appropriate antibiotic treatment for listeriosis. Finally, Li et al., (2020) observed that

cephalosporins were commonly administered to pregnant women initially in China, despite *L. monocytogenes* strains being resistant to these antibiotics. These findings may indicate a need for improved antibiotic prescribing practices and earlier detection of listeriosis in pregnant women. Overall, hospitalization rates for listeriosis are high in these pregnancy-related cases and length of stay can be long, especially for neonates. In these studies, neonates were almost always administered antibiotics, but the proportions of pregnant women given antibiotics before birth were generally low.

2.6.4 The use of administrative data

Several of the studies cited above used administrative data to study epidemiological and clinical features of pregnancy-related listeriosis. See Appendix A for details on these studies. In looking at the methods employed across these studies, the most common use of administrative data was to identify cases of listeriosis through national surveillance networks/databases. Clinical and hospital data were also often used to obtain information on factors such as healthcare utilization, outcomes, and risk factors.

Among these studies, several strengths in their use of administrative data in this context (pregnancy-related listeriosis) were evident. Most of these studies were retrospective and took place over a span ranging from 2 to 20 years. With listeriosis being a rare disease, the ability to conveniently access many years of listeriosis cases retrospectively allowed for a far greater sample size for fewer resources than studies collecting case data prospectively. For example, Jeffs et al., (2022) obtained case data for pregnancy-related listeriosis over a 20-year period using New Zealand's disease surveillance system, EpiSurv, as well as a national dataset for hospital discharge information. This allowed them a greater sample of cases (n=148) to describe

epidemiological trends and features, as well as a greater timeline that allowed them to examine whether the incidence had changed over that period.

However, studies that only used administrative data may have been limited in collecting additional data that may be of interest. For example, a study conducted in the US had access to data on foods consumed before diagnosis of listeriosis due to the implementation of the *Listeria* Initiative in the US (Jackson et al., 2010). This initiative was implemented in 2005 and includes an extended questionnaire about food exposures following reports of laboratory-confirmed listeriosis (CDC, 2022B). The remaining studies did not have comparable data and thus did not include food exposure as part of their analyses. Relying on administrative data may also limit the identification and further investigation of probable or suspected cases that would not be captured in surveillance or hospital databases. Some studies dealt with this limitation by expanding their definition for a case of listeriosis, using data available. For example, Jeffs et al. (2020) decided to account for probable cases by including people admitted to hospital with a code for listeriosis despite not being captured in the surveillance data. Overall, the use of administrative data is a popular method applied across the literature investigating the epidemiology of pregnancy-related listeriosis.

3. Study rationale and objectives

Listeriosis continues to be an important public health issue, with its ubiquity in food processing facilities and serious health consequences among high-risk groups. Pregnant women and their neonates are at particular risk of being infected with listeriosis and experiencing serious health outcomes such as pregnancy loss for women and serious illness and death for neonates. Epidemiologic studies done in other countries, such as the US, China, France, New Zealand, and England show that pregnant women make up a significant proportion of listeriosis cases and that the related pregnancy outcomes can be severe (Jackson et al.,, 2010; Craig et al., 2022; Li et al., 2020; Awofisayo et al., 2015; Charlier et al., 2020; Jeffs et al., 2020; Sapuan et al., 2017). However, there is a gap in Canadian-specific epidemiologic information on listeriosis in pregnancy. To bridge this gap, this thesis aimed to describe the epidemiologic characteristics, pregnancy outcomes, and direct healthcare costs of pregnancy-related listeriosis in British Columbia, Canada, during 2005-2014.

Specifically, the objectives of this thesis were to:

1. Describe the epidemiologic, demographic, and clinical characteristics of pregnancy-related listeriosis cases in British Columbia, 2005-2014.
2. Describe the proportion and timing of stillbirth among these individuals.
3. Estimate the fraction of stillbirth in the population attributable to listeriosis in pregnancy.
4. Compare direct healthcare use and costs of pregnant women and neonates with and without listeriosis.

4. Methods

4.1 The overall study and thesis approach

This thesis was part of an ongoing retrospective cohort study looking at the risk of sequelae for 14 foodborne infections in British Columbia (BC), Canada (Majowicz et al., 2020). These infections include: *Clostridium botulinum, Campylobacter, Cryptosporidium, Cyclospora, Giardia*, hepatitis A virus, *L. monocytogenes*, non-typhoidal *Salmonella spp, Salmonella Typhi, Salmonella Paratyphi*, Shiga toxin-producing *Escherichia coli, Shigella, Vibrio parahaemolyticus* or *Yersinia* (excluding *pestis*). The study population consists of residents of British Columbia, Canada, over the period of 2005-2014. Residents of BC are covered by the province's health insurance program, with the exception of First Nations individuals, refugees and recently landed immigrants who have been in the province less than 3 months, and the Canadian military, and the Royal Canadian Mounted Police (Government of British Columbia, n.d.).

To ensure privacy and security, all of the data and analyses for the larger study and my thesis are stored and completed with Population Data BC's virtual Secure Research Environment. Population Data BC has linked the eight databases, which will be described in the next section, using a unique personal health number (PHN) assigned to each individual. The detailed process of how Population Data BC performs these linkages is explained elsewhere (Population Data BC, n.d.). Further, as part of the data access agreement with Population Data BC, cell sizes of less than six cannot be reported for privacy protection reasons. Therefore, cell sizes of less than six appear as "1-5" throughout this thesis.

The aims of the overall study were to estimate the risk of sequelae and death following the foodborne infections mentioned above, describe the progression from acute illness to

sequelae, estimate the fraction of sequelae attributable to these foodborne infections, and quantify direct healthcare costs due to these infections and their sequelae. The full protocol for the study is published (Majowicz et al., 2020). This thesis focused on one of these 14 foodborne infections, *Listeria*.

4.2 Administrative data and data manipulation

4.2.1 Databases and variables used for this thesis

This thesis used administrative data from eight databases, over the time period of 2005-2014: Panorama, Discharge Abstract Database (DAD), Medical Services Plan (MSP), PharmaNet, Vital Statistics Deaths (VS Deaths), Vital Statistics Stillbirths (VS Stillbirths), Consolidation File, and Statistics Canada Income Bands.

Panorama is an electronic public health records system used in British Columbia (BCCDC, n.d.). It contains data on communicable diseases, outbreaks, immunizations, and vaccine inventory. For the larger study, data on all cases of the 14 reportable diseases listed in section 4.1 were requested. See Table 1 for a list of the fields within Panorama used in this thesis, with descriptions.

Table 1. Panorama: Data fields used with descriptions

Field	**Description**
Disease	The reportable disease, in this case, invasive listeriosis
Date_onset_symptom	Date of earliest symptom onset reported by case
Age_at_surveillance_reported_date_years	Age of case as of reported date, in years
Date_surveillance_reported_date	Date on which the case of reportable disease was reported to local health authority in BC
Surveillance_region	Health authority of residence for case

The DAD contains data on discharges, transfers, and deaths of hospital inpatients and day surgery patients from acute care hospitals in British Columbia (Canadian Institute for Health Information, 2019). See Table 2 for a list of the fields within the DAD used in this thesis, with descriptions.

Table 2. DAD: Data fields used with descriptions

Field	**Description**
Admission date	The calendar date that the patient was formally admitted as a patient to the facility.
Admission category	Indicates the urgency of the admission (e.g., elective, emergency).
Discharge (separation date)	The date that the patient was discharged (separated) from the hospital or facility.
Total length of stay	Total number of days the patient was hospitalized from admission to discharge.
Intensive care unit (days)	The total number of days spent in all Special Care Units during the patients hospital stay.
ICD-10-CA diagnosis codes	Diagnosis codes (ICD-10-CA).
Infant birth weight	The weight of the infant in grams.
Gestational age (until 2006)/clinical gestation (2007 onward)	The number of weeks of gestation for a newborn on the mother's delivery record. Measured from the first day of the last normal menstrual period. Not applicable for neonates.
Case Mix Group (CMG+)	Case Mix Groups (CMG) are assigned by CIHI to categorize cases that have an anticipated similar clinical course and resource requirements (measured in days of patient care).
Methodology year (CMG+)	Case Mix Group (CMG) Plus Grouper Methodology Year (from CMG/+ Grouper).
Inpatient Resource Intensity Weight (RIW)	Canadian Institute for Health Information (CIHI) Resource Intensity Weighting (RIW) Value
Inpatient RIW atypical code	Identifies atypical cases that do not receive the normal or predicted course of treatment associated with inpatients in a specific CMG, because they arrived at, or left, the facility in circumstances that made their total length of stay or costs unpredictable.

The MSP contains the records for services provided to eligible individuals in British Columbia for fee-for-service practitioners, billed to and paid by MSP (British Columbia Ministry of Health, 2018). See Table 3 for a list of the fields within MSP used in this thesis, with descriptions.

Table 3. MSP: Data fields used with descriptions

Field	Description
ICD 9 diagnostic code	Indicates the condition for which the patient is treated.
Paid for item (fee item)	A numeric code used to identify each service provided by a practitioner. Each fee item has an associated fee that is paid to the payee for the service provided.
Service date	The date on which the service was rendered by a practitioner.
Paid service units	The number of service units paid by the Medical Services Plan (MSP) to the practitioner in the fee-for-service claim.
Claim specialty code	Describes a practitioner's specialty associated with a claim.

The PharmaNet database contains all records of medications (drugs and medical supplies) dispensed in outpatient pharmacies in British Columbia (British Columbia Ministry of Health, 2019B). This includes medications paid by the province, private insurers, and individuals. The claim history excludes those who are federally insured. See Table 4 for a list of the fields within PharmaNet used in this thesis, with descriptions.

Table 4. PharmaNet: Data fields used with descriptions

Field	Definition
Date of service (date dispensed)	Date treatment, product or service was provided to the patient.
Drug cost billed by pharmacist	The amount of the submitted drug/ingredient cost by the pharmacist.
Professional fee (dispensing fee claimed by pharmacist)	Pharmacists fee submitted for professional and technical activities associated with

	providing the prescribed medicine or treatment.
Special services fee (total amount claimed by pharmacist for special service e.g., consulted prescriber, action Rx issue)	Total amount claimed by the pharmacist for performing special services for Pharmacare.

VS Deaths contains records of all deaths registered in British Columbia (British Columbia Ministry of Health, 2019C). See Table 5 for a list of the fields within VS Deaths used in this thesis, with descriptions.

Table 5. Vital Statistics Deaths: Data fields used with descriptions

Field	**Definition**
Year of death; month of death; day of death	Date the event was registered - set to the date that the registration document was signed by the Registrar.
ICD codes	A set of ICD9 or ICD10 codes representing the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury.

VS Stillbirths contains records of all stillbirths registered in British Columbia (British Columbia Ministry of Health, 2019D). See Table 6 for a list of the fields within VS Stillbirths used in this thesis, with descriptions.

Table 6. Vital Statistics Stillbirths: Data fields used with descriptions

Field	**Definition**
Mother study ID	Study ID of mother who had the stillbirth.
Year of stillbirth; month of stillbirth; day of stillbirth	Date of event.
Total number of children in this event	Indicates the total number of children (live born plus stillborn) born in this birth event.
Duration of pregnancy (gestation period)	The gestation period of pregnancy, in completed number of weeks.

The Consolidation File is an annual file, derived from Medical Service Plan registration and Premium Billing snapshot files, and contains demographic and geographic information on individuals eligible to receive services in BC (British Columbia Ministry of Health, 2019A). See Table 7 for a list of the fields within the Consolidation File used in this thesis, with descriptions.

Table 7. Consolidation File: Data fields used with descriptions

Field	Definition
Sex	Sex of the individual
Neighbourhood income SES quintile/decile	Neighbourhood Income (SES) quintile
Health authority	Health authority
Local health area	Local Health Are (LHA).
Start day registered in year	Start day registered in year (point in the year registration started).
Total days registered in year	Total days registered during the year.
Year of birth	Year of birth.
Month of birth	Month of birth.

The Statistics Canada Income Band data file contains 1000 income bands, which provide income information on the postal code area in which the individual resides (Statistics Canada, 2018). Income bands from years 2002 and 2006 are available. Individual-level income data is not available. This file was adapted by Population Data BC from Statistics Canada. See Table 8 for a list of the fields within the Statistics Canada Income Band data file used in this thesis, with descriptions.

Table 8. Statistics Canada Income Band File: Data fields used with descriptions

Field	Definition
Average equivalized disposable income	The average equivalized disposable income for a given Income Band, linked to the individual's postal code.
Average unadjusted disposable income	Average unadjusted disposable income for a given Income Band, linked to the individual's postal code.

4.2.2 Identifying cases of listeriosis

Confirmed cases of listeriosis

Individuals were considered a confirmed case of listeriosis if they had a laboratory confirmation of listeriosis reported in Panorama. For individuals with a lab-confirmed report of listeriosis in Panorama, the onset date was estimated based on the reported date in Panorama. During the period of 2005-2014, onset date was not readily recorded in Panorama, therefore this variable had significant missingness (98.8% among all foodborne infections; 100% among the pregnancy-related cases being described here). The team for the larger study used 2015-2019 data where onset date was more readily completed and calculated pathogen-specific median lag times between onset date and reported date (Gohari et al., 2022). The median lag for listeriosis was found to be five days (Gohari et al., 2022), which was applied in this thesis.

Potential cases of listeriosis

Additionally, individuals were considered a potential listeriosis case if they had an International Classification of Diseases (ICD) code for listeriosis in the DAD or MSP, but were not captured in Panorama. The ICD codes used to identify potential cases of listeriosis can be found in Table 9 (World Health Organization, 2019). For individuals found with ICD codes for listeriosis in the DAD or MSP, for which there was no coinciding report of listeriosis in Panorama, the estimated onset date was the date of that visit with the ICD code.

Table 9. International Classification of Diseases codes for listeriosis used to identify potential cases of listeriosis

ICD Codes	**Description**
ICD-9	
027.0	Listeriosis

ICD-10	
A32	Listeriosis
A32.0	Cutaneous listeriosis
A32.1	Listerial meningitis meningoencephalitis
A32.7	Listerial sepsis
A32.8	Other forms of listeriosis
A32.9	Listeriosis, unspecified
P32.7	Neonatal (disseminated) listeriosis

4.2.3 Identifying individuals who were pregnant

To identify whether an individual was pregnant, I searched the DAD for obstetric and birth ICD-10 codes. See Table 10 for a list of obstetric and birth ICD-10 codes searched. I also used Vital Statistics (VS) Stillbirths to determine pregnancies that resulted in stillbirth. To determine pregnancy timing, I used gestational age variables recorded in the DAD and VS Stillbirths. By subtracting the gestational age (in weeks) from the date of the hospital admission with an obstetric or birth code or date of stillbirth, I was able to estimate the start of pregnancy date, which gave me an approximate timeline for pregnancies. Note that while I did check the MSP for ICD-9 codes related to pregnancy for explorative reasons, I did not formally use the MSP to identify individuals who were pregnant. This was because the MSP does not contain a variable for gestational age and thus, I would not have been able to confirm whether the timing of pregnancy overlapped with the timing of listeriosis.

Table 10. International Classification of Diseases-10 codes used to identify pregnancy/birth hospital visits

ICD-10 Codes*	Description
O09-O09	Supervision of high risk pregnancy
O10-O16	Edema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium
O20-O29	Other maternal disorders predominantly related to pregnancy
O30-O48	Maternal care related to the fetus and amniotic cavity and possible delivery problems
O60-O77	Complications of labor and delivery
O80-O82	Encounter for delivery
O85-O92	Complications predominantly related to the puerperium
O94-O9A	Other obstetric conditions, not elsewhere classified
Z33	Pregnant state, incidental
Z34	Supervision of normal pregnancy
Z35	Supervision of high risk pregnancy
Z36	Antenatal screening
Z37	Outcome of delivery (single/twins/other multiple birth, live born/stillborn)

*ICD codes found from World Health Organization (2019).

4.2.4 Identifying cases of pregnancy-related listeriosis

Individuals with confirmed listeriosis during pregnancy

Individuals were considered a confirmed pregnancy-related case of listeriosis if they were a pregnant individual with a laboratory confirmation of listeriosis reported in Panorama during the pregnancy. First, I created a dataset of listeriosis cases in Panorama who were female, and then linked these individuals to the DAD and VS Stillbirths to search for any ICD codes related to pregnancy or birth or records of stillbirth among these females. I then further restricted this to only those who had a birth-related hospital code or stillbirth at any point. For these individuals,

the dates of their pregnancy/birth related hospital visits were individually examined using the method described in section 4.2.3 to determine if onset occurred during pregnancy. As a quality check, I also checked if any males with listeriosis had pregnancy/births related hospital visits.

Individuals with 'potential' listeriosis during pregnancy

Individuals were considered a potential pregnant listeriosis case if they were pregnant at the time they had an ICD code for listeriosis in the hospital database (DAD) or fee-for-service physician database (MSP), but were not captured in Panorama. Briefly, I first created a dataset with all individuals with ICD codes for listeriosis in the DAD or MSP. I then retrieved all DAD records and VS Stillbirths records for these individuals to look for the obstetric and birth ICD-10 codes listed in Table 10 or a record in VS Stillbirths. Where pregnancy/birth codes or a stillbirth were found, I determined the pregnancy timing, as described previously, and compared this to the date of listeriosis recorded in the DAD or MSP. If the individual and the specific pregnancy matched one of the confirmed cases, they were removed from the potential listeriosis group.

Neonates with listeriosis

To identify neonates, both among all individuals with a listeriosis infection reported in Panorama and among all individuals with ICD-10 codes for listeriosis in the DAD or MSP, I used age information (month and year) in Panorama and in the Consolidation File. However, because the definition of a neonate is specific down to the day, I also looked at the exact birth date of all infants recorded in the DAD. If the estimated listeriosis onset fell between 0-28 days of age (or earlier), the individual was considered a neonatal case of listeriosis.

4.2.5 Identifying mother-neonate pairs

The original intention was to be able to match all maternal listeriosis cases with their newborns and all neonatal listeriosis cases with their mothers and conduct analyses that would

treat these pairs as one pregnancy-related case. Typically, in cases of pregnancy-related listeriosis, *Listeria* is either isolated from the woman or neonate (M. Taylor, BCCDC, personal communication, February 14, 2023). However, there were data quality issues with the variable that links mothers and neonates in the DAD and this was not possible. Regardless, I wanted to explore if any of the maternal and neonatal cases that I identified could possibly be mother-neonate pairs who both tested positive for *Listeria* or had an ICD code for listeriosis. To explore this, I compared hospital birth admission dates, health authorities, and income bands for the individuals found above. I was unable to confirm these matches or compare this information to those who did not have confirmed or potential listeriosis.

4.3 Analyses

Descriptive epidemiology was applied to address research aims one to three and a matched cohort approach was conducted to address research aim four. All analyses were first completed for the confirmed cases (i.e. the confirmed maternal and confirmed neonatal cases separately) and then were repeated after including the potential cases of pregnancy-related listeriosis. Describing and analyzing the confirmed cases alone and then with the addition of potential cases served as sensitivity analyses, to account for both a more or less sensitive case definition of listeriosis.

4.3.1 Descriptive epidemiology

Incidence proportion and case-fatality rate

The proportion of pregnant women who had listeriosis was estimated by dividing the number of pregnancies with listeriosis by the total number of deliveries that resulted in a live birth or stillbirth. This denominator excludes pregnancies that resulted in early pregnancy loss and those that had a live birth outside of hospital, due to not having data on these pregnancies.

The proportion of newborns who had neonatal listeriosis was estimated by dividing the number of neonates with listeriosis by the total number of neonates born during the study. The total number of neonates born was determined by searching for all hospital newborn records in British Columbia during 2005-2014. This denominator excludes neonates born out of hospital.

The case fatality rates of pregnant and neonatal listeriosis cases were estimated by dividing the number of maternal or neonatal listeriosis cases (separately) who died during the study period by the number of maternal or neonatal listeriosis cases (separately). The number of deaths in the numerator was obtained by searching for the maternal and neonatal cases in Vital Statistics Deaths.

Case characteristics

Characteristics of these cases were obtained from their hospital records, consolidation file, and Statistics Canada Income Bands. These were described using proportions and medians (range). These include, proportion of singleton pregnancies, median number of births per person over the study period, median age at listeriosis onset, median gestational age at birth, proportions of trimester of onset, birth weight of neonates, season of onset, median average equivalized disposable income, health authorities, and a description of the most common pregnancy or birth complications found. Where trimesters are described, first trimester was defined as less than 15 weeks of gestation, second trimester was defined as 15-27 weeks of gestation, and third trimester was defined as 28 plus weeks Finally, the median number of days between estimated onset date, reported date in Panorama, ICD code for listeriosis reported in DAD or MSP, and birth reported in the DAD were calculated.

Proportion and timing of stillbirth

The occurrence of stillbirth, a well-established sequela of pregnancy-related listeriosis, was explored, addressing research aim two. To calculate the proportion of individuals with listeriosis in pregnancy that had a stillbirth, I divided the number of maternal listeriosis cases who had a stillbirth during the same pregnancy by the total number of maternal listeriosis cases. Additionally, the timing (median number of days) between estimated pregnancy start, estimated listeriosis onset, and stillbirth was explored.

Fraction of stillbirths attributable to listeriosis

To address research aim three, I first calculated the proportion of all stillbirths that occurred among those with *Listeria* infection during pregnancy, with the following formula: no. of stillbirths that followed a *Listeria* infection in the same pregnancy / total no. of stillbirths. I then calculated the fraction of stillbirths attributable to *Listeria* infection using the following formula: (observed number of cases of stillbirth among those exposed to listeriosis – the expected number of cases of stillbirth without exposure to listeriosis) / Total observed number of cases of stillbirth (Mansournia & Altman, 2018). To find the expected number of cases of stillbirth without exposure to listeriosis, I divided the number of stillbirths among those not exposed to listeriosis by the total number of pregnant individuals not exposed to listeriosis in the population (regardless of outcome) and multiplied this fraction by the total number of pregnant individuals exposed to listeriosis (regardless of outcome).

4.3.2 Healthcare use and costs analysis

A matched cohort study was conducted to estimate the direct healthcare costs of pregnancy-related listeriosis by comparing the healthcare utilization and costs among pregnant women and neonates (separately) with and without listeriosis. Median and mean healthcare utilization and costs were compared between groups. Sensitivity analyses with potential cases

and their matches added were also conducted. For each group, descriptive results on healthcare use and unadjusted costs were reported, followed by the results of the regression-adjusted ratios of total costs between cases and matches. In this cohort study, exposure was considered as being a case of listeriosis, and those who were not a case of listeriosis were considered unexposed.

Timing of follow-up

For pregnant women, the timing of healthcare use of interest was all hospital visits, fee-for-service physician visits, and out-of-hospital medications dispensed that occurred during the entire duration of the pregnancy for both cases and controls, plus a buffer window after the end of pregnancy. The index date was the estimated start of pregnancy date. The follow-up period was from the index date to the date of admission for the delivery, plus the buffer period. The buffer period was two weeks following the date of hospital admission for delivery. This was intended to account for those who had illness onset at the end of the pregnancy and who may have sought care shortly after delivery, as treatment for *Listeria* typically lasts up to two weeks (Wang et al., 2021). The reason that I wanted to look at costs over the duration of the entire pregnancy is that pregnant women with listeriosis may show non-specific symptoms or no symptoms at all, and thus their listeriosis onset date is likely not precise. This follow-up period also made the comparison to the control group less biased as I was not selecting an arbitrary index date for the controls, but instead following both groups for the maximum amount of time they are pregnant. For neonates, the healthcare use of interest was all hospital visits, fee-for-service physician visits, and out-of-hospital medications dispensed that occurred during the neonatal period (0-28 days following birth) plus a two-week buffer period to account for those with late-onset neonatal listeriosis who may still be receiving care after the neonatal period.

Matching

Pregnancy-related listeriosis cases were matched to unexposed pregnant controls at a 1:5 ratio. The pool of potential pregnant unexposed matches was created by retrieving all DAD records with a code for singleton births, given that all pregnant listeriosis cases had a singleton birth. Those who were not registered in BC's MSP for the entire follow-up period (duration of pregnancy, as described in the previous section) were excluded. The study identifications associated with these remaining birth records were merged with the MSP, DAD, consolidation file, and Statistics Canada datasets to obtain the matching variables described subsequently. Matching was done based on characteristics present at the year of the index date. For each case, I exact matched on: age, pre-existing diabetes, pre-existing HIV/AIDS, pre-existing malignancies, pre-existing metastatic tumors, Local Health Area (LHA), income quintile, and year. Radius matching was used to match on age, defined as age in five-year intervals, starting at 15-19 years old. The pre-existing comorbidities (diabetes, HIV/AIDS, malignancies, metastatic tumors) were defined as having an ICD code for any of these conditions in the DAD or MSP within two years before the index date. These ICD codes were obtained from Quan et al., (2005) and are summarized in Table 11. For each pregnant woman with listeriosis, I created a control pool of potential matches, based on the aforementioned matching criteria. Once each pregnant woman had their own pool of potential matches, I applied a random row selection procedure in SAS to select 5 matches.

The pool of potential neonatal matches was created by similarly retrieving all DAD records for newborns of singleton births, given that all neonates with listeriosis in this study were born from singleton deliveries. Those who were not registered in BC's MSP for the entire follow-up period (duration of neonatal period, as described in the previous section) were excluded. The study IDs of these newborns were merged with the MSP, DAD, registry, and

demographics datasets to obtain the matching variables described subsequently. Matching was done based on characteristics present at the year of the index date. For each case, I exact matched on: sex, year, LHA, and income quintile. I also used radius matching of plus or minus one month to match on month at index date. For each neonate with listeriosis, I created a control pool of potential matches, based on the aforementioned matching criteria. Once each neonate had their own pool of potential matches, I applied a random row selection procedure in SAS to select 5 matches.

Table 11. International Classification of Diseases codes used to identify pre-existing comorbidities as part of the matching process, adapted from Quan et al. (2005)

Selected comorbidities	ICD 10	ICD 9
Diabetes without chronic complication (excludes gestational)	E10.0, E10.1 E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0 E.12.1, E12.6, E12.8, E12.9, E13.0 E13.1, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	250.0-250.3, 250.7
Diabetes with chronic complication (excludes gestational)	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7	250.0-250.6
Any malignancy	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x	140.x-172.x, 174.x-195.8, 200.x-208.x
Metastatic solid tumor	C77.x-C80.x	196.x-199.1
AIDS/HIV	B20.x-B22.x, B24.x	042.x-0.44.x

Quantifying healthcare use

To quantify healthcare use among pregnant women and neonates with listeriosis and their matches, I looked at all-cause hospital visits, fee-for-service physician visits, and outpatient

pharmacy claims for these individuals during the specified follow-up period. For both cases with listeriosis and matches without listeriosis, I calculated the median and mean numbers of hospital visits, total number of days in hospital, number of physician visits, and number of pharmacy claims.

Costs of in-patient hospitalizations and same-day surgeries/procedures costs

I calculated the costs of in-patient hospitalizations and same-day surgeries or procedures for the pregnancy-related listeriosis cases and their matches. Case-mix methodology was used to obtain the costs for each hospital visit (Canadian Institute for Health Information [CIHI], n.d.). Specifically, I first obtained the Resource Intensity Weight (RIW) for the corresponding Case Mix Grouping (CMG+) of each hospital visit of interest (CIHI, n.d.). Next, I obtained the provincial-level Cost-of-Standard-Hospital-Stay (CSHS) for BC for each year that corresponds to the hospital visits of interest; this data was provided by the Canadian Institutes for Health Information (CIHI, n.d.). Note that the methodology used by CIHI to calculate the CSHS changed in 2010, meaning that there is variation in how the CSHS was calculated prior to 2010 versus after. Since it was not an aim of this research to do a comparison of costs over time, this does not significantly impact the global cost estimate for the population of interest. Finally, I multiplied the RIW by the corresponding CSHS for each hospital visit and summed up the cost estimates for each individual.

Costs of fee-for-service physician visits

I summed up the costs for fee-for-service physician visits found in the MSP records, for the MSP visits of the cases and matches described above. I defined a physician visit as a record in the MSP with a unique combination of study ID, service date, physician specialty code, with

service units of one or greater (Table 3). The cost of service based on the corresponding MSP fee schedule was provided within these records.

Costs of medications

Finally, I summed up the drug dispensing costs for all drugs in PharmaNet during the pregnancy or neonatal periods, for cases and matches. This dataset only included outpatient pharmacy information; the costs of medications dispensed in-hospital were included in the CSHS values, but these specific costs could not be separated from the CSHS and individually reported. Pharmacy costs were directly available in PharmaNet. The specific variables included in this costing were the amount billed by the pharmacist for the drug product/ingredient, the amount billed by the pharmacist for the professional service fee, and the amount billed by the pharmacist for special services.

Statistical analysis of differences between cases and matches

Analyses were performed in SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). Four groups were analyzed separately: 1) Pregnant women with confirmed listeriosis compared to their unexposed matches 2) Pregnant women with both confirmed and potential listeriosis compared to their unexposed matches (sensitivity analysis) 3) Neonates with confirmed neonatal listeriosis compared to their unexposed matches and 4) Neonates with both confirmed and potential listeriosis and their matches (sensitivity analysis). The median and mean number of healthcare visits by type of visit (i.e. inpatient hospital, fee-for-service physician, outpatient pharmacy) and median and mean unadjusted costs per type of visit were described for both those in the listeriosis and non-listeriosis groups. Differences in healthcare use and unadjusted costs were compared using the Mann-Whitney U test to account for the non-normal distribution of the data. A regression analysis was also used to estimate the cost ratio between total direct healthcare

costs of those with listeriosis compared to those without listeriosis, adjusted for age, health authority, and income quintile for pregnant women, and sex, income quintile, and presence of a congenital abnormality for neonates. A generalized linear model with a gamma distribution and log link was selected for all regression analyses because the distribution of the cost variable was highly positively skewed, as is expected when working with cost data (Barber & Thompson, 2004). A significance level of alpha= 0.05 was used to determine statistically significant results.

First, exploratory data analyses were conducted by exploring the univariate distributions, means, and frequencies of the costs and all predictors. Univariable and bivariable (covariate plus listeriosis) models were run, with cost regressed on each independent variable to assess the appropriateness of including them in the final models. The baseline covariates that I considered in the models for the pregnant women were: age, health authority, neighborhood income quintile, and year. The baseline covariates that I considered in the neonatal models were: sex, health authority, neighborhood income quintile, year, and presence of a congenital abnormality. While most of these variables were already matched on, I still wanted to account for any residual effect they may have on the relationship between having listeriosis and healthcare costs. Decisions for which variables to keep in the model were based on whether a predictor variable had a statistically significant effect on total cost alone or when listeriosis as a predictor was added into the model. Once I had a few models to choose from, I considered goodness-of-fit statistics, specifically the AIC value, and chose the model that allowed me adjust for the most factors without a large increase in AIC or over-fitting the model. For the pregnant women models, I ended up adjusting for age, health authority, and income quintile. For the neonatal models, I adjusted for sex, income quintile, and presence of a congenital abnormality.

Ethics approval

This research has received ethics approval from the University of Waterloo Research Ethics Committee (no 30645).

5. Results

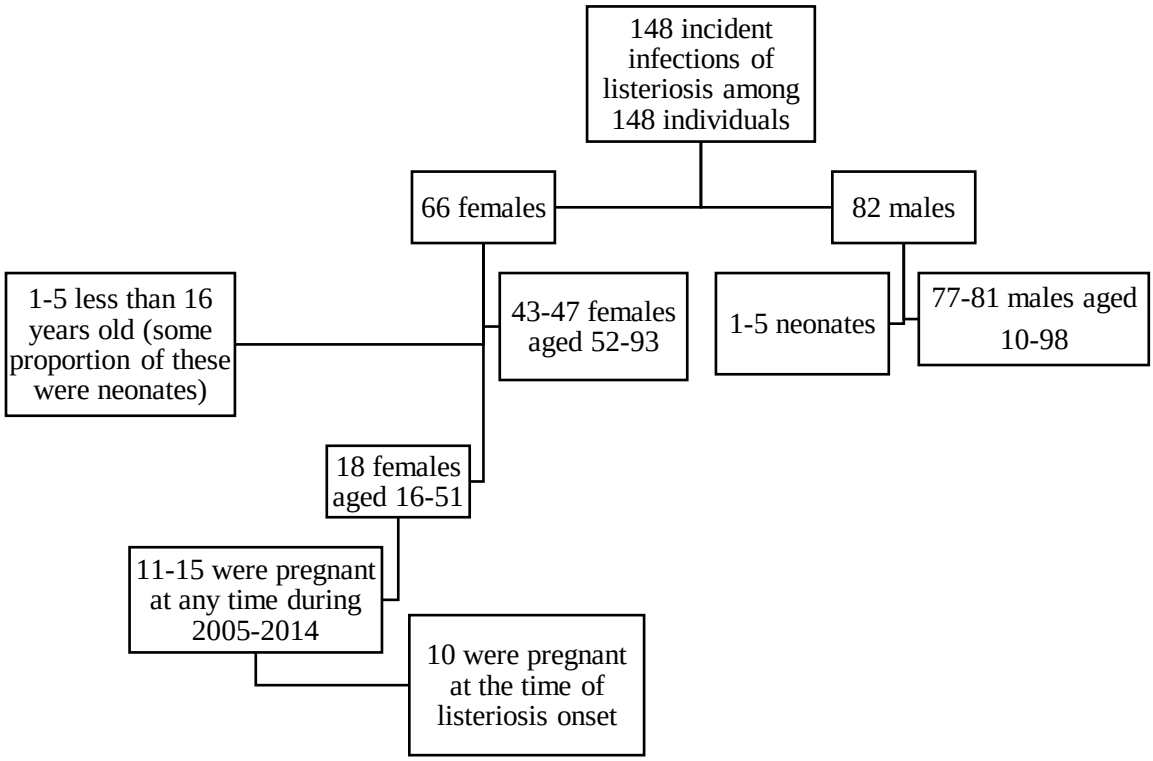
5.1 Pregnancy-related listeriosis cases

In BC during 2005-2014, there were 148 incident infections of listeriosis among 148 individuals. Of these listeriosis cases, 66 (45%) were female and 82 (55%) were male. Ages of females ranged from 0-93 years old. Ages of males ranged from 0-81 years old.

5.1.1 Confirmed cases of pregnancy-related listeriosis

Of the female listeriosis cases, there were 11-15 (17-23%) who were pregnant at any time during 2005-2014, with ages ranging from 16-51. Of these females, 10 (66-91%) were pregnant during the time of their estimated listeriosis onset. Overall, there were 1-5 neonates and 10 pregnant women with confirmed listeriosis.

Figure 1. Numbers of confirmed cases of listeriosis in BC, 2005-2014



5.1.2 Potential cases of pregnancy-related listeriosis

There were 155 hospitalizations among 128 individuals with an ICD code for listeriosis. Of these, 23 visits among 17 individuals were those who did not have a report of an enteric infection in Panorama. Among these 17 individuals, 1-5 were pregnant women and 1-5 were neonates at the time of the visit with the listeriosis ICD code.

There were 219 fee-for-service physician visits among 63 individuals with an ICD code for listeriosis. Of these, 92 visits among 40 individuals were those without any enteric infection reported in Panorama. Among these 40 individuals, 1-5 were pregnant women and 1-5 were neonates at the time of the visit with the listeriosis ICD code. There was no overlap with potential cases found in DAD versus MSP. See figures 2 and 3 for visuals of these findings.

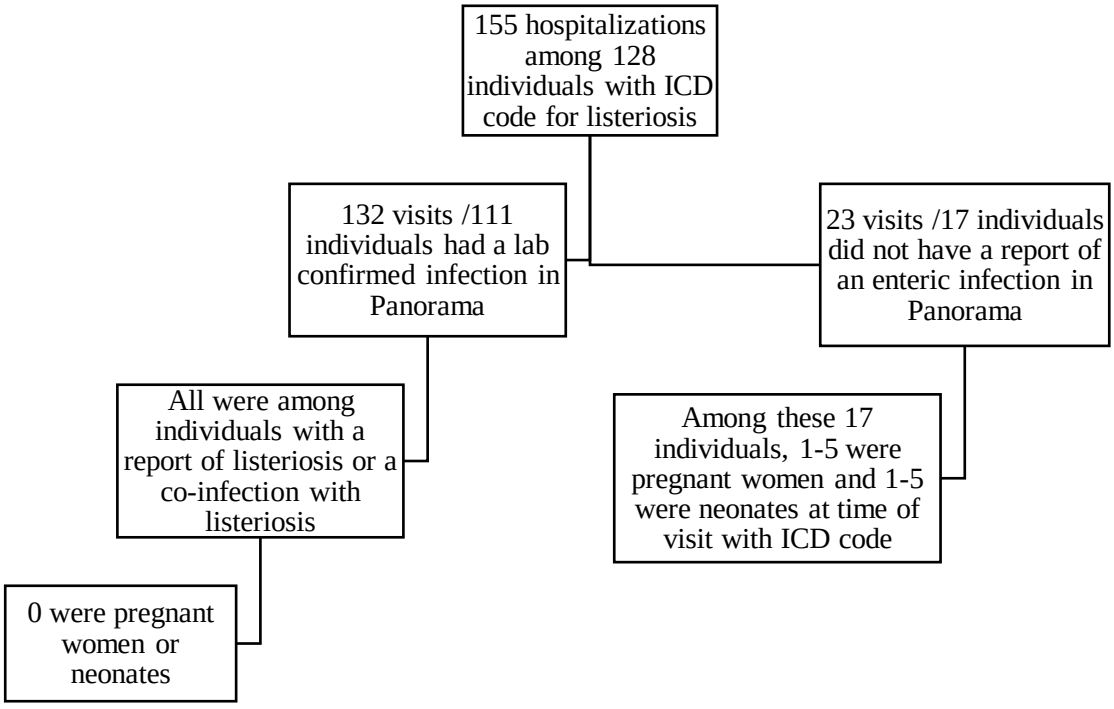


Figure 2. Numbers of hospital visits with ICD codes for listeriosis in BC, 2005-2014

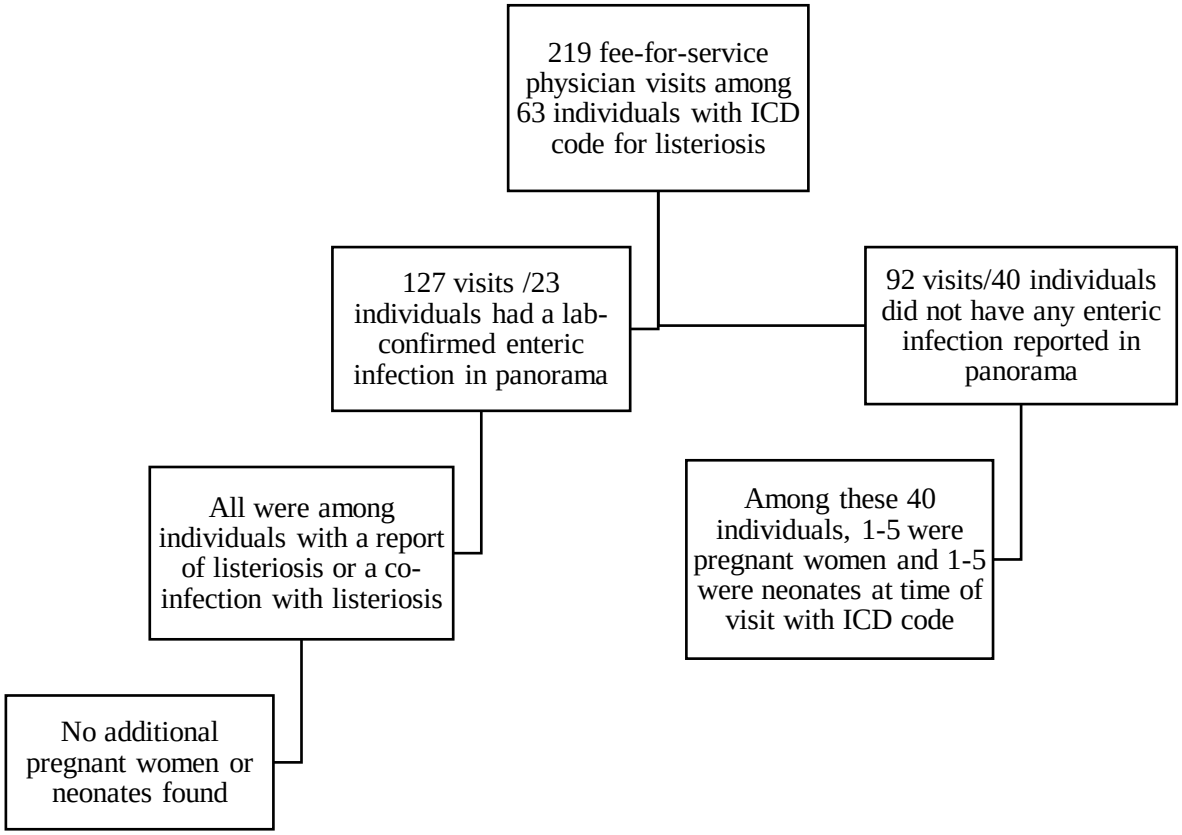


Figure 3. Numbers of physician visits with ICD codes for listeriosis in BC, 2005-2014

5.2 Descriptive epidemiology of pregnancy-related listeriosis cases

5.2.1 Overview of cases

Of the 148 laboratory-confirmed, provincially reported cases of listeriosis in British Columbia between 2005-2014, 11-15 were pregnancy-related (7.4%-10.1%). Of these 11-15 pregnancy-related cases, 10 were instances where *Listeria* was isolated from pregnant women and 1-5 were isolated from neonates. Based on comparing date of delivery of the pregnant women with the date of birth of the neonates, as well as health authority and income, it is likely that a small number (n=1-5) of the 11-15 confirmed individuals are mother-neonate pairs. I was unable to confirm these matches or find pairs for all mothers and neonates due to a missing variable on the hospital newborn records, that should have contained the mother's study ID.

There were an additional 7 (n=1-5 maternal, n=1-5 neonatal) individuals who had records with ICD codes for listeriosis in the DAD or MSP, but for which there was no confirmed report in Panorama. Of the 7 individuals with ICD codes for listeriosis and no report of listeriosis in Panorama, some (n=1-5) had the same hospital delivery/birth date, health authority, and income as an individual with confirmed pregnancy-related listeriosis and thus are likely a mother-neonate pair. Again, this could not be confirmed.

5.2.2 Pregnant women with confirmed listeriosis

There were 10 laboratory-confirmed, provincially reported, cases of listeriosis in pregnant women, in British Columbia during 2005-2014. The incidence proportion of listeriosis in pregnant women in British Columbia during this time was found to be 2.4 per 100,000 pregnancies (excludes pregnancies that resulted in early pregnancy loss and those that had a live birth outside of hospital; includes those that resulted in stillbirth).

All 10 of these pregnancies were singleton pregnancies. Among these women, their median number of deliveries during the study period was 2 (range= 2). All maternal cases experienced the onset of infection in either the second or third trimester. None were in the first trimester. The median gestational age at listeriosis onset was 31 weeks (range=19). The median gestational age at delivery for these women was 34 weeks (range= 19). At the estimated date of listeriosis onset, the median age of these women was 32 years (range= 21). Most of the infections occurred in the summer or fall months (June-November). These individuals resided in health authorities two, three, and four during the time of onset. The median average unadjusted disposable income for the postal code area in which the cases resided was $37,150 (range= $68,400).

Among the 10 maternal cases, there were 0 deaths during the study period. The most common pregnancy complications experienced were pre-term birth, fetal heart anomaly, infection of the amniotic sac, and gestational diabetes.

For these 10 cases, a number had an ICD code for listeriosis reported in the DAD or MSP. For these cases, the estimated onset date in Panorama preceded the date reported in hospital or MSP. The median number of days between estimated onset date and first report of a listeriosis ICD code in the DAD/MSP was 2 days (range=4). The median time between estimated onset date and birth (including stillbirths), was 3 days (range=125). For the number of cases where there was an ICD code for listeriosis reported in the DAD or MSP, the median time between the DAD/MSP report date and birth was 0 days (range=125).

5.*2.3 Sensitivity analysis: Pregnant women with confirmed and potential listeriosis*

When the potential pregnant cases of listeriosis were included in the count of pregnant individuals with listeriosis, the number of cases increased to between 11-15. Consequently, the incidence proportion during 2005-2014 increased to between 2.63 per 100,00-3.58 per100,000 pregnancies. Among these women, their median number of deliveries during the study period remained at 2 (range=3). The median gestational age at birth for these cases increased to 37 weeks (range=20). The median gestational age at listeriosis onset remained at 31 weeks (range=19). In all cases, the estimated onset of illness occurred during the second or third trimester. Most cases occurred between June and November. The median age of these mothers at the time of estimated onset remained at 32 years old (range=21). The average unadjusted disposable income for this group increased to $39,400 (range=$86,300). These individuals resided in health authorities one, two, three, and four. Along with the pregnancy-related complications described for the confirmed cases alone, postpartum hemorrhage additionally

became more common when potential cases were added in. There were zero deaths among these cases. Finally, the median time between the report of listeriosis in the DAD/MSP and birth was 0 days (range=125).

Table 12. Characteristics of pregnant women with listeriosis in British Columbia Canada, 2005-2014

	Pregnant women with lab-confirmed listeriosis (n=10)	**Pregnant women with lab-confirmed + potential listeriosis (n= 11-15)**
Incidence proportion	2.4/100,000 births	2.63/100,000-3.58/100,000 births
Proportion singleton births	10/10 (100%)	100%
Median number of births during the study period (range)	2 (2)	2 (3)
Median age at onset in years (range)	32 (21)	32 (21)
Median gestational age at onset in weeks (range)	31 (19)	31 (19)
Median gestational age at delivery in weeks (range)	34 (19)	37 (20)
Trimester at onset	All in 2nd or 3rd trimester	All in 2nd or 3rd trimester
Season of onset	Most cases were in the summer or fall	Most cases were in the summer or fall
Median average equivalized disposable income (range)	$25,300 (42,300)	$23,700 (51,300)
Median average unadjusted disposable income (range)	$37,150 (68,400)	$39,400 (86,300)
Health authority	2, 3, 4	1, 2, 3, 4
Number of deaths	0	0

5.2.4 Neonates with confirmed listeriosis

There were 1-5 laboratory-confirmed, provincially reported, cases of neonatal listeriosis in British Columbia during 2005-2014. The incidence proportion for this 10-year period was less than 1.44 cases of neonatal listeriosis per 100,000 live births.

All neonates were of singleton births. The median birthweight of these neonates was 2915 g. The median average unadjusted disposable income for the postal code area in which the cases resided was $39,400. There were no trends found with regards to season in which infection occurred.

The most common complications experienced by these neonates were sepsis, meningitis, and respiratory distress. None of the neonates died during the study period.

For the number of cases with an ICD code for listeriosis reported in the DAD or MSP, the estimated onset date preceded the date reported in hospital or MSP. The median number of days between estimated onset date and first report of listeriosis in the DAD/MSP was 2.5 days. The median number of days between estimated onset of listeriosis and birth of the neonate was 0. The median age (in days) of neonates at estimated onset was 0. The median age (in days) that listeriosis was first reported in the hospital or MSP records was 11.5 days (for those with a hospital/MSP ICD code).

5.2.5 Sensitivity analysis: Neonates with confirmed and potential listeriosis

When the potential neonatal cases with listeriosis were included in the count of neonates with listeriosis, the number of cases was 7. The incidence proportion during 2005-2014 went up to 1.68 per 100,000 live births. All cases were of singleton births. Their median birthweight went down to 2,710g (range= 2,101g). Most cases experienced onset of listeriosis between the months of June to November. These neonates resided in health authorities two, three, and four. The

average unadjusted disposable income for this group remained at $39,400 (range= $ 67,700). The proportion of those with low birth weight and who were born pre-term increased. The number of deaths among these cases remained at zero.

The median time between birth and estimated onset date of listeriosis (based on appearance of an ICD code)/median age at onset was 0 days (range=19).

Table 13. Characteristics of neonates with listeriosis in British Columbia, Canada, 2005-2014

	Neonates with lab-confirmed listeriosis (N= 1-5)	**Neonates with lab-confirmed + potential listeriosis (N= 7)**
Incidence per 100,000 births	< 1.44/100,000 live births	1.68/100,000 live births
Proportion singleton births	100%	100%
Median age at onset in days (range)	0	0 (19)
Median birthweight in grams (range)	2,915	2,710 (2,101)
Season of onset	No trends	Most cases were in the summer or fall
Median average equivalized disposable income in CAD$ (range)	$26,900	$26,900 (39,800)
Median average unadjusted disposable income in CAD$ (range)	$39,400	$39,400 (67,700)
Health authorities	Suppressed	2, 3, 4
Number of deaths	0	0

5.3 Proportion and timing of stillbirth

The number of stillbirths that occurred among the 10 pregnant women with listeriosis was 1-5/10 (10-50%). Among the pregnant listeriosis cases who had a stillbirth, their median number of weeks of gestation at which listeriosis onset occurred was approximately 20 weeks. The median number of weeks of gestation at which stillbirth occurred was 20 weeks. The median number of days between estimated listeriosis onset and stillbirth was 4 days. The median timing between pregnancy start, estimated listeriosis onset, and stillbirth for these 1-5 individuals is illustrated in Figure 4. None of the pregnant women with potential listeriosis went on to have a stillbirth.

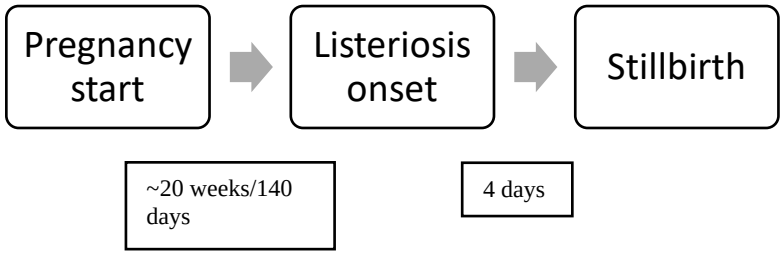


Figure 4. Median time between pregnancy start, listeriosis onset, and stillbirth among pregnant women

5.4 Fraction of stillbirths attributable to listeriosis

The number of stillbirths that occurred among pregnant women with listeriosis was between 1-5. There were a total of 2088 stillbirths reported in BC during 2005-2014. The proportion of all stillbirths that occurred among those with a listeriosis infection was between 0.048% and 0.239%, or between 0.48 and 2.39 per 1,000 stillbirths. The fraction of stillbirths in the population attributable to listeriosis during pregnancy was between 0.045% and 0.237%, or between 0.45 and 2.37 per 1,000 stillbirths.

Sensitivity analysis

There were no stillbirths that occurred among the 1-5 pregnant women with potential listeriosis. Thus, the proportion of all stillbirths that occurred among those with a listeriosis infection remained the same. When the additional 1-5 pregnant women with potential listeriosis were added to the relative risk used to calculate the PAF, the PAF remained at about the same, between 0.44 and 2.36 per 1,000 stillbirths.

5.5 Healthcare utilization and costs

5.5.1 Healthcare utilization and costs during pregnancy

Matching of pregnant women with listeriosis to pregnant women without listeriosis was successful, as exact matches were achieved on the baseline characteristics of health authority, index year, income quintile, and presence of select pre-existing comorbidities. The mean baseline age of pregnant women with listeriosis was 28.9 (median of 31.5) and the mean age of pregnant women without listeriosis was 29.7 (median of 31). The goal of five matches was achieved for most cases, and at least four matches were found for every case.

When compared to their pregnant matches without listeriosis, the overall healthcare utilization was higher among the pregnant women with listeriosis during pregnancy compared to without listeriosis. Specifically, pregnant women with listeriosis had a higher number of hospital admissions, cumulative days in hospital, fee-for-service physician visits, and pharmacy claims, compared to pregnant women without listeriosis (Table 14). However, only the difference in hospital visits and cumulative days in hospital were statistically significant.

Unadjusted direct healthcare costs by type of service were also higher in the group with listeriosis. Specifically, pregnant women with listeriosis had higher hospital costs, fee-for-service physician costs, and pharmacy costs (Table 14). The mean unadjusted total direct healthcare costs were larger by over two-fold in the group with listeriosis at $14,307, compared to $5,879 in

the group without listeriosis. All cost differences were statistically significant except for the costs of pharmacy claims.

Table 14. Healthcare utilization and unadjusted healthcare costs during pregnancy (plus two-week buffer period) among the matched *Listeria* and non-*Listeria* cohorts, when potential cases of listeriosis are included

	Listeriosis in pregnancy (n=10)	**No listeriosis in pregnancy (n= 49)**	**p**
Hospitalizations			
Median no. of admissions (range)	2.0 (2.0)	1.0 (1.0)	0.0005
Mean no. of admissions (SD)	1.8 (0.79)	1.1 (0.31)	
Median cumulative days in hospital (range)	12.5 (23.0)	2.0 (14.0)	<.0001
Mean cumulative days in hospital (SD)	12.7 (7.95)	2.57 (2.25)	
Median unadjusted cost in CAD$ (range)	8,137 (21,640)	2,730 (10,946)	<.0001
Mean unadjusted cost in CAD$ (SD)	10,617 (6,635)	3,313 (1,943)	
Physician visits			
Median no. of visits (range)	32 (51)	27 (53)	0.2335
Mean no. of visits (SD)	33.6 (15.13)	27.79 (9.44)	
Median unadjusted cost in CAD$ (range)	3,396 (3,372)	2,248 (4,148)	0.0202
Mean unadjusted cost in CAD$ (SD)	3,466 (1,289)	2,456 (832)	
Pharmacy claims			
Median no. of claims (range)	3.5 (28)	2.28 (17)	0.1172
Mean no. of claims (SD)	6.4 (8.68)	1 (3.54)	
Median unadjusted cost in CAD$ (range)	123 (669)	25 (1053)	0.1957
Mean unadjusted cost in CAD$ (SD)	225 (259)	111 (226)	
Total cost			
Median unadjusted total cost in CAD$ (range)	11,784 (24,794)	5,057 (15,048)	<.0001

Mean unadjusted total cost in CAD$ (SD)	14,307 (7,521)	5,879 (2,608)	

In the final model, adjusting for age, health authority, and income, the patients with listeriosis had 2.48 times higher mean costs than those without listeriosis (p<.0001) (Table 15), meaning that on average, the healthcare costs for a pregnancy with listeriosis is 2.48 times greater than for a pregnancy unaffected by listeriosis, while holding all other variables constant. Results of univariable models are shown in Appendix B, Tables 1-4. Results from bivariable models are shown in Appendix B, Tables 5-7.

Table 15. Association between having listeriosis in pregnancy and total direct healthcare cost of the pregnancy, adjusted for health authority, income quintile, and age

Parameter		**Estimate log (95% CI)**	**Estimate exponentiated (95% CI)**	**Pr > ChiSq**
Intercept		8.96 (8.56, 9.37)	7796.26 (5208.25, 11731.12)	<.0001
Listeria		0.91 (0.65, 1.16)	2.48 (1.92, 3.19)	<.0001
Health authority*	2	-0.32 (-0.71, 0.06)	0.72 (0.49, 1.06)	0.0971
	3	-0.37 (-0.74, -0.01)	0.69 (0.48, 0.99)	0.0468
	4	ref	ref	-
Income quintile	1	-0.08 (-0.36, 0.33)	0.92 (0.70, 1.39)	0.5616
	2	-0.01 (-0.34, 0.33)	0.99 (0.71, 1.39)	0.9687
	3	ref	ref	-
Age	15-19	0.12 (-0.29, 0.53)	1.13 (0.74, 1.70)	0.5744
	20-24	-0.06 (0.56, 0.44)	0.94 (1.74, 1.55)	0.8163
	25-29	0.13 (-0.16, 0.41)	1.13 (0.85, 1.51)	0.3825
	30+	ref	ref	-

*There were no people in health authorities 1 or 5.

5.5.2 Sensitivity analysis: Healthcare utilization and costs during pregnancy

When the potential cases of listeriosis among pregnant women and their matches were included, baseline characteristics between those with versus without listeriosis were exactly the

same with the exception of age (Table 16). The mean age of those with listeriosis was 28.1 (median of 29) and then median age of those without listeriosis was 29.7 (median of 30).

Compared to their pregnant matches without listeriosis, the overall healthcare utilization was higher among the pregnant women with listeriosis during pregnancy compared to without listeriosis. Specifically, pregnant women with listeriosis had a higher mean number of hospital admissions, cumulative days in hospital, fee-for-service physician visits, and pharmacy claims, compared to pregnant women without listeriosis. All differences were statistically significant except for the difference between number of physician visits (Table 16).

Unadjusted direct healthcare costs by type of service were also higher in the group with listeriosis. Specifically, pregnant women with listeriosis had higher mean hospital costs, fee-for-service physician costs, and pharmacy costs. The mean unadjusted total direct healthcare cost was significantly higher in the group with listeriosis, compared to the group without listeriosis. All differences were statistically significant except for the difference between number pharmacy costs (Table 16).

Table 16. Healthcare utilization and unadjusted healthcare costs during pregnancy (plus two-week buffer period) among the matched *Listeria* and non-*Listeria* cohorts, when potential cases of listeriosis are included

	Listeriosis in pregnancy (n=11-15)	**No listeriosis in pregnancy (n=55-75)**	**p**
Hospitalizations			
Median no. of admissions (range)	2.0 (2.0)	1.0 (1.0)	<.0001
Mean no. of admissions (SD)	1.7 (0.73)	1.1 (0.26)	
Median cumulative days in hospital (range)	8.5 (2-25)	2.0 (14.0)	<.0001
Mean cumulative days in hospital (SD)	11.2 (7.1)	2.6 (2.6)	
Median unadjusted cost in CAD$ (range)	7,826 (21,639)	2,412 (11,151)	<.0001
Mean unadjusted cost* (SD)	9,530 (5,909)	3,246 (2,037)	
Physician visits			
Median no. of visits	31.0 (51.0)	26.0 (53.0)	0.2335
Mean no. of visits (SD)	32.5 (13.0)	27.90 (9.91)	
Median unadjusted cost in CAD$ (range)	4,383 (8,879)	2,248 (4,148)	0.0004
Mean unadjusted cost in CAD$ (SD)	4,903 (2,768)	2,440 (852)	
Pharmacy claims			
Median no. of claims (range)	4 (28)	1 (0-17)	0.0176
Mean no. of claims (SD)	5.7 (7.3)	2.2 (3.2)	
Median unadjusted cost in CAD$ (range)	75 (669)	29 (1,053)	0.2234
Mean unadjusted cost in CAD$ (SD)	180 (230)	101 (196)	
Total cost			
Median unadjusted total cost in CAD$ (range)	12,633 (24,794)	4,897 (15,048)	<.0001
Mean unadjusted total cost in CAD$ (SD)	14,613 (6,471)	5,787 (2,723)	

In the final model, adjusting for age, health authority, and income, the patients with listeriosis had 2.57 times higher mean costs than those without listeriosis (p<.0001) (Table 17), meaning that on average, the healthcare costs for a pregnancy with listeriosis was 2.57 times greater than for a pregnancy unaffected by listeriosis, while holding all other variables constant. Results of univariable models are shown in Appendix B, Tables 8-11. Results from bivariable models are shown in Appendix B, Tables 12-14.

Table 17. Association between exposure to listeriosis in pregnancy and total direct healthcare costs of the pregnancy, when potential cases of listeriosis are included, adjusted for health authority, income quintile, and age

Parameter		**Estimate log (95% CI)**	**Estimate exponentiated (95%CI)**	**Pr > ChiSq**
Intercept		8.95 (8.62, 9.27)	7694.03 (5541.39, 10614.75)	<.0001
Listeria		0.9452 (0.72, 1.16)	2.57 (2.05, 3.19)	<.0001
Health authority*	1	0.01 (-0.07, 0.078)	1.01	0.9815
	2	-0.34 (-0.64, -0.05)	0.71 (0.53, 1.05)	0.0225
	3	-0.34 (-0.59, -0.09)	0.71 (0.55, 1.09)	0.0087
	4	ref	ref	-
Income quintile	1	-0.07 (-0.33, 0.19)	0.93 (0.72, 1.21)	0.5956
	2	-0.01 (-0.31, 0.29)	0.99 (0.73, 1.34)	0.9366
	3	ref	ref	-
Age	15-19	0.09 (-0.30, 0.48)	1.01 (0.74, 1.62)	0.6647
	20-24	-0.04 (-0.40, 0.32)	0.96 (0.67, 1.38)	0.8365
	25-29	0.02 (-0.20, 0.23)	0.98 (0.82, 1.26)	0.8688
	30+	ref	ref	-

*There were no people in health authority 5.

5.5.3 Healthcare utilization and costs among neonates

Matching of neonates with listeriosis to neonates without listeriosis was successful, as exact matches were achieved on the baseline characteristics of sex, health authority, year, income

quintile, and presence of a congenital abnormality. The goal of selecting five matches for every case was achieved.

Overall, healthcare utilization was higher among the neonates with listeriosis compared to without listeriosis in most types of services. Specifically, neonates with listeriosis had a higher median/mean number of hospital admissions, cumulative days in hospital, and fee-for-service physician visits, compared to pregnant women without listeriosis (all statistically significant, Table 18). The mean number of pharmacy claims was slightly higher in the neonates without listeriosis, but this difference was not statistically significant (Table 18).

Unadjusted direct healthcare costs by type of service were higher by most types of services in the group with listeriosis. Specifically, neonates with listeriosis had astronomically higher median/mean hospital costs and fee-for-service physician costs than those without, and the differences were statistically significant (Table 18). Again, pharmacy costs were slightly higher among neonates without listeriosis (but not statistically significant). The mean unadjusted total direct healthcare cost was significantly higher in the group with listeriosis, compared to the group without listeriosis by over 20-fold (Table 18). Note that ranges and standard deviations for the 1-5 neonates with confirmed listeriosis were not shown due to small cell size restrictions.

Table 18. Healthcare utilization and unadjusted healthcare costs among neonates (plus two-week buffer period) among the matched *Listeria* and non-*Listeria* cohorts

	Neonates with listeriosis (n=1-5)$^{+}$	**Neonates without listeriosis (n= 5-25)**	**p**
Hospitalizations			
Median no. of admissions (range)	2.0	1 (0)	0.0025
Mean no. of admissions (SD)	1.6	1 (0)	
Median cumulative days in hospital (range)	17	1.0 (2.0)	<.0001

Mean cumulative days in hospital (SD)	27.8	1.6 (0.7)	
Median unadjusted cost in CAD$ (range)	17,466	834 (2,920)	<.0001
Mean unadjusted cost in CAD$ (SD)	33,770	1,191 (776)	
Physician visits			
Median no. of visits (range)	11	4.0 (9.0)	<.0001
Mean no. of visits (SD)	20.60	4.28 (2.72)	
Median unadjusted cost in CAD$ (range)	2,565	295 (1268)	<.0001
Mean unadjusted cost in CAD$ (SD)	3,627	361 (328)	
Pharmacy claims			
Median no. of claims (range)	0	0.0 (5.0)	0.4674
Mean no. of claims (SD)	0	0.52 (1.19)	
Median unadjusted cost in CAD$ (range)	0	0 (88)	0.4674
Mean unadjusted cost in CAD$ (SD)	0	8 (20)	
Total cost			
Median unadjusted total cost in CAD$ (range)	20,953	1,160 (4,224)	<.0001
Mean unadjusted total cost in CAD$ (SD)	37,398	1,560 (1,049)	

In the final model, adjusting for sex, presence of a congenital abnormality at birth, and income, this cost ratio was 14.48 ($p<0.0001$) (Table 19), meaning that on average, the healthcare costs for a neonate with listeriosis were 14.48 times greater than for neonates without listeriosis, while holding all other variables constant. Results of univariable models are shown in Appendix B, Tables 15-18. Results from bivariable models are shown in Appendix B, Tables 19-21.

Table 19. Association between exposure to listeriosis in neonates and total direct healthcare cost during the first 42 days of life, adjusted for sex, income quintile, and congenital abnormality

Parameter	Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept	6.57 (5.85, 7.29)	713.80 (347.23, 1465.57)	<.0001
Listeria	2.67 (2.12, 3.22)	14.48 (8.33, 25.03)	<.0001
Sex*	*	*	Not significant
Income*	*	*	At least one category was significant
Congenital abnormality	0.89 (0.16, 1.61)	2.43 (1.17, 5.00)	0.0163

*Number of categories and/or details of categories cannot be shown due to suppression of small cell sizes.

5.5.4 Sensitivity analysis: Healthcare utilization and costs among neonates

Overall, healthcare utilization was higher among the neonates with listeriosis compared to without listeriosis in most types of services. Specifically, neonates with listeriosis had a higher number of hospital admissions, cumulative days in hospital, and fee-for-service physician visits, compared to neonates without listeriosis (all statistically significant, Table 20). The mean number of outpatient pharmacy claims was slightly higher in the neonates without listeriosis, but this difference was not statistically significant (Table 20).

Unadjusted direct healthcare costs by type of service were higher by most types of services in the group with listeriosis. Specifically, neonates with listeriosis had substantially higher hospital costs and fee-for-service physician costs than those without, and the difference was statistically significant (Table 20). Again, pharmacy costs were slightly higher among neonates without listeriosis but this difference was not statistically significant. The mean

unadjusted total direct healthcare cost was significantly higher in the group with listeriosis, compared to the group without listeriosis by over 20-fold (Table 20).

Table 20. Healthcare utilization and unadjusted healthcare costs among neonates (plus two-week buffer period) among the matched *Listeria* and non-*Listeria* cohorts, when potential cases of listeriosis are included

	Neonates with listeriosis (n=7)	**Neonates without listeriosis (n= 35)**	**p**
Hospitalizations			
Median no. of admissions (range)	2.0 (1.0)	1.0 (0.0)	0.0003
Mean no. of admissions (SD)	1.6 (0.5)	1.0 (0.0)	
Median cumulative days in hospital (range)	17.0 (62.0)	2.0 (76.0)	<.0001
Mean cumulative days in hospital (SD)	28.0 (22.2)	3.9 (12.7)	
Median unadjusted cost in CAD$ (range)	17,466 (108,703)	835 (716-163,228)	<.0001
Mean unadjusted cost* (SD)	30,699 (37,264)	5,852 (27,395)	
Physician visits			
Median no. of visits (range)	11.0 (39.0)	4.0 (13.0)	0.0027
Mean no. of visits (SD)	18.4 (13.9)	5.11 (3.3)	
Median unadjusted cost in CAD$ (range)	2,565 (8,510)	308 (3,838)	0.0002
Mean unadjusted cost in CAD$ (SD)	3,266 (2,800)	489 (660)	
Pharmacy claims			
Median no. of claims (range)	0.0 (0.0)	0.0 (5.0)	0.3261
Mean no. of claims (SD)	0.0 (0.0)	0.4 (1.0)	
Median unadjusted cost in CAD$ (range)	0 (0)	0 (87)	0.3261
Mean unadjusted cost in CAD$ (SD)	0 (0)	6.1 (17)	
Total cost			

Median unadjusted total in CAD$ cost (range)	20,953 (116,282)	1,439 (166,305)	<.0001
Mean unadjusted total cost in CAD$ (SD)	33,964 (39,872)	6,348 (27,984)	

In the final model, adjusting for sex, presence of a congenital abnormality at birth, and income, this cost ratio was 9.85 ($p<0.0001$) (Table 21), meaning that on average, the healthcare costs for neonates with listeriosis were 9.85 times greater than for neonates without listeriosis, while holding all other variables constant. Results of univariable models are shown in Appendix B, Tables 22-25. Results of bivariable models are shown in Appendix B, Tables 26-28.

Table 21. Association between exposure to listeriosis in neonates and total direct healthcare cost during the first 42 days of life, when potential cases of listeriosis are included, adjusted for sex, income quintile, and congenital abnormality

Parameter		**Estimate log (95% CI)**	**Estimate exponentiated (95% CI)**	**Pr > ChiSq**
Intercept		7.05 (6.25, 7.84)	1148.72 (519.05, 2541.98)	<.0001
Listeria		2.29 (1.72, 2.85)	9.85 (5.60, 17.34)	<.0001
Sex	F	0.20 (-0.35, 0.75)	1.22 (0.70, 2.12)	0.4771
	M	ref	ref	-
Income	1	0.61 (-0.14, 1.37)	1.85 (0.86, 3.94)	0.1125
	2	-0.05 (-0.76, 0.66)	0.95 (0.47, 1.93)	0.8947
	3	0.16 (-0.80, 1.11)	1.17 (0.45, 3.03)	0.7465
	5	ref	ref	-
Congenital abnormality		3.11 (2.36, 3.87)	22.53 (10.55, 48.12)	<.0001

6. Discussion

6.1 Epidemiology of pregnancy-related listeriosis

The incidence of pregnancy-related listeriosis in British Columbia during 2005-2014 was low. For pregnant women in this study, the incidence was 2.4 per 100,000 deliveries (between 2.6/100,000-3.58/100,000 in sensitivity analysis). This is lower than what has been reported in studies in other countries. For example, the incidence was 5.6 cases per 100,000 pregnancies in France between 2001 to 2008 and 12 cases per 100,000 women giving birth in New Zealand during 1997-2016 (Goulet et al., 2012; Jeffs et al., 2020). For neonates in this study, the incidence was less than 1.44 per 100,000 live births (1.66/100,000 if we include potential cases). This is again lower than what was found in other studies, including the only other Canadian study that looked at the epidemiology of neonatal listeriosis (Abu-Raya, 2017). It is of note that there could be differences in incidence across Canada and thus there should be caution with generalizing these results to all of Canada. As an example, when looking at within-country differences, Silk et al. (2012) found that the incidence of pregnancy-related listeriosis in the US varied greatly by state, from 0.27 in Minnesota to 5.61 in Georgia, per 100,00 pregnancies; it is unknown if significant variation may exist across Canada as well.

The case fatality rate for both pregnant and neonatal cases (regardless of inclusion of potential cases) was 0%, which has not been reported in similar studies, particularly for neonates. In studies with greater numbers of cases (n=128-189), the case fatality rate for neonates ranged from 0.68-21.0% (Elinav et al., 2014; Jackson et al., 2010; Charlier et al., 2022; Jeffs et al., 2020). Even in studies with very small numbers of cases (n=11-14), at least one neonatal death was reported (Benshushan et al., 2002; Li et al., 2020; Ke at al., 2022; Abu-Raya et al., 2021). Death following listeriosis in pregnant women is very rare and therefore the finding that none of

the pregnant women in this study died is unsurprising. The survival of all cases in this study could be due to timely and effective treatment. However, hospital treatment details were unavailable and the sample size may be too small for speculation; nonetheless, this is a salient finding.

In terms of the demographic and clinical characteristics of pregnant women with listeriosis in this study, their age at the time of onset (32 years) was comparable to the average age of a woman giving birth in British Columbia during that time, which was 30.2 years old in 2005 and 31.3 years old in 2014, with age steadily increasing between those years (Statistics Canada, 2022).

It was expected to find that most cases occurred in the summer or fall months. A recent study conducted in Ontario, Canada which looked at seasonal trends of foodborne infections reported higher rates of listeriosis in the summer (John et al., 2022). This is thought to be due to warmer temperatures that promote growth of the bacteria as well as social factors such as increased social gatherings with food (Rajda & Middleton, 2006).

Clinically, it was notable to find the median gestational age at delivery for confirmed cases of listeriosis in pregnancy was 34 weeks, which is below what is considered a full-term or at term pregnancy. In the US the definition of a “full-term” pregnancy is now 39 weeks and while there is no formal definition for “full-term” in Canada, 37-42 weeks is often considered “at term” (Eunice Kennedy Shriver National Institute of Child Health and Human Development, 2022; HealthLinkBC, n.d.). However, when potential cases were included, this median did go up to 37 weeks. When using these findings to inform prevention, care, or policy regarding listeriosis and pre-term birth, there should be caution in deciding whether to use the more specific or sensitive definition of a listeriosis case. Other studies likewise found pre-term birth to be a

common outcome of pregnancy-related listeriosis (Ke et al., 2022; Jeffs et al., 2020; Craig et al., 2022; Charlier et al., 2022)

Additionally, all pregnant cases experienced onset in the second or third trimester, which is consistent with previous literature. For example, of the 278 cases with known onset date in the Awofisayo et al. (2015) study in England and Wales, 98% experienced onset in second or third trimester. They also found that the odds of a live birth increased by 157-fold if the mother's onset was in the third trimester (Awofisayo et al., 2015). This could offer one reason why the proportion of fetuses and neonates that survived in this present study was so high. Furthermore, all pregnant cases experienced pregnancy and birth complications, but some complications reported in this study have not been reported in other studies, such as fetal heart anomaly and infection of the amniotic sac. Given that the median time between delivery and the first appearance of an ICD code for listeriosis in the DAD or MSP was 0 days, it is plausible that birth complications are what leads to the testing and diagnosis of listeriosis.

For neonates in this study, the median age at onset was 0 days. However, for those with early-onset neonatal listeriosis, the estimate of onset for neonates is likely not representative of the true time of onset, given that early-onset neonatal listeriosis begins in utero (Swaminathan & Gerner-Schmidt, 2007). If I would have been able to link mothers and neonates, the mother's onset date may have been a more representative onset date for their neonate. For those whose estimated onset date was at greater than 7 days old, the estimated onset date should be more representative of the true onset date. Regardless, a median age at onset of 0 days shows that the average neonate in the study had early-onset neonatal listeriosis. This finding is reflected in the literature, where the proportion of neonates with early-onset listeriosis is higher than those with

late-onset neonatal listeriosis across all studies. For example, Charlier et al. (2022) found that 70% of the infants in their study had early-onset neonatal listeriosis.

Among the lab-confirmed neonatal listeriosis cases alone, there were no trends in seasonality observed, but when the potential cases were added in, as with the pregnant women, most cases occurred in the summer or fall. Again, this is consistent with what we would expect based on existing literature (John et al., 2022).

Clinically, the most common birth complications reported on the neonatal DAD records were sepsis, meningitis, and respiratory distress. This is in line with what has been reported in epidemiologic studies describing the outcomes for neonates with listeriosis (Jackson et al., 2010; Chalier et al., 2022; Jeffs et al., 2020). Finally, the median birthweight among these neonates was quite low at 2,915g (2,710g in sensitivity analysis). This is significantly lower than the median birthweight in British Columbia in 2015, which was 3,415g (Statistics Canada, 2015). However, because mothers and neonates could not be linked, the gestational age associated with the neonatal birthweights is unknown and there should be caution with comparing pre-term birth birthweights to those of at-term births. The median birth weight found in the present study was still above 2,500g, which is the threshold for what is clinically considered a low birth weight (Statistics Canada, 2015). On the other hand, clinically defined low birth weight was found in neonates with listeriosis in several studies, such as 2,280g (median) and 2,320g (mean) in Vergnano et al. (2021) and Jeff et al. (2020)'s studies in the UK and New Zealand, respectively. Nevertheless, public health professionals should ensure to communicate the risk of lower-than-average birth weight for those at risk of pregnancy-related listeriosis in Canada.

Finally, the proportion of women in the study who went on to have a stillbirth was between 10-50%. This is higher than the general proportion of total births in British Columbia

that resulted in a stillbirth between 2005 and 2014, which was 8.4 stillbirths per 1,000 births, or 0.84% (Statistics Canada, 2022). My findings are reflective of what has been reported in other studies, generally finding the rate of fetal loss to be between 16 and 45%. Further, I found that in cases where stillbirth occurred, it occurred on average very soon after the estimated listeriosis onset. This points to the importance of prompt diagnosis and treatment in pregnant who are suspected to have listeriosis. Additionally, this is the first study of my knowledge to report a population attributable fraction of stillbirth to listeriosis in pregnancy, which was between 0.45 and 2.37 per 1,000 stillbirths. This is important knowledge for those working with pregnant women and for pregnant women themselves to help prevent one potential cause of stillbirth.

6.2 Healthcare use and cost analysis

In this thesis, I found that healthcare usage was higher among pregnant women and neonates with listeriosis, compared to those without listeriosis. Specifically, pregnant women with listeriosis on average experienced significantly more hospital visits, physician visits, and pharmacy claims; and longer hospital length of stay. Neonates experienced more hospital visits and physician visits and longer hospital length of stay, but not more outpatient pharmacy claims. Because antibiotics for listeriosis treatment are administered intravenously and neonates with listeriosis spend so many more days in hospital than those without listeriosis, it makes sense that they would have little to no outpatient pharmacy claims.

Prior epidemiologic studies in the US have found high rates of hospitalizations and significantly longer hospital stays for pregnant women with compared to without listeriosis (Silk et al., 2012; Craig et al., 2022; Jackson et al., 2010). For example, Craig et al. (2022) looked at hospitalization outcomes for pregnant women with listeriosis in the US and found average length of stay to be 4 days for those with listeriosis vs. 2.3 days for those without ($p<.001$). While I

calculated the average total days in hospital across the entire pregnancy (as opposed to for a single visit), I did find the mean length of days in hospital for pregnant women with listeriosis to be about 10 days longer much longer than for those without listeriosis. In France, Charlier et al. (2022) found that neonates with listeriosis spent a median of 16 days in hospital, which is very similar to what was found in this thesis, which was a median 17 days in hospital.

In terms of direct healthcare costs, pregnant listeriosis cases also had higher average direct healthcare costs among all three categories of healthcare use, however, only hospital, physician, and total costs were significantly higher. Neonates with listeriosis also had higher hospital and physician costs than those without listeriosis.

In the Canadian literature, as mentioned, these studies are rare and the ones that exist were focused on outbreaks and did not report costs of pregnancy-related listeriosis. For instance, Thomas et al. (2015) estimated that the mean cost of illness per case during the 2008 listeriosis outbreak in Canada was $13,666 CAD. While this study did not focus on pregnancy-related cases, this was close to what I found to be the mean total healthcare costs for pregnant women ($14,613 CAD for confirmed cases; $14,307 CAD in sensitivity analysis). However, average healthcare costs per neonatal case in our study were much higher ($37,398 CAD for confirmed cases; $33,964 CAD in sensitivity analysis). This may suggest that the healthcare costs of listeriosis in pregnant women may be comparable to that of the average individual with listeriosis, regardless of their higher susceptibility to listeriosis. For neonates on the other hand, they contributed much higher costs and their associated costs should not be compared to those of an average listeriosis case. A study done in 1993 by the US Department of Agriculture reported that the direct healthcare costs per case of listeriosis was $12,117 USD for maternal cases and

$48,466 USD for neonatal cases. This greater ratio of neonatal to maternal healthcare costs was also found in this thesis (approximately 2.6 times bigger for neonates).

Furthermore, using a matched cohort approach to estimate the costs allowed me to control for a few select potential confounders and other covariates and provide an adjusted ratio of how much a pregnancy or newborn costs in healthcare costs for those with listeriosis compared to without. The matching was successful in balancing the covariates between the listeriosis vs. non-listeriosis groups, especially because exact matching was used where possible. I also included some of these covariates into the regression models to assess the influence of these variables despite matching on them. For pregnant women, after adjusting for age, health authority, and income, having listeriosis, on average, was associated with 2.48 times higher healthcare costs (2.57 with potential cases). For neonates, after adjusting for sex, income, and presence of a congenital abnormality, having listeriosis, on average, was associated with 14.48 times higher healthcare costs (9.85 with potential cases). There was a notable difference between the crude and adjusted cost ratios for the neonatal models, as well as between the model with only confirmed neonatal cases and the sensitivity model. This is likely because with the sample size being so small, the addition of any new individuals into the model is expected to influence the mean more drastically, especially if individuals vary on factors that were not matched on. In this case, the effect of the presence of a congenital abnormality significantly influenced the effect of *Listeria* in both models.

6.3 Contributions of this thesis

This is the first study to focus on the epidemiology and the costs of pregnancy-related listeriosis in Canada. This thesis adds to the body of research that supports listeriosis awareness and prevention in Canada. From the literature, we know that there is a high case-fatality rate

from listeriosis and especially for neonates, that *L. monocytogenes* can persist on foods in cooler temperatures and is difficult to control in food processing facilities, and that the rise of antibiotic resistance could affect vital listeriosis treatment in the future (Moghadam & Larsen, 2019). This thesis specifically highlights that in British Columbia during 2005-2014, average birthweight among neonates was low, gestational age at birth among pregnant women was low, a significant proportion of pregnant women had a stillbirth, and the hospital/physician visits and the associated healthcare costs were substantially higher than for pregnant women or neonates without listeriosis. Finally, this thesis demonstrated ways to work around some of the challenges of using administrative data in this context, such as identifying pregnant cases without a pregnancy/birth registry and identifying cases of listeriosis that may have been missed in the surveillance database. Having access to linked hospital, reportable disease, vital statistics, and other databases over a 10-year period has allowed me to provide a comprehensive examination of epidemiological characteristics, trends, and costs of pregnancy-related listeriosis.

6.4 Limitations

The small sample size was a limitation to the analysis and the generalizability of the results presented. A small number of cases was to be expected as listeriosis is a rare disease and I focused on a sub-population of cases within one province, compared to other studies that had country-level data. Further, listeriosis, like many foodborne infections, is understood to be underreported, and possibly even more so for pregnant women because they may not show obvious symptoms of listeriosis. Another factor that limited the sample size was not being able to link all pregnant women to their newborns and vice versa. A newborn with early-onset listeriosis should have had a mother that was exposed to listeriosis during pregnancy, even if they were asymptomatic and undiagnosed. Therefore, with this linkage I would have at least added these

pregnant women to the sample as confirmed or at least potential cases. The restriction of not being able to report cell sizes less than six also meant that some results could not be precisely presented, and I recognize this may make it difficult to apply and compare those numbers.

Note that where the sample size was exceptionally small, such as with the number of neonates with listeriosis, there should be caution with reporting means as the average. The mean is more influenced by extreme values and the median may be a more robust measure of the average in these cases. This is why I chose to report medians when describing the listeriosis cases only and both medians and means in the cost analysis.

Further, this being a retrospective study using secondary data meant that I could not collect additional variables that may have been of interest but were not available in the data. For example, other studies have shown that race and ethnicity may be risk factors for listeriosis, but I did not have access to this information to be able to describe these characteristics in cases. Other information that would have been useful would have been treatment details within hospital, specifically antibiotic use. This information may have provided more context to factors such as the neonatal survival rates and costs of a hospital visit. The available data on miscarriages was also insufficient to determine whether a pregnancy resulting in a miscarriage coincided with having listeriosis. While there are ICD codes for miscarriage, these codes are not accompanied with a gestational age in the DAD, nor did we have access to a different dataset that would contain such information.

Finally, because the hospital costs are estimated based on the individual's case mix group and not their actual individual costs, the hospital costs may not accurately reflect the true cost of a particular patient. For the same reason, I could not separate out various components of a hospital visit, such as pharmacy/treatment information and thus I did not have details about any

treatment that occurred in hospital. This explains why despite listeriosis treatment being so vital, the number of outpatient pharmacy claims and costs were relatively low, as we expect most pharmaceutical treatment to be prescribed as an inpatient.

6.5 Future research and recommendations

Future research should build on this thesis by investigating similar epidemiologic indicators and characteristics of pregnancy-related listeriosis in other provinces or across Canada and comparing this to those found in this study. Because the cases from this research also took place about 10-20 years ago, a comparable study should be conducted to examine data from recent years to reflect any potential changes that may have occurred in listeriosis prevention since then. It would also be interesting to contextualize some of these findings by looking at specifically at how pregnancy-related listeriosis cases are being treated in BC. For example, when and which antibiotics are administered to cases? What is the protocol when a patient presents with pregnant or neonatal listeriosis? How are physicians coding for listeriosis symptoms in medical records? Additionally, future research would benefit from having access to a registry with all pregnancies and/or births regardless of outcome, as well as including those who gave birth outside of hospital. The ability to link mothers and neonates would also be beneficial, as neonatal listeriosis is most often an outcome of listeriosis in pregnancy. If future studies are able to access a larger sample of pregnancy-related listeriosis cases and mother-newborn linkage is possible, it would be interesting to do a cohort study to further examine the relationship between listeriosis in pregnancy and outcomes such as pregnancy loss and neonatal listeriosis.

6.6 Conclusion

The overarching aim of this thesis was to provide a comprehensive examination of the epidemiology and costs of pregnancy-related listeriosis in British Columbia, Canada over the years of 2005-2014. Generally, pregnancy-related listeriosis was rare in British Columbia during this time. A notable proportion of pregnant cases experienced stillbirth, but no deaths among maternal or neonatal cases were reported. However, all maternal cases experienced pregnancy complications and all neonatal cases experienced birth complications. Pre-term delivery among pregnant women and low birth weight among neonates were common. Furthermore, compared to pregnant women and neonates without listeriosis, healthcare utilization and costs were on average significantly higher for pregnant women and neonates with listeriosis. Future research expanding this work to look at pregnancy-related listeriosis in all of Canada would be beneficial in order to increase the sample size and generalizability of these findings. This study has highlighted important information for public health specialists, clinicians, and policy makers.

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Appendix A: Epidemiologic studies focused on pregnancy-related listeriosis that used administrative data

Table 1. Summary of epidemiologic studies focused on pregnancy-related listeriosis that used administrative data

Study	Population	Country	Years	Research Aim(s)	Study design
Abu-Raya et al., 2021	12 infants	Canada and Switzerland	2015-2018	To determine the incidence, clinical manifestations, and outcomes of listeriosis in infants <6 months	Prospective surveillance
Awofisayo et al., 2015	462 pregnancy-associated	England and Wales	1990-2010	To examine the epidemiology of pregnancy-related listeriosis cases and identify clinical and social risk factors	Retrospective review of all cases reported to Public Health England Centre for Infectious Disease Surveillance and Control
Benshushan et al., 2002	11 pregnant women	Israel	1990-1991	To investigate outcomes and severity of listeriosis in pregnant population	Retrospective chart review, case series
Charlier et al., 2022	189 infants	France	2009-2017	To analyze the features of neonatal listeriosis	Prospective cohort study
Craig et al., 2021	134 pregnant women	US	2007-2018	To evaluate and describe maternal and obstetric outcomes associated with *Listeria* infection in pregnancy	Retrospective cohort study using National Inpatient Sample
Elinav et al., 2014	166 pregnancy-associated	Israel	1998-2007	To identify and analyze pregnancy-related listeriosis cases, as well as geospatial analysis to identify possible clusters.	Retrospective cohort analyzing 3 different types of databases
Jackson et al., 2010.	128 pregnancy-associated	US	2004-2007	To describe illness and food exposures related to listeriosis in pregnancy.	Retrospective analysis of surveillance data from the Listeria Initiative

Jeffs et al., 2020	147 pregnancy-associated	New Zealand	1997-2016	To describe epidemiology of notified listeriosis and hospitalizations in pregnant women and children 1997-2016	Population-based descriptive study using notifiable disease and hospital data Case data obtained from NZ surveillance system EpiSurv and the national dataset of hospital discharge information NMDS.
Ke et al., 2022	14 pregnancy-associated	China	2013-2021	To analyze the clinical characteristics and outcomes of pregnancy-related listeriosis to better understand listeriosis in Ningbo and provide more info for formulating appropriate therapeutic and control strategies.	Retrospective study using hospital admission information and blood cultures
Kuang et al., 2022	29 pregnant women	West China	2010-2019	To summarize and analyze clinical features and pregnant outcomes.	Retrospective analysis of hospital records
Li et al., 2020	12 pregnant women	China	2013-2018	To describe the characteristics and outcomes of perinatal listeriosis.	Descriptive, retrospective review of records of lab-confirmed cases
Mylonakis et al., 2002	11 pregnant women	US	1990-2000	To examine clinical characteristics of pregnancy-related listeriosis.	Case series retrospectively using administrative records
Qu et al., 2022	40 total, 13 pregnant women, 27 newborns	Xi'an, China	2011-2020	To investigate epidemiological and clinical features of maternal-neonatal listeriosis in Xi'an	Retrospective; collected data from the hospital's electronic medical records.
Sapuan et al,. 2017	21 neonates	United Kingdom	2004-2014	To define clinical features and outcomes of neonatal listeriosis	Prospective study with cases identified through an infection surveillance network
Silk et al., 2012	762 listeriosis cases (126-preg associated; 234 nonpregnancy-associated)	US	2004-2009	To describe the epidemiology and incidence of pregnancy-associated and nonpregnancy-associated listeriosis by age and ethnicity	Descriptive analysis comparing pregnancy-associated an nonpregnancy-associated listeriosis cases

Vergnano et al., 2021	27 infants <90 days old	UK and Ireland	2017-2019	To describe the epidemiology, age at infection, clinical characteristics, and outcomes of listeria for young infants.	Prospective 2-year surveillance
Xu et al., 2022	16 pregnant women that were lab-confirmed in the hospital; 77 cases that were obtained from lit review	China	2013-2020	To describe the clinical characteristics and treatment methods of listeriosis in pregnant women	Retrospective analysis of hospital patient data as well as a literature search for neglected cases

Appendix B: Regression outputs of univariable and bivariable models for predictors that were included in final total healthcare costs models

Table 1. Confirmed maternal univariable model output for total cost regressed on Listeria

Parameter	Estimate log (95%CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept	8.66 (8.55, 8.77)	5787.76 (5166.75, 6438.17)	<.0001
Listeria	0.89 (0.63, 1.16)	2.44 (1.88, 3.19)	<.0001

Table 2. Confirmed maternal univariable model output for total cost regressed on health authority

Parameter		Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept		8.97 (8.68, 9.27)	7895.12 (5884.05, 10614.75)	<.0001
Health authority*	2	-0.20 (-0.62, 0.22)	0.82 (0.53, 1.25)	0.3507
	3	-0.09 (-0.43, 0.25)	0.91 (0.65, 1.28)	0.6077
	4 (ref)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

*There were no people in health authorities 1 and 5.

Table 3. Confirmed maternal univariable model output for total cost regressed on income quintile

Parameter		Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept		8.82 (8.52, 9.11)	6758.80 (5014.05, 9045.29)	<.0001
Income quintile	1	0.01 (-0.35, 0.37)	1.01 (0.70, 1.44)	0.9629
	2	0.15 (-0.22, 0.51)	1.16 (0.80, 1.67)	0.4237

	3 (ref)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

Table 4. Confirmed maternal univariable model output for total cost regressed on age

Parameter		Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept		8.80 (8.63, 8.97)	6640.88 (5597.07, 7863.60)	<.0001
Age	15-19	0.3539 (-0.13, 0.83)	1.42 (0.88, 2.29)	0.1495
	20-24	0.13 (-0.32, 0.57)	1.14 (0.73, 1.77)	0.5720
	25-29	0.16 (-0.18, 0.49)	1.17 (0.84, 1.63)	0.3546
	30+ (ref)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

Table 5. Confirmed maternal bivariable model output for total cost regressed on Listeria and health authority

Parameter		Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept		8.87 (8.65, 9.08)	7081.92 (5710.15, 8777.97)	<.0001
Listeria		0.93 (0.68, 1.19)	2.54 (1.97, 3.29)	
Health authority*	2	-0.30 (-0.60, 0.00)	0.74 (0.55, 0.00)	0.0490
	3	-0.26 (-0.51, -0.01)	0.77 (0.60, 0.99)	0.0391
	4 (ref)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

*There were no people in health authorities 1 and 5.

Table 6. Confirmed maternal bivariable model output for total cost regressed on Listeria and income quintile

Parameter		Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept		8.61 (8.39, 8.83)	5493.39 (4402.82, 6836.29)	<.0001
Listeria		0.89 (0.62, 1.15)	2.43 (1.86, 3.16)	<.0001
Income quintile	1	0.02 (-0.24, 0.29)	1.02 (0.79, 1.34)	0.8623
	2	0.11 (-0.16, 0.38)	1.12 (0.85, 1.46)	0.4248
	3 (ref)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

Table 7. Confirmed maternal bivariable model output for total cost regressed on Listeria and age

Parameter		Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept		8.63 (8.50, 8.76)	5610.53 (4914.77, 6374.11)	<.0001
Listeria		0.90 (0.64, 1.17)	2.47 (1.90, 3.22)	<.0001
Age	15-19	0.07 (-0.29, 0.43)	1.07 (0.74, 1.53)	0.7014
	20-24	0.26 (-0.06, 0.59)	1.30 (0.94, 1.80)	0.1136
	25-29	0.04 (-0.21, 0.29)	1.04 (0.81, 1.33)	0.7378
	30+ (ref)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

Table 8. Maternal sensitivity analysis univariable model output for total cost regressed on Listeria

Parameter	Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept	8.66 (8.57, 8.75)	5786.60 (5271.13, 6310.69)	<.0001
Listeria	0.93 (0.71, 1.15)	2.53 (2.03, 3.16)	<.0001

Table 9. Maternal sensitivity analysis univariable model output for total cost regressed on health authority

Parameter		Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept		8.96 (8.72, 9.21)	7804.85 (6124.18, 9996.60)	<.0001
Health authority*	1	0.89 (-0.15, 1.93)	2.44 (0.86, 6.89)	0.0930
	2	-0.14 (-0.49, 0.20)	0.87 (0.61, 1.22)	0.4081
	3	-0.10 (-0.39, 0.18)	0.90 (0.68, 1.19)	0.4750

	4 (ref)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

*There were no people in health authority 5.

Table 10. Maternal sensitivity analysis univariable model output for total cost regressed on income quintile

Parameter		Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept		8.82 (8.53, 9.12)	6798.79 (5064.44, 9136.20)	<.0001
Income quintile	1	-0.02 (-0.36, 0.32)	0.98 (0.70, 1.38)	0.9013
	2	0.19 (-0.15, 0.54)	1.21 (0.86, 1.72)	0.2730
	3 (ref)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

Table 11. Maternal sensitivity analysis univariable model output for total cost regressed on age

Parameter		Estimate log (95% CI)	Estimate (exponent-iated)	Pr > ChiSq
Intercept		8.82 (8.67, 8.97)	6772.33 (5825.50, 7863.60)	<.0001
Age	15-19	0.34 (-0.14, 0.81)	1.40 (0.87, 2.25)	0.1664
	20-24	0.37 (-0.02, 0.76)	1.45 (0.98, 2.14)	0.0612
	25-29	0.03 (-0.23, 0.28)	1.03 (0.79, 1.32)	0.8469
	30+ (ref)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

Table 12. Maternal sensitivity analysis bivariable model output for total cost regressed on Listeria and health authority

Parameter		Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept		8.88 (8.71, 9.06)	7218.48 (6063.24, 8604.15)	<.0001
Listeria		0.96 (0.74, 1.18)	2.61 (2.10, 3.25)	<.0001

Health authority*	1	0.01 (-0.75, 0.77)	1.01 (0.47, 2.16)	0.9794
	2	-0.30 (-0.54, -0.06)	0.74 (0.58, 0.94)	0.0136
	3	-0.30 (-0.50, -0.09)	0.74 (0.61, 0.91)	0.0041
	4 (ref)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

*There were no people in health authority 5.

Table 13. Maternal sensitivity analysis bivariable model output for total cost regressed on Listeria and income quintile

Parameter		**Estimate log (95% CI)**	**Estimate exponentiated (95% CI)**	**Pr > ChiSq**
Intercept		8.61 (8.39, 8.83)	5499.98 (4402.81, 6836.29)	<.0001
Listeria		0.91 (0.69, 1.14)	2.50 (1.99, 3.13)	<.0001
Income quintile	1	0.04 (-0.21, 0.29)	1.04 (0.81, 1.33)	0.7553
	2	0.09 (-0.17, 0.34)	1.09 (0.84, 1.40)	0.4927
	3 (ref)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

Table 14. Maternal sensitivity analysis bivariable model output for total cost regressed on Listeria and age

Parameter		**Estimate log (95% CI)**	**Estimate exponentiated (95% CI)**	**Pr > ChiSq**
Intercept		8.66 (8.55, 8.77)	5753.71 (5166.75, 6438.17)	<.0001
Listeria		0.91 (0.69, 1.13)	2.49 (1.99, 3.10)	<.0001
Age	15-19	0.04 (-0.31, 0.39)	1.04 (0.73, 1.48)	0.8161
	20-24	0.21 (-0.08, 0.05)	1.23 (0.92, 1.05)	0.1502
	25-29	-0.06 (-0.25, 0.13)	0.94 (0.78, 1.14)	0.5238
	30+ (ref)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

Table 15. Confirmed neonatal univariable model output for total cost regressed on Listeria

Parameter	**Estimate log (95% CI)**	**Estimate exponentiated (95% CI)**	**Pr > ChiSq**

Intercept	7.35 (7.11, 7.60)	1560.25 (1224.15, 1998.20)	<.0001
Listeria	3.18 (2.58, 3.77)	23.97 (13.19, 43.38)	<.0001

Table 16. Confirmed neonatal univariable model output for total cost regressed on sex

Parameter	Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept	9.38 (8.61, 10.14)	11849.01 (5486.25, 25336.47)	<.0001
Sex	*	*	Not significant

*Number of categories and/or details of categories cannot be shown due to suppression of small cell sizes.

Table 17. Confirmed neonatal univariable model output for total cost regressed on income quintile

Parameter	Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept	8.49 (7.50, 9.48)	4865.87 (1808.04, 13095.19)	<.0001
Income quintile*	*	*	At least one category was significant

*Number of categories and/or details of categories cannot be shown due to suppression of small cell sizes.

Table 18. Confirmed neonatal univariable model output for total cost regressed on congenital abnormality

Parameter	Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept	8.22 (7.79, 8.65)	3718.59 (2416.32, 5710.15)	<.0001
Congenital abnormality	2.42 (1.05, 3.79)	11.24 (2.86, 44.26)	0.0005

Table 19. Confirmed neonatal bivariable model output for total cost regressed on Listeria and sex

Parameter	Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept	7.35 (6.95, 7.74)	1557.44 (1043.15, 2298.47)	<.0001
Listeria	3.18 (2.56, 3.79)	24.05 (12.93, 44.26)	<.0001
Sex	*	*	*

*Number of categories and/or details of categories cannot be shown due to suppression of small cell sizes.

Table 20. Confirmed neonatal bivariable model output for total cost regressed on Listeria and income quintile

Parameter	Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept	7.09 (6.62, 7.56)	1206.04 (749.94, 1919.84)	<.0001
Listeria	2.99 (2.39, 3.58)	19.91 (10.91, 35.87)	<.0001
Income quintile	*	*	None of the categories were significant

*Number of categories and/or details of categories cannot be shown due to suppression of small cell sizes.

Table 21. Confirmed neonatal bivariable model output for total cost regressed on Listeria and congenital abnormality

Parameter	Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept	7.29 (7.07, 7.52)	1476.31 (1176.15, 1844.57)	<.0001
Listeria	2.73 (2.10, 3.36)	15.37 (8.17, 28.79)	<.0001
Congenital abnormality	0.91 (0.13, 1.70)	2.51 (1.14, 5.47)	0.0212

Table 22. Neonatal sensitivity analysis univariable model output for total cost regressed on Listeria

Parameter	Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq

Intercept	8.75 (8.29, 9.21)	7115.28 (3983.83, 9996.60)	<.0001
Listeria	1.6772 (0.55, 2.79)	5.35 (1.73, 16.28)	0.0034

Table 23. Neonatal sensitivity analysis univariable model output for total cost regressed on sex

Parameter		**Estimate log (95% CI)**	**Estimate exponentiated (95% CI)**	**Pr > ChiSq**
Intercept		9.65 (9.08, 10.23)	15521.79 (8777.97, 27722.51)	<.0001
Sex	F	-1.20 (-2.08, -0.32)	0.30 (0.12, 0.76)	0.0070
	M	0.00 (0.00, 0.00)	(0.00, 0.00)	

Table 24. Neonatal sensitivity analysis univariable model output for total cost regressed on income quintile

Parameter		**Estimate log (95% CI)**	**Estimate exponentiated (95% CI)**	**Pr > ChiSq**
Intercept		8.48 (7.38, 9.59)	4817.44 (1603.59, 14617.87)	<.0001
Income quintile	1	1.11 (-0.16, 2.38)	3.03 (0.85, 10.80)	0.0884
	2	-0.50 (-1.86, 0.84)	0.60 (0.16, 2.34)	0.4641
	3	1.49 (-0.07, 3.05)	4.48 (0.93, 21.24)	0.0616
	5	0.0000 (0.00, 0.00)	0.00 (0.00, 0.00)	-

Table 25. Neonatal sensitivity analysis univariable model output for total cost regressed on congenital abnormality

Parameter	**Estimate log (95% CI)**	**Estimate exponentiated (95% CI)**	**Pr > ChiSq**
Intercept	8.3907 (8.0172, 8.7642)	4405.90 (3010.92, 6374.11)	<.0001
Congenital abnormality	2.8092 (1.5988, 4.0195)	16.60 (4.90, 55.15)	<.0001

Table 26. Neonatal sensitivity analysis bivariable model output for total cost regressed on Listeria and sex

Parameter		Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept		9.12 (8.61, 9.63)	9136.20 (5486.25, 15214.43)	<.0001
Listeria		1.98 (0.95, 3.01)	7.24 (2.58, 20.29)	0.0002
Sex	F	-1.59 (-2.36, -0.82)	0.20 (0.09, 0.44)	<.0001
	M	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

Table 27. Neonatal sensitivity analysis bivariable model output for total cost regressed on Listeria and income quintile

Parameter		Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept		7.21 (6.24, 8.18)	1352.89 (512.86, 3568.85)	<.0001
Listeria		2.41 (1.32, 3.50)	11.13 (3.74, 33.12)	<.0001
Income quintile	1	2.10 (1.01, 3.20)	8.17 (2.75, 24.53)	0.0002
	2	0.00 (-1.14, 1.15)	1.00 (0.32, 3.16)	0.9953
	3	0.81 (-0.54, 2.18)	2.25 (0.58, 8.85)	0.2405
	5	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-

Table 28. Neonatal sensitivity analysis bivariable model output for total cost regressed on Listeria and congenital abnormality

Parameter	Estimate log (95% CI)	Estimate exponentiated (95% CI)	Pr > ChiSq
Intercept	7.41 (7.16, 7.67)	1660.54 (1285.62, 2143.08)	<.0001
Listeria	2.33 (1.73, 2.93)	10.32 (5.64, 18.73)	<.0001
Congenital abnormality	3.31 (2.55, 4.06)	27.42 (12.81, 58.56)	<.0001