Incidence, Distribution, and Risk Factors of Five Major Enteric Diseases Commonly Transmitted by Food in Ontario, Canada

by

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A thesis

presented to the University of Waterloo

in fulfillment of the

thesis requirement for the degree of

Doctor of Philosophy

in

Health Studies and Gerontology

Waterloo, Ontario, Canada, 2022

EXAMINING COMMITTEE MEMBERSHIP

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AUTHOR'S DECLARATION

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

I understand that my thesis may be made electronically available to the public.

STATEMENT OF CONTRIBUTIONS

The three manuscripts that are included in the thesis, including those that have been published or prepared for publication, are the work of Patience I. John, in collaboration with her co-authors and committee members. Exceptions to sole authorship include:

Chapter 2: John P, Varga C, Cooke M, Majowicz SE. Incidence, demographic, and seasonal risk factors of infections caused by five major enteric pathogens, Ontario, Canada, 2010-2017. *Foodborne Pathogens and Disease* 2022 Jan 19 doi: 10.1089/fpd.2021.0034. Online ahead of print.

Chapter 3: John PI, Varga C, Cooke M, Majowicz SE. Temporal, spatial, and space-time distribution of infections caused by five major enteric pathogens, Ontario, Canada, 2010-2017. Prepared for submission to *Foodborne Pathogens and Disease*.

Chapter 4: John PI, Varga C, Cooke M, Majowicz SE. Socioeconomic Determinants of *Campylobacter* and Non-Typhoidal *Salmonella* infections in Ontario, Canada, 2015-2017: An Ecological Study. Prepared for submission to *Epidemiology & Infection*.

As the lead author of these three manuscripts, I was responsible for the conceptualization of the studies; for obtaining, organizing, and analyzing the data; and for drafting the manuscripts. Throughout the process, my co-authors provided guidance on conceptualizing the studies, the methodologies, data analysis, and the review and editing of the manuscripts. Dr. Varga provided training on the use of the various statistical software used in the studies, on data organization and analysis, and created the choropleth maps for the spatial, space-time, and disease clustering analyses.

ABSTRACT

Enteric diseases are a major public health concern in both developing and developed countries, including Canada. Studies examining enteric disease distributions in different parts of Canada show temporal, regional, and socio-demographic differences in disease incidence rates. However, research studies on the distributions and risk factors for *Campylobacter, Yersinia,* and *Listeria* infections have not been performed in Ontario. Therefore, the goal of this thesis was to investigate the distributions of major enteric diseases in humans commonly transmitted by food, in Ontario, Canada (2010-2017). The specific objectives were to: estimate the incidence, seasonal, and demographic risk factors of *Campylobacter spp*., non-typhoidal *Salmonella spp*., Verotoxin-producing *Escherichia coli* (VTEC), *Yersinia spp*., and *Listeria monocytogenes* reported infections; examine temporal, spatial, and space-time clustering of these reported infections; and identify area-level socioeconomic risk factors for reported infections caused by *Campylobacter spp*. and non-typhoidal *Salmonella spp.,* the two most commonly reported enteric bacterial infections in Ontario.

De-identified, laboratory-confirmed disease surveillance data on cases of *Campylobacter spp*., non-typhoidal *Salmonella spp*., VTEC, *Yersinia spp*., and *Listeria*, reported between 2010 and 2017 inclusive, in Ontario, Canada (population ~13,500,000) were analyzed. Incidence rates were calculated at the public health unit (PHU) level and multivariable Poisson and negative binomial regression models were used to estimate incidence rate ratios (IRRs) for seasonal and demographic risk factors. *Campylobacter* and *Salmonella* infections had the highest incidence rates while *Listeria* infections had the

lowest. The rates of infections caused by all five bacteria were highest in the summer. Rates of *Campylobacter*, *Salmonella*, *Yersinia*, and VTEC infections were highest in children 0–4 years old, while *Listeria* rates peaked in adults 60 years and older. Age-specific rates of *Campylobacter*, *Salmonella*, and VTEC infections also varied by sex, e.g., *Campylobacter* and *Salmonella* rates in youths (10-19 years) were higher in males than in females.

Retrospective Poisson scan statistic in SaTScan was used to detect high-rate infection clusters in Ontario's 35 PHUs, and space and space-time clusters were visualized using choropleth maps. *Campylobacter*, *Salmonella*, VTEC, and *Listeria* tended to cluster in the spring/summer, sometimes extending into fall, while *Yersinia* showed a less clear temporal pattern. *Campylobacter*, *Salmonella*, and VTEC infections clustered spatially in the southwestern and central-western regions of Ontario, and *Yersinia* and *Listeria* in the central-eastern region. Significant *Salmonella*, VTEC, and *Listeria* infection clusters contained high proportions of cases linked to disease outbreaks.

The number of laboratory-confirmed cases of *Campylobacter* and *Salmonella* infections, reported between 2015 and 2017 inclusive, was aggregated at the forward sortation area (FSA) level, and univariable and multivariable negative binomial regression were used to examine the association between the number of cases and FSA-level socioeconomic factors (median household income; percent of the population with bachelor degree or higher; unemployment rate; and the percent visible minorities, Aboriginals (as defined by Statistics Canada), total immigrants, recent immigrants, and lone-parent families), adjusting for the population of the FSA from the 2016 Census. *Campylobacter* infection rates were significantly lower with an increase in median household income, unemployment rate,

percent visible minorities, Aboriginals, and lone-parent families; and significantly higher with an increase in percent population with bachelor degree or higher, and total immigrants. *Salmonella* infection rates were significantly lower with an increase in percent visible minorities and Aboriginals; and significantly higher with an increase in median household income and percent total immigrants.

This thesis demonstrates the incidence rates distribution and clustering of major enteric infections, as well as their seasonal, demographic, and socioeconomic risk factors, across Ontario, especially for *Campylobacter, Yersinia,* and *Listeria* that have not been previously studied in Ontario. Future research may investigate these risk factors and the mechanisms through which they affect disease rates in different communities.

ACKNOWLEDGEMENTS

I am extremely grateful to my supervisor, **Dr. Shannon Majowicz**, for the opportunity to enroll in the PhD program in public health, at the University of Waterloo. She did not hesitate to accept me as her student when I contacted her. I thank her for helping me develop my research, and for her guidance and support throughout my journey in the doctorate degree program. I thank her for her constant prompting and for her patience with me when I lagged behind. Special thanks to her for the constructive critiques of my writings. She has made me a better writer of scientific literature.

I would like to thank my incredible committee members for helping me develop the manuscripts included in this thesis, and for their reviews and feedback. I was fortunate to have them on my committee. I sincerely thank **Dr. Csaba Varga** for everything, for helping me develop my research objectives, for training me on Stata and SaTScan software, and Poisson and negative binomial regression analyses, for his mentorship, support, encouragement, and being there for me anytime of the day, throughout the course of my thesis. I thank him for assisting me with my data analyses, for answering all my questions, and for making time for me whenever I needed it. He literally took my hands and guided me through the paths I needed to take, to successfully complete my thesis. I thank **Dr. Martin Cooke**, for his assistance in developing the research questions, for taking the time to review my research proposal and the manuscripts included in this thesis, and for the constructive feedback. I thank him for this support, guidance, and encouragement throughout the process of my thesis.

I thank **Dr. Scott Leatherdale**, the instructor for one of my courses, for lifting up my spirit when he said to me at one time, *"...but you have not given up"*. It was one of my low moments, and those words resonated with me and gave me more hope to keep pushing on. Many thanks to the **Administrative staff**, including the **Information Systems & Technology staff**, of the School of Public Health Sciences, for their support.

I would like to thank **Public Health Ontario** for providing me with the surveillance case data used for the studies. I thank **Jonathan Morgan**, a former staff member of the Geospatial Centre, University of Waterloo, for providing the census population and socioeconomic data, and for being there to answer all my questions.

I thank my family members, friends, and colleagues, for all the support and encouragement I receive from them throughout my program. Special thanks to my husband, **Sunday John**, for encouraging me to enroll in the program, for all the understanding and sacrifices, assistance, constant support, and his belief in me. He was always by my side to lift me up when I seemed to be giving up. I thank him for patiently putting up with and listening to my "complaints", and for always reminding me of the reasons to complete the program. Many thanks to my sister, **Florence Igue**, my brothers, **Odia Igue** and **Edehi Igue**, and to all my friends, including late **Sister Bridgid Nwosu**, for their prayers, support, and encouragement. I would not have done this without you all. I love you all.

Finally, and most of all, I thank **God** and **Our Blessed Mother, Mary**, for the opportunity, grace, and strength, to begin and end this journey, and for providing me with good health, and all the resources I needed and more.

DEDICATION

To Mary, Our Lady, for her intercession.

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LIST OF ABBREVIATIONS

CI	Confidence Interval
DALYs	Disability-Adjusted Life Years
ETEC	Enterotoxigenic Escherichia coli
FBD	Foodborne Disease
FDA	Food and Drug Administration
FSA	Forward Sortation Area
GIS	Geographic Information System
HALYs	Health-Adjusted Life Years
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
iPHIS	Integrated Public Health Information System
IR	Incidence Rate
IRR	Incidence Rate Ratio
MOHLTC	Ministry of Health and Long-Term Care
OAHPP	Ontario Agency for Health Protection and Promotion
OMAFRA	Ontario Ministry of Agriculture, Food and Rural Affairs
ON	Ontario
ORE	Office of Research Ethics
PHO	Public Health Ontario

PHU	Public Health Unit
QALYs	Quality-Adjusted Life Years
RR	Relative Risk
RTE	Ready-to-eat
SDH	Social Determinant of Health
SES	Socioeconomic Status
VTEC	Vero toxin-producing Escherichia coli
WHO	World Health Organization

Chapter 1
Introduction and Literature Review

Introduction

Foodborne diseases (FBDs) remain a significant and increasing public health problem around the world (Kirk et al, 2015; McLinden et al, 2014; Rocourt et al, 2003; World Health Organization, WHO, 2015). In 2010, 600 million cases of FBDs and 420,000 FBD-related deaths were estimated to occur worldwide, resulting in 33 million disability-adjusted life years (DALYs, WHO, 2015). An estimated 47.8 million cases of FBDs (about 1 in 6 people) occur annually in the United States (U.S., Scallan et al, 2011a; Scallan et al, 2011b). This estimate is slightly higher than the Canadian annual estimate of approximately four million domestically-acquired cases (about 1 in 8 people), 11,600 hospitalizations and 238 deaths (Thomas et al, 2013; Thomas et al, 2015).

FBDs consist of a broad range of illnesses, amongst which enteric disease, also known as acute gastrointestinal (AGI) disease, is the most frequent clinical condition, with symptoms of diarrhea, nausea, abdominal pain, fever, headaches and even paralysis (Lee & Middleton, 2006; Rocourt et al, 2003; Walsh & Fanning, 2008). These illnesses are usually mild and self-limiting, requiring no medical treatment (Rocourt, et al, 2003). However, more serious illnesses requiring hospitalization, or resulting in long-term sequelae or even deaths have been reported (Lindsay, 1997; Moorin et al, 2010; Ruzante et al, 2011; Walsh & Fanning, 2008). Enteric infections affect all persons, but the occurrence and severity of the infection is much higher in vulnerable population such as the elderly, pregnant women, immune-compromised persons and children under five years of age (Barkley et al, 2016; Black et al, 2010; Kirk et al, 2015; Majowicz et al, 2007; WHO, 2015). These groups of

people are relatively less able to resist or recover from diseases due to their inherent vulnerability, aggravated by other factors such as unhealthy food practices, and the socioeconomic circumstances in which they live (Jackson & Meah, 2018).

Most enteric diseases result from the consumption of food contaminated with a wide range of pathogens, including bacteria and their toxins, viruses, parasites, and prions (Food and Drug Administration [FDA], 2012; Newell et al, 2010; WHO, 2015;). In Canada, norovirus, *Clostridium perfringens*, *Campylobacter spp.*, non-typhoidal *Salmonella spp.*, pathogenic *Escherichia coli*, and *Listeria monocytogenes*, are amongst the major pathogens of public health importance (Thomas et al, 2013; Thomas et al, 2015). Many of these pathogens, such as *E. coli* and *Salmonella*, occur naturally in the intestines of humans and animals as part of their normal intestinal flora (Aslam et al, 2014; Logue et al, 2017; National Disease Surveillance Centre [NDSC] 2004), while others such as *Clostridium spp.* and *Bacillus spp.* can be found naturally in the soil (Alam et al, 2015).

Enteric disease pathogens are transmitted to humans through the oral-faecal route via any vehicle in contact with animal or human faeces (NDSC, 2004; Newell et al, 2010; Todd et al, 2007a); however, food is the primary transmission vehicle for many of these pathogens (Butler et al, 2015; Medeiros et al, 2001; Pires et al, 2009). A variety of the pathogens, including antibiotic resistant ones, are commonly isolated from different food sources (for example, meat, poultry, and fresh produce), including retail foods (Agunos et al, 2013; Allen et al, 2013; Aslam et al, 2014; Comery et al, 2013; Crago et al, 2012; Weese et al, 2009). The reason for this is that food can contain the nutritional and environmental requirements,

such as temperature, moisture, oxygen, and pH that are necessary for pathogens survival and growth (Farber et al, 2014; University of Rhode Island, URI, 2018).

Food contamination can occur at any stage across the food production chain, from farm to table (Alam et al, 2015; Kirk et al, 2015; Lukacsovics et al, 2014; Nascimento et al, 2018; Rocourt et al, 2003; Zbrun et al, 2013); however, private homes and food service facilities are amongst the most significant risk settings for contamination and FBD outbreaks (Broner et al, 2010; Lee & Middleton, 2003; Todd et al, 2007; Varga et al, 2015; Vrbova et al, 2012). The risk factors traditionally investigated for the transmission of FBDs in these and various other settings are predominantly individual-level factors such as improper food handling practices, types of foods consumed, and consumption behaviors (Badowski et al, 2011; Carrasco et al, 2012; Green et al, 2006a; Lukacsovics et al, 2014; Medeiros et al, 2001; Nesbitt et al, 2009; Sewell & Farber, 2001; Todd et al, 2007a). However, community-level factors such as socioeconomic status, a significant component of the social determinants of health (SDH), have been shown to influence a wide range of health outcomes, including enteric infections, in both developing and developed countries (Marmot, 2005; Shavers, 2007; Simonsen et al, 2008; WHO, 2010).

Socioeconomic status (SES) is the status of individuals, families, households, census tracts, or other aggregates, regarding their capacity to create or consume goods that are valued in the society (Miech & Hauser, 2001). When investigating its relationship with health, SES is measured using variables such as income, education, occupation, or deprivation indices that combine these variables (Chan et al, 2015; Demissie et al, 2000; Denny & Davidson, 2012; Gillespie et al, 2010; Ontario Agency for Health Protection and

Promotion[OAHPP], 2013). Although low SES has been demonstrated to be a predictor of poorer health outcomes and higher disease burden for a wide range of illnesses all over the world, including Canada (Carrie & Kozyrsky, 2006; Disano et al, 2010; Majowicz et al, 2007; Pardhan-Ali et al, 2013; Varga et al, 2013a), the direction and strength of association between SES and enteric diseases vary considerably with the pathogen characteristics, different individual-level factors, as well as community-level factors such as socioeconomic, and geographical factors (Newman et al, 2015, Pearl et al, 2009; Simonsen et al, 2008; Varga et al, 2013a). Therefore, the effect of SES on enteric diseases is yet to be fully understood.

Canada is a country with a high standard of living, and has a system of universal access to healthcare, yet health inequality remains a major concern (Bryant et al, 2011; Raphael et al, 2008). The overall goal of this thesis, therefore, was to investigate the distributions and risk factors of major enteric diseases in humans commonly transmitted by food, in Ontario, Canada (2010-2017). Knowledge of these risk factors can be used to inform public health interventions, especially concerning vulnerable groups in the population (Barkley et al, 2016). This knowledge becomes even more important as inequity in food access, resulting from increase in average life expectancy and food prices, becomes vital in determining the incidences of foodborne diseases in the future (Gillespie et al, 2010).

Literature Review

Foodborne Diseases

FDBs are acquired through the consumption of food contaminated with pathogenic microorganisms (foodborne infection), or their toxins (foodborne intoxication), and result in substantial morbidity and mortality worldwide (Kirk et al, 2015; Lindsay, 1997; WHO, 2015). The occurrence of FBDs is dependent upon the presence of pathogen in food; the survival and multiplication of the pathogen to reach an infective dose (the quantity of pathogen required to cause an infection), or the production of toxins in the food before it is ingested; and individual's susceptibility to the pathogen level ingested (Bryan, 1988). Therefore, the infective dose varies by pathogen (FDA, 2012), and ranges, for example, from as low as one cell as in the case of non-typhoidal *Salmonella*, from 10 to 200 cells as in the case of *E. coli* O157:H7 and *Shigella spp.*, several thousand cells as in the case of *Yersinia enterocolitica*; and from 10 million to 10 billion as in the case of enterotoxigenic *E. coli* (ETEC, FDA, 2012).

Most FBD-related deaths occur in developing countries, and children, the elderly, pregnant women, and persons with compromised immune systems are at greatest risk for developing serious complications resulting from FBDs; however, FBDs also occur in developed countries such as Canada and the U.S., and can affect all persons (Black et al, 2010; Kirk et al, 2015; Newell et al, 2010; Stein et al, 2007; Scallan et al, 2011a; Scallan et al, 2011b; Thomas et al, 2013; Thomas et al, 2015; WHO, 2015).

FBDs consist of a broad range of illnesses, amongst which enteric disease is the most frequent clinical condition, with symptoms of abdominal pain and cramps, diarrhea, nausea,

vomiting, fever, headaches and even paralysis (Lee & Middleton, 2006; Rocourt et al, 2003; Walsh & Fanning, 2008). These illnesses are usually mild and self-limiting, requiring no medical treatment (Beatty et al, 2009; Lee & Middleton, 2006; Rocourt et al, 2003; Walsh & Fanning, 2008). However, more serious illness requiring hospitalization, or resulting in long-term sequelae or even death have been reported (Lindsay, 1997; Moorin et al, 2010; Ruzante et al, 2011; Walsh & Fanning, 2008). Some of the chronic sequelae are renal disease, ankylosing spondylitis, cardiac and nutritional disorders, Guillain-Barré syndrome, haemolytic-uraemic syndrome, reactive arthropathies, and Reiter's syndrome (Lee & Middleton, 2003; Kirk et al, 2015; Lindsay, 1997; Moorin et al, 2010; Ruzante et al, 2011; Walsh & Fanning, 2008).

Burden of Foodborne Diseases

WHO defines disease burden as "the incidence and prevalence of morbidity, disability, and mortality associated with acute and chronic manifestations of diseases" (WHO, 2007). Indicators of disease burden, as measured by morbidity, mortality, and financial cost, are used to estimate the annual number of illnesses, hospitalizations, and deaths (WHO, 2015; Scallan et al, 2011a; Scallan et al, 2011b; Thomas et al, 2013; Thomas et al, 2015); cost of illness, for example, costs from physician visit, hospitalization, and loss in wages from illness (Majowicz et al, 2006; McLinden et al, 2014; Ruzante et al, 2010); and loss of health-related quality of life as measured by Health-Adjusted Life Years (HALYs) metrics, including metrics such as Quality-Adjusted Life Years (QALYs) and Disability-Adjusted Life Years (DALYs, Hoffmann et al, 2012; Ruzante et al, 2010; WHO, 2015).

The disease burden measures commonly used amongst epidemiologists are prevalence and incidence. The main difference between the two measures is the time of disease onset. Prevalence, expressed as a proportion, measures existing cases of disease at a specific point in time, and reflects the burden of diseases or other health indicators in a population (Noordzij et al, 2010). Incidence, on the other hand, is the number of new cases of diseases in a population within a given time period and thus reflects recent trends in disease epidemiology; incidence assumes that all cases are free of the health outcome of interest at the start of the study (Noorddzij et al, 2010). Incidence can be expressed as a risk (the probability that an individual or a group will develop a disease over a specified follow-up period), or as a rate (the number of new cases in a population at risk per person-time, Dohoo et al, 2012).

Data used to estimate the burden of FBDs typically come from sources such as cross-sectional or cohort studies, reportable disease and syndrome surveillance, or survey data (Dohoo et al, 2012; Haagsma et al, 2013; Majowicz et al, 2005; Scallan et al, 2011a; Scallan et al, 2011b; Thomas et al, 2013; Thomas et al, 2015; Varga et al, 2013a; Vrbova et al, 2012; WHO, 2015). These estimates show that FBDs assert considerable burden and economic costs at both individual and societal levels in different countries (Havelaar et al, 2012; Hoffman et al, 2012; Lake et al, 2010; Mangen et al, 2015; McLinden et al, 2014; McPherson et al, 2011; Rocourt et al, 2003; Scallan et al, 2011a; Scallan et al, 2011b; Thomas et al, 2013; Thomas et al, 2015). For example, in the U.S., an estimated 47.8 million cases of FBDs (1 in 6 persons) occur annually; of these cases, 9.4 million with 55,961 hospitalizations and 1,351 deaths are caused by 31 major pathogens, while the remaining 38.4 million cases

with 71,878 hospitalizations, and 1,686 deaths are caused by unspecified agents (Scallan et al, 2011a; Scallan et al, 2011b).

In Canada and in Ontario, FBDs also present a significant burden (Drudge et al, 2019; Thomas et al, 2017; Turgeon et al, 2017). Approximately four million domestically-acquired cases (1 in 8 Canadians) of FBD are estimated to occur annually in Canada, with about 11,600 hospitalizations and 238 deaths. Of the total number of cases, 1.6 million are caused by 30 known pathogens, with norovirus, *C. perfringens*, *Campylobacter spp*., and non-typhoidal *Salmonella spp*. causing 90% of the cases; while 2.4 million cases are caused by unspecified agents (Thomas et al, 2013; Thomas et al, 2015). Estimates in other regions in Canada show that foodborne enteric diseases also presents a significant economic impact. In British Columbia, the estimate was a mean annual cost of CAN$128.61 per capita, and a mean annual cost of CAN$113.70 per case, with an overall economic burden of CAN$514.2 million (Henson et al, 2008; Henson et al, 2011). The estimated cost for the year 2001 in Hamilton, Ontario, by Majowicz and colleagues was CAN$56 million, CAN$115 per capita, and CAN$91 per case. According to the researchers, the estimated annual cost of enteric diseases in Canada would be CAN$3.7 billion if the cost obtained were generalized to the whole of Canada (Majowicz et al, 2006; Majowicz et al, 2011).

Disease burden indicators such as incidence rate help to examine how disease occurrence may differ by FBD pathogens, amongst different groups over time, or in different geographical regions, and used to determine the effects of, and factors associated with, diseases or other health outcomes (Dohoo et al, 2012; Naumova et al, 2000; Varga et al, 2015). For example, in New Brunswick, Canada, Valcour et al (2016) reported a higher

incidence rate of *Giardia spp*. infections in the spring compared to the other seasons, while the incidence of *E. coli* O157 and *Campylobacter* peaked in the summer. In Ontario, Canada, Varga et al (2015) also demonstrated variations in incidence rates of *Salmonella* Enteridiidis infections by phage types, month, and geographical regions.

Diarrheal disease agents, especially norovirus, non-typhoidal *Salmonella spp.*, *Campylobacter spp., E. coli, Vibrio cholerae* and *Shigella spp*, result in 54% of the global economic burden. As well, forty percent (40%) of the FBD burden worldwide is amongst children <5 years of age (WHO, 2015). Therefore, estimates of FBD burden are important in identifying populations at risk, and to prioritize health research, plan public health preventive actions, assess the performance of healthcare systems, and to guide public health policies on improved food safety in different populations (Dohoo et al, 2012; Hoffmann et al, 2012; Kirk et al, 2015; McLinden et al, 2014).

Microbial Agents of Foodborne Diseases

Microbial agents of FBDs include bacteria and their toxins, viruses, parasites, and prions. These pathogens cause infections by invading and replicating within the intestinal lining or other tissues, or by releasing toxins in the intestines (FDA, 2012; Logue et al, 2017; Newell et al, 2010; Scallan et al, 2011a; Thomas et al, 2013; WHO, 2015). Enteric bacteria and viruses are responsible for the majority of FBDs (Farber et al, 2014), and in most countries, are the most investigated and monitored causes of enteric infections (Newell et al, 2010).

According to the WHO, the bacteria that resulted in the largest number of FBD cases worldwide in 2010 were *Campylobacter spp.*, enterotoxigenic *E. coli* (ETEC), *Salmonella*

spp., and *Shigella spp*. (Kirk et al, 2015). In the U.S., norovirus, *Salmonella spp*., *C. perfringens*, and *Campylobacter spp.* are amongst the leading causes of FBDs, while *Salmonella spp.* is the leading cause of death, followed by *Toxoplamsa gondii, L. monocytogenes,* norovirus, and *Clostridium botulinum* (Scallan et al, 2011a). Amongst the 30 specific pathogens known to cause FBDs in Canada (Thomas et al, 2013; Thomas & Murray, 2014), the pathogens of significant public health importance include the bacteria, *C. perfringens*, *Campylobacter spp*., non-typhoidal *Salmonella spp*., *Bacillus cereus*, *Y. enterocolitica*, *Staphylococcus aureus*, *E. coli*, and *L. monocytogenes*; the viruses, norovirus, sapovirus, rotavirus, adenovirus, astrovirus, and Hepatitis A virus; and the parasites, *T. gondii*, *Giardia spp*., *Cyclospora cayetanensis*, and *Cryptosporidium spp*. (Thomas et al, 2013; Thomas et al, 2015). Norovirus, *C. perfringens*, *Campylobacter*, and *Salmonella* cause the highest number of domestically-acquired FBDs (Thomas et al, 2013), while *L. monocytogenes* causes the highest number of deaths, followed by *Salmonella*, Verotoxin-producing *Escherichia coli* (VTEC), and *Campylobacter* (Thomas et al, 2015).

It is worthy to mention that although listeriosis, the disease caused by *Listeria spp*., is relatively rare, it has a relatively high fatality rate (Barton et al, 2011; Choi et al, 2018). A fatality rate as high as 21% was reported in the U.S. Centers for Disease Control and Prevention (CDC, 2013). An outbreak that occurred in South Africa between January 2017 and May 2018 resulted in 1,034 cases and 208 deaths (case fatality rate of 20%); 435 (42%) of the cases and 91 (43.8%) of the fatalities occurred in neonates (less than four weeks old, Department of Health, South Africa, 2018). These occurrences underscore *Listeria spp.* as a foodborne pathogen of significant public health importance. Multiple outbreaks of listeriosis

have also occurred in Ontario and in Canada (Currie et al, 2015; Hanson et al, 2019; Knabel et al, 2012; McIntyre et al, 2015). Particularly, the outbreaks that occurred in Canada between June and November 2008 resulted in 57 cases and 24 (42%) deaths (Currie et al, 2015). These outbreaks were linked to different food items, such as cheese, chocolate milk, ready-to-eat (RTE) meats, as the risk factors for these outbreaks, and traced back to the food manufacturing facilities or production process as the major sources of contamination.

Several other FBD pathogens have been implicated in various outbreaks in U.S., and in Canada and Ontario, with many of these outbreaks linked to different foods and animal contact as sources (Faulder et al, 2017; Greig et al, 2007; Luna et al, 2018; Ravel et al, 2009; Taylor et al, 2018; Vrbova et al, 2012; Vrbova et al, 2018). However, FBD pathogens have different health impacts, depending on pathogens virulence factors and various host attributes relating to vulnerability and risk of disease exposure to diseases. Consequently, disease occurrence is usually associated with specific host characteristics and measured for specific diseases or pathogens.

Sources of Transmission of Foodborne Pathogens

Foodborne pathogens can be found in different natural habitats (FDA, 2012). Many of these pathogens are zoonotic in nature, often present in the gastrointestinal tracts of humans, domestic and wild animals, and birds, as commensal bacteria of normal intestinal flora (NDSC, 2004; Nguyen-The, 2012; Ribas et al, 2016). For example, *E. coli* are commonly found as commensals in the gastrointestinal tracts of humans and animals (Aslam et al, 2014; Logue et al, 2017; NDSC, 2004), and most strains are non-pathogenic (Logue et al, 2017; FDA, 2012). *Salmonella spp.* colonize the intestines of poultry (Newell et al, 2010; Ribas et

al, 2016), while *Campylobacter spp*. are found in a range of animal hosts including poultry as the primary source, lamb, cattle, and pigs (Ravel et al, 2017; Sahin et al, 2015). These pathogens are shed into the environment through faeces, leading to the contamination of meat, other food products, and the environment (Cummings et al, 2018; FDA, 2012; Newell et al, 2010). However, some pathogens such as *C. botulinum, C. perfringens,* and *B. cereus* can be found naturally in the soil, while *L. monocytogenes* can be found in decaying vegetables (Alam et al, 2015).

Foodborne pathogens are transmitted to humans through the faecal-oral route (NDSC, 2004; Newell et al, 2010; Todd et al, 2007a), from the consumption of contaminated food or water, contaminated soil, contaminated environment, contact with birds and animals (domestic, farm, and wild animals) that actively shed the pathogens, and direct contact with infected persons (Agunos et al, 2014; Alam et al, 2015; Pires et al, 2009; Rangel et al, 2005; Vrbova et al, 2012). Indeed almost any fomite in contact with animal faeces is a potential source of foodborne pathogens (Newell et al, 2010), with several risk factors intricately intertwined, and with variable and complex transmission pathways leading to human gastrointestinal diseases (Butler et al, 2016). Therefore, knowledge and understanding of the sources and mechanisms of transmission of FBDs is an important step in identifying and preventing the health-related risk factors for FBDs (Butler et al, 2015; Pires et al, 2009).

Risk Factors for Foodborne Diseases

A risk factor "is any attribute, characteristic, or exposure of an individual that increases the likelihood of developing a disease or injury" (WHO, 2017). The risk factors for FBDs result from conditions or practices that encourage microbial growth, or failure to eliminate

pathogens (Lukacsovics et al, 2014). These risk factors can be broadly classified as individual-level and community-level risk factors. Individual-level risk factors are traditionally investigated for the transmission of FBDs. However, community-level factors such as socioeconomic status (SES), a significant component of the social determinants of health (SDH), have been shown to be important risk factors for a wide range of health outcomes, and responsible for the gross health inequalities observed within and across countries, including developed countries (Majowicz et al, 2007; Marmot, 2005; Shavers, 2007; Simonsen et al, 2008; WHO, 2010).

Stages in the food supply chain

Food can be contaminated at any stage in the farm-to-fork continuum (Nascimento et al, 2018; Zbrun et al, 2013); at the primary production or pre-harvest stage, post-harvest stage, manufacturing and processing stage, retailers/wholesaler, and final home preparation and consumption stage (Alam et al, 2015; Lukacsovics et al, 2014; Todd et al, 2007a). For example, the contamination of meat and poultry can occur at the farm level (primary production stage), or during slaughter, when the meat is exposed to intestinal contents containing foodborne pathogens. Fruits and vegetables can be contaminated if washed or irrigated with contaminated water (Comery et al, 2013). In their study, Heyndrickx et al (2002) showed that the horizontal transfer of *Salmonella* to poultry meat was mainly due to the unhygienic conditions and practices in the broiler farm and at the slaughter plant. However, inadequate food handling practices and behaviours (e.g., cross-contamination of various food items, undercooking of meats) at the final food preparation, and consumption

stage in private homes or restaurants can also encourage the proliferation of foodborne pathogens and could affect food safety (Lukacsovics et al, 2014). Proper food safety practices are particularly important at the final food preparation stage after cooking as no additional heat treatment takes place to inactivate the pathogens if cross-contamination occurs before consumption (Smadi and Sargeant, 2013).

Risk settings

Different settings have the potential to transmit enteric diseases through contaminated food. Some of the important risk settings for FBDs are private homes, catered events, institutional settings such as hospitals and long-term care homes, day nurseries, schools, and food service facilities such as restaurants and retail food outlets (Al Mamun et al, 2013; Koro et al, 2010; Meldrum et al, 2009; Smadi & Sargeant, 2013; Trindade et al, 2014), including farmers' markets (Levy et al, 2015). However, food safety risks are particularly high for foods prepared in private homes and food service facilities, especially restaurants (Lee and Middleton, 2003; OzFoodNet Working Group, 2018; Todd et al, 2007b). For example, private homes and restaurants have been identified as leading risk settings for FBDs in both the U.S. and Canada (Lee & Middleton, 2003; Nygren et al, 2013). One reason that FBD risk for Canadians may be particularly high in restaurants is because going out to restaurants is one of the most preferred activities for spending time with families and friends for Canadians (Restaurants Canada, 2017). It is reported that 7.5 million Canadians visit restaurants daily in Ontario, circa 2017 (Restaurants Canada, 2017).

However, low SES and minority populations may be at even greater risk as they have more access to smaller, independent food facilities that may have lower food safety standards or serve food with lower food microbial quality (Quinlan, 2013; Yapp & Fairman, 2006). These inequities in food access lead to food insecurity (limited food choices and costly food items) that ultimately cause consumers to seek food of low quality that exposes them to foods of poorer microbial quality (Quinlan, 2013). Minority neighborhoods and lower income areas in the U.S. have higher number of small grocery stores or corner markets, and fewer supermarket than higher income and white neighborhoods (Moore & Diez Roux, 2006). These small- and medium-sized retail establishments have been found to have higher rates of food safety non-compliance. For example, in Detroit, Michigan in the U.S., Pothukuchi et al (2008) demonstrated that grocery stores and other retail establishments located in neighbourhoods with high poverty rates, and higher proportions of African-Americans, had more critical food safety violations than their counterparts. Some of the barriers to compliance in these establishments include: inadequate facilities; deficient equipment and utensils; poor personal hygiene; improper food handling behaviour and practices; lack of time, money, experience, knowledge in food safety regulations, and access to information; and lack of trust in food safety officers (Quinlan, 2013; Trindade et al, 2014; Yapp & Fairman, 2006).

Travel

Travel-related FBDs also represent a large proportion of all enteric infections, and are one of the most common consequences among travellers (Nesbitt et al, 2012; Tighe et al, 2012; Vrbova et al, 2012; WHO, 2012). The most common pathogens associated with

travellers' diarrhoea are norovirus, *Campylobacter*, *Salmonella,* enterotoxigenic *E. coli,* and *Shigella spp.* (Bramwell, 2016; Kendall et al, 2012). International travel accounted for 36% and 51.9% of *Salmonella* Enteritidis cases occurring, respectively, in Canada and Ontario (Nesbitt et al, 2012; Tighe et al, 2012).

The most important determinant of developing travel-related FBD is the travel destination. The risk (exposure) is higher in regions where there is lack of food safety regulations, high level of unsanitary water supply, lack of food hygiene, fluctuating electricity supply for effective refrigeration, and lack of or limited education (Bramwell, 2016). Therefore, persons travelling from regions of higher standards of hygiene and sanitation to lower standards are at higher risk of developing travellers' diarrhoea (WHO, 2012).

Food safety knowledge and behaviour

Food safety knowledge and behaviour affect the probability of introduction, transmission, and growth of pathogens. These factors include, but are not limited to, poor personal hygiene such as inadequate hand washing, cross contamination, insufficient cooking, inadequate storage temperature or time, unsafe food sources, and preferences for high-risk foods (Badowski et al, 2011; Carrasco et al, 2012; Lukacsovics et al, 2014; Medeiros et al, 2001; Middleton et al, 2014; Nesbitt et al, 2009; Sewell & Farber, 2001; Todd et al, 2007a).

Poor hygiene is a significant risk factor for FBD transmission (Bryan, 1988; Freeman et al, 2014; Medeiros et al, 2001; Todd et al, 2007a). Of particular importance is the failure to wash hands or improper hand washing, as the hands are the most significant vehicles for

pathogen transfer from the infected skin or other contaminated areas to food, leading to FDB outbreaks (Beatty et al, 2009; Bryan, 1988; Green et al, 2006a; Medeiros et al, 2001; NDSC, 2004; Todd et al, 2007a). A prospective case-control study in Ontario, Canada, showed that not washing hands after handling of raw eggs was a significant risk factor for domestically-acquired salmonellosis (Middleton et al, 2014).

These poor food handling practices present high potential for cross-contamination whereby pathogens are transmitted directly through a direct contact with contaminated or raw food, or indirectly from a contaminated or raw food, equipment, food contact surfaces, or hands, to non-contaminated foods (Byran 1988; Carrasco et al, 2012; Chapman et al, 2010). In Mexico, the microbial contamination level on farm workers' hands was shown to highly correlate with the contamination level of fresh produce in farms (Bartz et al, 2017). Cross-contamination has also led to FBD outbreaks in countries such as the U.S. where about 47% of produce-related outbreak of *E. coli* 0157:H7 infection was reported from 1982 to 2002 (Rangel et al, 2005), and in Australia (OzFoodNet Working Group, 2018). Cross-contamination of RTE foods from raw ingredients of animal origin in the U.S. also led to 18 outbreaks associated with non-typhoidal *Salmonella*, *S. aureus*, *Campylobacter* and *E. coli* (Todd et al, 2007a).

In spite of this evidence, observations of food consumers food preparation practices indicate that hygienic practices are often inadequately carried out (Chapman et al, 2010; Diplock et al, 2018; Green et al, 2006a; Shiferaw et al, 2000). For example, consumers do not always wash their hands after handling raw meat or poultry, and do not always wash their cutting boards after cutting raw chicken (Diplock et al, 2018; Shiferaw et al, 2000). Although

the reason for these improper practices may be that workers are not sure when to wash their hands (Green et al, 2006a); in some cases, the individuals are knowledgeable of the risk of these unhygienic behaviours, yet do not put them into practice (Badowski et al, 2011; Nesbitt et al, 2009). In fact, Nesbitt et al (2009) and Shiferaw et al (2000) found that educational level negatively correlated with proper hand-washing practices; however, intrinsic factors such as pride or satisfaction had a higher influence on food service employees to follow safe food handling practices (Ellis et al, 2010).

Self-reported food safety knowledge amongst high school students (14-18 years of age) was reported to be low in Ontario, Canada; several respondents (24.3%) believed that using hand sanitizers (as opposed to washing hands with soap and running water) was the best option for proper hand hygiene (Majowicz et al, 2015). Although safe food handling practices, such as hand hygiene, was observed to improve after a food handling education intervention, risky food handling behaviour was still observed amongst some students following the intervention (Diplock et al, 2018). These findings show that this age group presents a potential risk for FBD, especially because they tend to work in food services facilities that offer food to the public (Majowicz et al, 2015).

The consumption of high-risk foods (for example, raw or undercooked foods, raw milk, sprouts, leafy green vegetables, or foods that have not been properly stored) also presents a risk for FBDs. Such consumption behaviour has been associated with foodborne disease outbreaks in the U.S., Canada, and other countries, such as Germany and China (Chen et al, 2019; Simon et al, 2018; Taylor et al, 2018; Whitehead & Lake, 2018). Bacteria such as *E. coli*, *Salmonella spp.*, *Campylobacter*, *L. monocytogenes*, and *S. aureus* were amongst the

pathogens implicated in these outbreaks (Chen et al, 2019; Medeiros et al, 2001; Todd et al, 2007a).

High risk consumption behaviours are more prevalent in particular socioeconomic and demographic groups (Chen et al, 2019; Nesbitt et al, 2009; Shiferaw et al, 2000). In Canada, as an example, Nesbitt et al (2009) showed that the consumption of unpasteurized milk, undercooked egg, and raw shellfish increased with increasing educational level, and the consumption of undercooked egg increased with increasing age and income. In a U.S. study, the consumption of undercooked hamburger was shown to be more common in men than in women (Shiferaw et al, 2000). Invariably, these different risk factors make food one of the major vehicles for enteric diseases.

Food as a risk factor for enteric diseases

Most cases of enteric diseases result from the transfer of microbial contamination from food to humans (Butler et al, 2015; Medeiros et al, 2001; Pires et al, 2009). Using expert elicitation method for source attribution, Butler et al (2015) determined that food was the primary transmission route for several pathogens such as *E. coli, Salmonella, Campylobacter, L. monocytogenes, C. perfringens, and Cyclospora spp.,* in Canada. Food is also frequently associated with enteric disease outbreaks in Canada (Gaulin et al, 2014; Lee & Middleton, 2003; Middleton et al, 2014; Ryu et al, 2012; Smadi & Sergeant, 2013; Todd et al, 2007a). As an example, between 1997 and 2001 in Ontario, Canada, 74.0% of the reported 44,451 FBD cases were transmitted by food (Lee & Middleton, 2003). Food was

also identified as the primary source of the cases that were reported between 2007 and 2009 in Ontario (Vrbova et al, 2012).

The proportion of FBDs transmitted to human varies by food type, pathogen, geographic region, as well as several host factors (Butler et al, 2016; Scallan et al, 2011a). Using data for 2,107 FBD outbreaks that covered a 30-year span (between 1976 and 2005) in Canada, Ravel et al (2009) showed that poultry was the primary source for campylobacterioris and salmonellosis, beef for *E. coli* infection; pork for yersiniosis, seafood for *Vibrio spp*. infection, and ready-to-eat (RTE) food for listeriosis. Ravel et al (2017) also identified poultry as the leading source of human campylobacteriosis in Canada.

Food being the major source of enteric infections is not surprising as foodborne pathogens are commonly isolated from a variety of food sources and commodities such as retail poultry, meat, and fresh produce in Canada (Agunos et al, 2013; Allen et al, 2013; Aslam et al, 2014; Comery et al, 2013). Food has also been shown to contain antimicrobial resistant bacteria and resistance genes in different countries. For example, resistant *E. coli* and resistance genes were isolated from fish and seafood in Korea (Ryu et al, 2012), and from retail meat in Canada (Sheikh et al, 2012); resistant *Staphylococcus spp*. from RTE foods in Poland (Chajęcka-Wierzchowska et al, 2014); and resistant *E. coli* from retail veal meat in Canada (Cook et al, 2011).

Unfortunately, inequities in the quality of food available to groups of different SES and ethnic groups are also known to exist at the retail level. In their study, Koro et al (2010) demonstrated that there was higher microbial burden on produce from low-SES areas in Philadelphia, U.S., while ground beef from high-SES areas contained higher microbial

burden. Similarly, RTE vegetables from low-SES and Asian areas of Philadelphia contained the highest percentage of faecal coliforms, whereas sandwiches from high-SES areas had higher coliform counts (Signs et al, 2011). These results indicate that the microbial burden in food items depend on the food type, the pathogen characteristics, the individual-level risk factors discussed in previous sections, as well as socioeconomic factors discussed in detail in the following sections.

Social Determinants of Health

Community-level factors or the conditions in which people live and work, referred to as the social determinants of health (SDH), also pose as risk factors for many health outcomes, including foodborne diseases (Marmot, 2004; Mikkonen & Raphael, 2010; Pearl et al, 2009). The WHO Commission on Social Determinants of Health conceptual framework on the SDH demonstrates how social, economic, and political structures result in a set of economic situations whereby societies are stratified according to socioeconomic factors such as income, education, occupation, social class, gender, and race/ethnicity (WHO, 2010).

These factors then operate through different mechanisms to affect conditions of daily life and to bring about different health outcomes (WHO, 2010; Adler & Newman, 2002; Marmot, 2004), as shown in Figure 1.1. According to the WHO, these mechanisms include material circumstances (e.g., living and working conditions, access for food), psychosocial circumstances (e.g., psychosocial stressors, stressful living/working conditions and relationships, coping mechanisms), behavioral factors (e.g., physical activity, tobacco and alcohol consumption), biological factors (e.g., genetic factors), and health system (e.g., access to adequate health care) (WHO, 2010). Thus individuals or groups are placed in the

society based on a set of socioeconomic factors, resulting in inequities or inequalities in their socioeconomic status (WHO, 2010; Marmot, 2004).

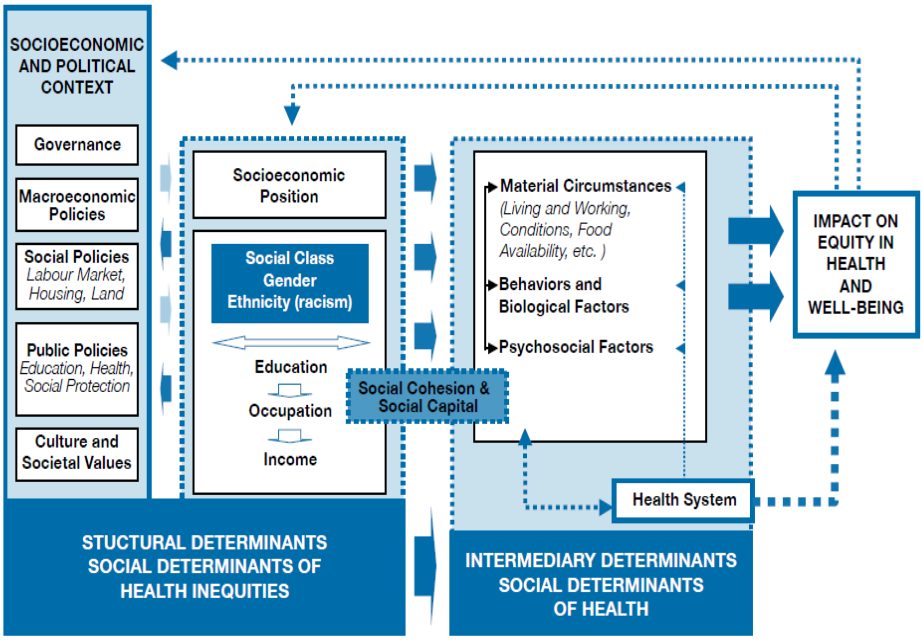


Figure 1.1: The Commission on Social Determinants of Health Conceptual Framework, adapted from WHO, 2010.

Social Status in Health Studies

Socioeconomic status (SES) is the social and economic standing of individuals, families, households, census tracts, or other aggregates within a hierarchical social structure based on their income, education, occupation or employment status, working conditions, health and social services, access to quality education, food, and housing and other factors or variables (Miech & Hauser, 2001). Examinations of SES often reveal an uneven distribution of these factors which are the basis of a social gradient that ultimately results in inequity or inequality in health (Miech & Hauser, 2001; Mikkonen & Raphael, 2010; WHO, 2010). One

study that significantly illustrated the impact of this uneven distribution of SES is the Whitehall study of British civil servants (Marmot et al, 1978). This prospective study reported the coronary heart disease mortality rate for men with different grades of employment, where the risk was highest in men in the lowest grade of employment.

Thus, in every country, health and disease follow a social gradient such that the lower the SES the poorer the health outcome (Marmot, 2004; Marmot et al, 1978; Mikkonen & Raphael, 2010; Pearl et al, 2009; White et al, 2011; WHO, 2010). However, populations that suffer health inequities are those "with a significant disparity in the overall rate of disease incidence, morbidity, mortality and survival rates in the population as compared to the health of the general population" (Shavers, 2007).

Measurement of Socioeconomic Status in Health Studies

Measuring SES in health studies involves classifying populations into appropriate socioeconomic groups. It can be measured at the individual, household, or community (neighbourhood, area-based) level (OAHPP, 2013). Examples of individual-level SES indicators are income, education, wealth, employment, social class, gender, and race/ethnicity (Arcaya et al, 2015; OAHPP, 2013; Shavers, 2007; WHO, 2010). An individual-level measure is considered the standard measure of SES and the most direct way of dividing individuals by socioeconomic information (OAHPP, 2013). However, individual-level data may be unavailable or may be sensitive for the individuals; in such cases, area-based socioeconomic measures, at the neighbourhood or community level, are used as proxies for individual-level SES measures (Demissie et al, 2000; Denny & Davidson, 2012).

This approach is based on the assumption that SES characteristics are homogeneous and stable within a geographic area (Demissie et al, 2000; Denny & Davidson, 2012). Another reason for using area-based measures is that they capture area-level characteristics that individual-level measures do not (Denny & Davidson, 2012). Area-based measures can also be analyzed with standard and spatial statistical software and geographic information systems (GIS) to identify areas high with rates of infections, and to create maps of social distribution of health outcomes across different areas (Denny & Davidson, 2012).

Area-based measures include single-component measures such as neighbourhood income, median income, proportion of educated and unemployed persons in the population; and also include composite scales from combining these variables such as deprivation (Chan et al, 2015; Demissie et al, 2000; Denny & Davidson, 2012; Gillespie et al, 2010). Examples of multiple-component area-based measures in Canada are the Canadian Marginalization Index (CAN-Marg), the Ontario Marginalization Index (ON-Marg), the index of material and social deprivation created by the institute National de Santé Publique de Québec (INSPQ), the quintile of adjusted income per person equivalent (QAIPPE), the socioeconomic factor index (SEFI), and the Vancouver area neighbourhood deprivation index (VANDIX, Denny & Davidson, 2012; OAHPP, 2013).

Each of these measures depicts an aspect of SES (Shavers, 2007). However, income, education, and occupation or employment status are the most important societal stratifiers (WHO, 2010), and these indicators are mostly studied in public health research (Adler & Newman, 2002; Lahelma et al, 2004; Miech & Hauser, 2001; Shavers, 2007; WHO, 2010). These three major SES variables are discussed below.

Income

Income is the variable that most directly measures the material component of SES as it influences the overall living conditions, and access to services that may improve health, self-esteem, and social status (Galobardes et al, 2006; Mikkonen & Raphael, 2010; WHO, 2010). Low income predisposes individuals to material and social deprivation such that the greater the deprivation, the less likely one can afford the basic necessities of life such as food, clothing, and housing (Mikkonen & Raphael, 2010). Deprivation also makes it difficult to avoid risks, prevent illness, and treat injuries and diseases, and to partake in social activities; this social exclusion in turn affects overall health and reduces the capacity to live a fulfilling life (Mikkonen & Raphael, 2010; White et al, 2011). In addition, limited resources can create stress, and affect psychological functioning that influences health-related behaviours such as tobacco use, excessive alcohol use, and physical activity, access to food and safe housing (Braveman, 2011; WHO, 2010). It therefore follows that persons with lower income are generally less healthy than those with higher income. This effect spans across the whole SES hierarchy, although the impact is greater for those below the poverty line (Adler & Newman, 2002; Marmot, 2004).

The effect of income on health can be expressed as the net income of an individual, or the net income of household members and adjusting for the size of the household (WHO, 2010). Individual income measures individual material characteristics, while household income reflects the many components of assets (for example, wages, dividends, and pensions), and consumption (for example, tax deductions and social contributions) that are shared among household members (WHO, 2010).

Education

Education affects health outcomes through its impact on occupation and income, as it influences future occupational opportunities and earning potential (Adler & Newman, 2002; Lahelma et al, 2004; Pinillos-Franco & Garcia-Prieto, 2017). Education provides the formal qualifications and knowledge to acquire the occupational position that relates to paid employment from which income is derived to provide the necessary resources required to maintain good health (Lahelma et al, 2004). Education also increases the overall knowledge and skills of how one's health can be improved through personal actions and behaviours (Adler & Newman, 2002; Mikkonen & Raphael, 2010; Pinillos-Franco & Garcia-Prieto, 2017).

Education can be measured as a continuous variable by determining the years of completed education, or as a category variable by assessing educational milestones, such as the attainment of high school diplomas or higher degrees (WHO, 2010; Adler & Newman, 2002; Gallardo et al, 2017). However, these measures may contain no information about the quality of the educational experience; this is important if applying the role of education to health outcomes specifically related to knowledge, cognitive skills, and analytical abilities (WHO, 2010).

Formal education can be conceived as a measure of early life SES (WHO, 2010) as it is typically the first to be acquired in young adulthood, across the life span, and it is strongly related to parental characteristics such as occupation or employment status (Lahelma et al, 2004; WHO, 2010). However, childhood illness can limit educational attainment and

predispose an individual to disease in adulthood, resulting in a "health selection effect on health inequalities" (WHO, 2010).

Occupation and Employment Status

Occupation influences health through various mechanisms; it has a strong association with income, and therefore has a direct association with material resources, material living standards, and health. Occupation also reflects a person's social position that allows access to privileges such as good education, better housing, and better healthcare, through its influence on income status (Adler & Newman, 2002; Galobardes et al, 2006; WHO, 2010). In Canada, however, the effect of occupation status may be minimal due to the universal healthcare system (Bryant et al, 2011; Raphael et al, 2008). Occupation also affects health outcomes through psychosocial processes as it reflects social networks, work-related stress, control, and autonomy (Adler & Newman, 2002; Galobardes et al, 2006; WHO, 2010). Thus, lower-job status predisposes individuals to higher physical, psychosocial, and environmental risk factors relating to occupation (Steenland et al, 2003).

Occupation is often measured using a person's current or longest held occupation (WHO, 2010; Marmot, 2004; Miech & Hauser, 2001). However, due to the growing awareness of the life course perspective on SES, some studies use both parental occupation as a reflection of childhood SES and a person's occupation in adult life (WHO, 2010, Yilgwan & Okolo, 2012).

Since occupation cannot be used to classify persons who are not employed (Galobardes et al, 2006), employment status is used to compare employed persons to unemployed persons (Adler & Newman, 2002; Shavers, 2007). This is based on the premise that employed

persons are generally healthier than unemployed persons, although some of the observed relationship between employment and health may be a function of the "healthy worker effect" (Adler & Newman, 2002; Shavers, 2007; WHO, 2010).

Impact of Socioeconomic Status on Health Outcomes

There is a substantial body of knowledge identifying the role that socioeconomic factors play in influencing health and disease outcomes, for a wide range of illnesses, including non-communicable (Disano et al, 2010; Rivera et al, 2015) and infectious diseases (Gillespie et al, 2008; Gillespie et al, 2010; Semenza, 2010). Although there are variable degrees of association, low SES has been demonstrated to be a predictor of poorer health outcomes and higher disease burden. For example: low SES has been linked to higher hospitalization rates and longer hospital stay (Carrie & Kozyrsky, 2006; McGregor et al, 2006); poorer self-rated health (Gallardo et al, 2017); limited access to healthcare (Lebrun & Dubay, 2010); limited healthcare utilization (Allin, 2008); adverse birth outcome, including low birth weight (Clayborne et al, 2016); and mortality rates (DesMeules et al, 2005; Marmot et al, 1978). Low SES (e.g., social status) is also strongly related to high-risk behaviours such as smoking (Jahnel et al, 2017) and alcohol abuse (Pape et al, 2018).

In Canada, positive correlations between SES and hospital admission rates for chronic obstructive pulmonary disease, diabetes, and asthma have been demonstrated (Disano et al, 2010; Rivera et al, 2015). Examples of other health variables which have been shown to vary by SES include hospitalization rate (Carrie & Kozyrsky, 2006; Disano et al, 2010), hospital length of stay (McGregor et al, 2006), and various infectious diseases (Baker et al, 2012; Braveman, 2011; Pini et al, 2019; Semenza, 2010), including enteric diseases (Majowicz et

al, 2007; Varga et al, 2013a). In Canada, *E. coli* O157 disease burden is greater in vulnerable populations such as the Indigenous peoples, immigrants, the homeless, and people with poor literary skills, than other populations in Canada; these vulnerable populations are also less likely to receive adequate health care (Lebrun & Dubay, 2010; Pearl et al 2009).

Several theories, in addition to personal characteristics such as cognitive ability, have been proposed to help explain the persistence of health inequalities in different populations; these include the life course perspective and social selection theories (Mackenbach, 2012). The life course perspective posits that health outcomes observed in adulthood are partly determined by exposure to social and biological factors in childhood, and these factors and exposure interact throughout the life span to affect SES inequality and health outcomes (Hargrove & Brown, 2015; Mackenbach, 2012;). The social selection theory suggests that individuals are organized into different social statuses based on their health or health determinants (Mackenbach, 2012). Therefore, persons with poorer health are likely to remain low on the socioeconomic hierarchy (WHO, 2010). For example, persons with disabilities are more likely to have periods of unemployment compared to non-disabled persons (Cadden & Arnett, 2015).

Impact of Socioeconomic Status on Infectious Diseases

Humans have been susceptible to pathogenic infections throughout history (Weiss & McMichael, 2004). Currently, there are 1,415 known species of infectious agents that are pathogenic to human, including 538 bacteria and rickettsia, 217 viruses and prions, 287 helminths, 66 protozoa, and 307 fungi (Taylor et al, 2001). Most of these agents are zoonotic

in nature, that is, they can be transmitted between animals and humans (FDA, 2012; Taylor et al, 2001).

Although the leading causes of disease burden in low income countries are infectious diseases due to poor social and economic conditions (Weiss & McMichael, 2004), infectious diseases also cause significant morbidity and mortality in high income countries such as New Zealand (Baker et al, 2012), Denmark (Biering-Sorensen et al, 2012), the U.S. (Yousey-Hindes & Hadler, 2011) and Canada (McGregor et al, 2006). However, even in high income countries, current studies on SES and certain infectious diseases such as tuberculosis, influenza, and HIV/AIDS (Cohen et al, 2007; Yousey-Hindes & Hadler, 2011) reveal poorer health outcomes with lower SES as an overall trend.

Impact of Socioeconomic Status on Enteric Diseases

The relationship between SES and enteric diseases has also been explored in multiple ways, using different socioeconomic variables. Recent systematic reviews and meta-analysis on the risk of SES for FBDs examined the types of SES variables and FBD pathogen combinations that have been investigated in high income countries. Amongst the SES variables that have been studied, income, education, and occupation or employment status are the most studied (Adams et al, 2018a; Newman et al, 2015).

Income Status and Enteric Diseases

The importance of income as a determinant of enteric diseases has been demonstrated in several studies in different countries. In Finland, the proportion of low income households with children was found to be a risk for VTEC infections, due most likely to the consumption

habits in those households (Jalava et al, 2011). In contrast, a Denmark-based study found that the risk for *Salmonella* Enteriditis, *Campylobacter*, *Shigella*, and *Yersinia* infections in adults (≥ 18 years of age) increased in persons with higher income, while the risk for Shiga toxin-producing *E. coli* decreased with higher income (Simonsen et al, 2008). Whitney et al (2015) reported that the proportion of persons living below the poverty level was negatively associated with the overall crude incidence rates of *Salmonella* and Shiga toxin-producing *E. coli* infections in Connecticut, USA.

The association between income and enteric disease was also assessed in a Canadian study where income was shown to be negatively associated with the odds of illness. Specifically, the odds of enteric illness in respondents with household incomes between $40,000 and $60,000 was 1.32 times lower than the respondents with household incomes of less than $20,000 (Majowicz et al, 2007). While the inverse relationship between income and enteric disease may be unanticipated, high income earners are known consume raw or undercooked food, and more likely to engage in poor food handling practices than low income earners (Nesbitt et al, 2009; Patil et al, 2005; Shiferaw et al, 2000). Those with high income may also engage more frequently in international travel (Varga et al, 2013a), a factor which has been shown to pose significant risk for enteric diseases (Nesbitt et al, 2012; Tighe et al, 2012).

Educational Status and Enteric Diseases

Education is the most studied SES risk factor for enteric diseases (Newman et al, 2015; Adams et al, 2018a). Although there is conflicting evidence in the literature regarding the

association between education and enteric diseases (Jalava et al, 2011; Newman et al, 2015; Simonsen et al, 2008), most of the SES/pathogen combinations studied showed a positive relationship between educational status and enteric disease. For example, Simonsen et al (2008), in Denmark, found that the risk of *Campylobacter, Shigella,* and *Yersinia* infections in adults increased, while the risk of *Salmonella* Typhimurium decreased, with higher education. The incidence rates of *Salmonella, Shigella,* and *E. coli* O157:H7 infections also increased with increase in the percentage of educated people in some U.S. communities (Chang et al, 2009). In a study in Canada however, the association between education and the odds for enteric illness was not significant (Majowicz et al, 2007).

Surprisingly, knowledge of safe food handling practices is not always an indication or predictor of actual behaviour (Diplock et al, 2018; Patil et al, 2005). A large difference was observed between knowledge and reported use of safe food practices amongst individuals with higher than high school education (Patil et al, 2005). People with higher education appear to consume unsafe food such as raw or improperly cooked food more frequently than those with lower education (Nesbitt et al 2009; Patil et al, 2005).

Occupational and Employment Status, and Enteric Diseases

Compared to income and education, there are relatively fewer studies on occupation or employment status as a risk factor for enteric disease (Newman et al, 2015; Adams et al, 2018a). In England and Wales, the incidence of campylobacteriosis was higher in individuals in managerial and professional occupations (white-collar workers) than in those in manual work (blue-collar workers); incidence was highest amongst persons in semi-routine

occupations such as receptionists, sales assistants, and housewives (Gillespie et al, 2008). Similarly, one study in Italy reported a significantly increased risk for *Salmonella* infections for children of unemployed or blue-collar parents as compared to inpatient or outpatient controls (Borgnolo et al, 1996). In contrast, a longitudinal study in the UK showed a lower incidence rate of intestinal disease among persons in routine or manual occupations than those in managerial or professional occupations (Adams et al, 2018b). Broner et al (2010) in Catalona, Spain, showed a positive association between reported FBD outbreak incidence rate and household task (unpaid housework), and a negative association between incidence rate and unemployment rate. However, Chang and colleagues in the U.S. reported a negative association between county-level unemployment rate and *Salmonella* and *E. coli* O157:H7 infections, but no association with *Shigella* infection (Chang et al, 2009). The authors hypothesized that the negative association between unemployment rate and incidence of infection may be due to healthcare access limitation experienced by unemployed persons. In Canada, persons employed in agricultural settings have a higher risk for *Campylobacte*r infections due to exposure to farm animals (Green et al, 2006b). These variabilities in results demonstrate that the relationship between occupation or unemployment status and enteric infection also vary by pathogen type and other risk factors such as exposure to farm animals, foreign travels, risk settings, and consumption behaviour (Adams et al, 2018b).

Other Socioeconomic Risk Factors for Enteric Diseases

Risk of enteric diseases also varies with other socioeconomic and demographic factors as such place of residence, the number of children or people in the household, ethnicity or

cultural background, marital status, age and sex, as well as seasonal factors, although the strength and direction of the associations also vary by pathogen type (Chang et al, 2009; Majowicz et al, 2007; Simonsen et al, 2008; Varga et al, 2013a; Younus et al, 2006). For example, in Denmark, married persons had a higher risk of *Campylobacter, Salmonella* Typhimurium, and *Salmonella* Enteriditis infections than unmarried persons (Simonsen et al, 2008). The number of people in the household, culture, and sex were also significantly associated with the odds for enteric illness in two Canadian communities (Majowicz et al, 2007).

In Northwest Territories, Canada, communities with higher proportions of "households in core need" (inadequate, unsuitable, or unaffordable housing) had an increased risk of *Salmonella* infection up to 42% after which the risk decreased with increasing core need (Pardhan-Ali et al, 2013). In the Greater Toronto Area, Canada, community-level SES factors such as average median family income, average number of children per census family, and proportion of visible minorities, were significantly associated with the risk of *Salmonella* Enteritidis infection; the risk of *Salmonella* infection was found to be highest in areas with high average number of children per census family (Varga et al, 2013a).

In terms of ethnicity or cultural background, ethnic minority populations usually live in poorer neighourhoods in many countries (Daoud et al, 2017; Krieger et al, 2011). The educational and job opportunities of these minority groups are usually limited by racial discriminations at both the policy level and interpersonal level (Krieger et al, 2011). For example, in the U.S., the incidence rates of salmonellosis and shigellosis were positively correlated with the percentage of black or Hispanic populations (Chang et al, 2009). Using

surveillance data for *Campylobacter* infections reported in Wales and England from 2000 to 2003, age- and sex-specific variations in the incidence rates of infections were also observed in different ethnic groups. For instance, incidence rates were significantly higher in white males than in white females at age <20 years, but not at 20-29 years. On the other hand, no significant differences by age or sex were observed in the Black or Indian populations (Gillespie et al, 2008).

Composite community-level SES measures have also been used to study the associations between SES and enteric diseases. Using indices of deprivation (consisting of income, education, skills and training, employment, health deprivation and disability, living environment, barriers to housing and services, and crime and disorder), Gillepsie and others demonstrated that the incidence of *L. monocytogenes* infection was highest in the most deprived areas of England (Gillepsie et al, 2010). Similarly, the rate of hospital admissions for enteric diseases was also shown to increase with increased neighbourhood deprivation in England and Wales (Pockett et al, 2011).

Age is one of the most important determinants of risk for FBD (Barkley et al, 2016). In fact, age is a significant potential effect modifier of the relationship between SES and enteric infections (Adams et al, 2018a). A systematic review of the literature revealed that, in many of the studies reviewed, children of lower SES are at higher risk for gastrointestinal infections, whereas, adults of higher SES are at higher risk (Adams et al, 2018a). Similarly, there was no indication of increasing risk for *Salmonella* Enteriditis or *Y. enterocolitica* diseases in children of families with higher average income, unlike in adults where an increasing risk was observed for those with higher average income (Simonsen et al, 2008).

Higher incidence rates of enteric diseases also occur amongst children <5 years of age (Chang et al, 2009;Varga et al, 2013b; Whitney et al, 2015; Younus et al, 2006) mainly because of their under-developed immune system (Barkley et al, 2016). Communities in the U.S. with higher proportion of children <5 years and adults ≥65 years had a higher incidence of *Salmonella* infections than communities with lower proportions, likely due to the inherent vulnerability of these extreme age groups (Chang et al, 2009). For this reason, cases are often stratified by age when analyzing enteric disease data for association with SES variables, as observed in several epidemiological studies (Varga et al, 2013a; Whitney et al, 2015; Younus et al, 2006).

Thesis rationale and objectives

Enteric diseases remain a global public health issue and pose significant health and economic burden in Canada and in Ontario. In addition to the individual-level risk factors that have traditionally being investigated for the diseases, there is mounting evidence in the literature that sociodemographic risk factors (e.g., income, education, employment, race), play a significant role in exposure and transmission of enteric diseases in the population. Due to the nature of infectious diseases and the complex interactions among the causative pathogens, the human hosts, and the environment to produce a health outcome, the spatial and temporal patterns of these diseases vary across different geographic regions and across different populations. Given Canada's commitment to reduce health inequalities through improvements to, or by mitigating the risk factors for infectious diseases, more understanding of the distribution, inequalities, and risk factors of these diseases in sub-populations is important for potential public health interventions.

Thus, the overall purpose of this thesis was to determine the distributions of, and risk factors for, major enteric diseases in humans commonly transmitted by food, in Ontario, Canada (2010-2017). The specific objectives were to:

1. Estimate the incidence, seasonal, and demographic risk factors of *Campylobacter spp*., non-typhoidal *Salmonella spp*., Verotoxin-producing *Escherichia coli* (VTEC), *Yersinia spp*., and *Listeria monocytogenes* reported infections.
2. Examine temporal, spatial, and space-time clustering of these reported infections.
3. Identify area-level socioeconomic risk factors for reported infections caused by *Campylobacter spp*. and non-typhoidal *Salmonella spp*.

Chapter 2

Incidence, demographic, and seasonal risk factors of infections caused by five major enteric pathogens, Ontario, Canada, 2010-2017

Manuscript as published in Foodborne Pathogens and Disease with two corrections[1] *Formatting,*[2] *including referencing and citations, follows journal standards.*

John P, Varga C, Cooke M, Majowicz SE. Incidence, demographic, and seasonal risk factors of infections caused by five major enteric pathogens, Ontario, Canada, 2010-2017. Foodborne Pathogens and Disease 2022 Jan 19 doi: 10.1089/fpd.2021.0034. Online ahead of print.

[1] On page 43, third paragraph, 35% was corrected to 0.64%; on page 45, last paragraph, 1.4% was corrected to 20.4%.

[2] Table and Figure numbering revised to match thesis formatting.

Abstract

In Canada, enteric infections cause significant health and economic burden. We evaluated the individual characteristics of laboratory-confirmed cases of *Campylobacter spp*. (n=28,728), non-typhoidal *Salmonella spp*. (n=22,640), *Yersinia spp*. (n=1,674), Verotoxin-producing *Escherichia coli* (VTEC; n=1,340), and *Listeria monocytogenes* (n=471), reported between 2010 and 2017 inclusive, in Ontario, Canada (population ~13,500,000). We calculated overall and pathogen-specific annual and mean incidence rates (IRs) for Ontario. We used multivariable Poisson and negative binomial regression models to estimate incidence rate ratios (IRRs) for years, seasons, age groups, and sexes, and included two-way age and sex interaction terms in the models. *Campylobacter* and *Salmonella* infections had the highest IRs while *Listeria* infections had the lowest IRs. None of the infections showed long-term trends over the eight-year study period, however, rates of all five infections were elevated in the summer. More *Salmonella*, VTEC, and *Listeria* infections were linked to disease outbreaks than were *Campylobacter* and *Yersinia* infections. Overall, mean IRs of *Campylobacter*, *Salmonella*, *Yersinia*, and VTEC infections were highest in children 0–4 years old, while *Listeria* IRs peaked in adults 60 years and older. Higher mean IRs of *Campylobacter* were observed in males. No other differences by sex were statistically significant. The same mean rate was observed in both sexes for *Listeria*. Adjusting for all other factors, significant age- and sex-specific differences in IRs were observed in *Campylobacter*, *Salmonella*, and VTEC infection rates. No significant interactions of age and sex were found for *Yersinia* and *Listeria* infections. Future research should focus on the

pathogen-specific socioeconomic, environmental, or agricultural risk factors that might be responsible for these infections.

Introduction

In Canada, enteric infections cause significant health (Drudge *et al*., 2019; Thomas *et al*., 2017) and economic (Majowicz *et al*., 2006; Majowicz *et al*., 2011; Thomas *et al*., 2015a) burden. Amongst the leading causes are *Campylobacter spp*., non-typhoidal *Salmonella spp*., *Yersinia spp*., Verotoxin-producing *Escherichia coli* (VTEC), and *Listeria monocytogenes*, with *L. monocytogenes* causing the highest mortality rate (Drudge *et al*., 2019; Thomas *et al*., 2013; Thomas *et al*., 2015b).

Canadian studies examining enteric disease distributions, and related socio-demographic factors, in Manitoba (Green *et al*., 2006), Northwest Territories (Pardhan-Ali *et al*., 2012), Alberta (Pearl *et al*., 2006), New Brunswick (Valcour *et al*., 2016), and Ontario (Michel *et al*., 1999; Paphitis *et al*., 2020; Varga *et al*., 2013a; Varga *et al*., 2013b; Varga *et al*., 2020; Varga *et al*., 2021), showed temporal, seasonal, and demographic variations in rates of *Salmonella* and VTEC infections, with higher rates observed mostly in children 0-4 years old and in summer. However, research studies on the incidence rate (IR) distributions and risk factors for other infections (e.g., *Listeria*, *Yersinia* infections) have not been conducted. Given that enteric disease patterns are pathogen-specific (Drudge *et al*., 2019), and vary due to individual- and area-level factors such as socio-demographic, environmental, and neighborhood characteristics (Arsenault *et al*., 2012; Daoud *et al*., 2017; White *et al*., 2011), our objectives were to: (i) examine and compare overall and pathogen-specific crude IRs by year, season, age, and sex, and (ii) < *Campylobacter*, *Salmonella*, *Yersinia*, VTEC, and *Listeria* infections in Ontario, Canada, reported from January 1, 2010, to December 31, 2017, inclusive.

Methods

Study area and population

Ontario is Canada's most populous province (13,448,494 inhabitants; ~40% of the Canadian population; Statistics Canada, 2017) with the third-largest land area (917,741 km^2, Statistics Canada, 2020). Ontario has two primary regions; northern Ontario contains about 6% of Ontario's population across 88% of the total land area, while southern Ontario is more densely populated (94% of Ontario's population; Statistics Canada, 2017; Statistics Canada, 2020). Ontario is divided into 35 local public health unit (PHU) areas. PHUs are local government health agencies established by one or more municipalities to deliver health promotion and disease prevention programs (Ontario Ministry of Health and Long-term Care, MOHLTC, 2020). Importantly, Ontario has the most farms (including fruit and cash crops as well as poultry, dairy, and beef cattle) among Canadian provinces. About 95% of the cattle in Ontario are in southern Ontario (Ontario Ministry of Agriculture, Food and Rural Affairs, OMAFRA, 2021), and most are concentrated in the southwestern region with some in central and eastern Ontario (Government of Ontario, 2019).

Case Data

Under Ontario's *Health Protection and Promotion Act* (Government of Ontario, 2020), private and public health laboratories are required to report several infectious diseases, including the five pathogens being examined in this investigation, to local PHUs. Disease data are managed in Ontario's Ministry of Health and Long-term Care's (MOHLTC) integrated Public Health Information System (iPHIS) surveillance database using standard case definitions (MOHLTC, 2019).

We obtained data on all cases of *Campylobacter, Salmonella*, *Yersinia*, VTEC, and *Listeria*, reported in Ontario with episode dates from January 1, 2010, to December 31, 2017 inclusive, via a request to Public Health Ontario (the provincial public health organization). This study was approved by a University of Waterloo Research Ethics Committee (ORE # 40133).

Each case included the date of disease onset, five-year age category, sex, PHU of residence, and whether the case was domestic versus travel-acquired, and sporadic versus outbreak-associated. A case is considered travel-related if out-of-province travel occurred within the disease incubation period. In these data, the month and calendar year of occurrence were used as the disease onset date. When these were not available, the earliest of the sample collection date or the date the case was reported was used as a proxy.

Analysis

Data were compiled in Excel 2013 (Microsoft Corporation, One Microsoft Way, Redmond, Washington, USA), and checked for missing observations. Data for four (year, age, PHU, and link to outbreaks) of the six variables were 100% complete, while both sex and travel status had missing observations (Table 2.1). For sex, 0.64% of the data had missing observations and these were excluded from sex-specific IR determinations. For travel status, only 58.6% of the cases had valid data and in one of the years (2010), travel was not reported. We therefore only included travel in our descriptive analysis.

Cases were descriptively analyzed using Stata version 14.2 (StataCorp LLC, College Station, Texas, USA) and Excel 2013. We used seven age categories (Table 2.1), as guided by previous studies (Barkley *et al*., 2016; Varga *et al*., 2013b; Vrbova *et al*., 2012), and

aggregated cases monthly and seasonally, where season was classified as winter (January, February, and March), spring (April, May, and June), summer (July, August, and September), or fall (October, November, and December).

Overall and group-specific annual and mean IRs per 100,000 person-years, and monthly IRs per 100,000 person-months were calculated (Dohoo *et al*., 2012). Denominators for the IR calculations were the annual inter-censal population estimates (overall, by age and sex) based on the 2016 Census (Statistics Canada, 2019). For this study, we defined a long-term trend as an increase or a decrease in IRs for five consecutive years or longer. For each pathogen, monthly IRs with 3-month moving averages were charted in Excel, as were the average IRs across the eight years.

To compare annual IRs and identify significant demographic and seasonal factors, we built five separate multivariable Poisson regression models for each pathogen. The dependent variable was the total number of cases. Independent variables were year, season, age group, and sex. The population estimates for each covariate pattern were used as the offset variable. Incident rate ratios (IRRs) and their corresponding 95% confidence intervals and p-values were estimated. The IRR was the IR of the category of interest compared to the IR of the reference category (the category with the lowest IR). To determine whether the effect of age group on infection rates varied between males and females, two-way interaction terms were introduced in the models. However, no significant interactions of age and sex were found for *Yersinia* and *Listeria*, therefore, the interactions were excluded from these models. The overall fit of each model was assessed for over-dispersion using the deviance and Pearson χ^2 goodness-of-fit tests (Dohoo *et al*., 2012). The Poisson models for all the pathogens, except

Listeria, indicated a significant lack of fit (over-dispersion), since χ^2 was significant at p <0.05. Negative binomial models were, therefore, estimated for *Campylobacter*, *Salmonella*, *Yersinia*, and VTEC. We also compared the models using Akaike's Information Criteria (AIC) and the Bayesian Information Criteria (BIC). The model with the lower index indicated a better fit for analysis.

Results

From 2010 to 2017, 54,853 laboratory-confirmed cases of *Campylobacter* (28,728; 52.4%), *Salmonella* (22,640; 41.3%), *Yersinia* (1,674; 3.1%), VTEC (1,340; 2.4%), and *Listeria* (471; 0.9%) were reported. Of the five *Campylobacter spp.* identified and reported, *C. jejuni* (14,387/28,728; 57.2%), *C. jejuni/coli* (10,275/28,728; 40.8%) and *C. coli* (495/28,728; 2.0%) predominated. Of the 63 *Salmonella* serotypes reported, *S.* Enteriditis (7,946/22,640; 57.6%), *S.* Typhimurium (2,544/22,640; 18.4%), *S.* Heidelberg (2,228/22,640; 16.1%), and *S.* Thompson (1,088/22,640; 7.9%) predominated. The majority (1,490/1,674; 89%) of *Yersinia spp.* reported were *Y. enterocolitica.* All reported *E. coli* strains were VTEC (with no differentiation between O157 and non-O157 serotypes), and all reported *Listeria spp.* were *L. monocytogenes.*

The distribution of cases by pathogen, year, season, age, sex, travel, and outbreak status is given in Table 2.1. *Campylobacter* and *Salmonella* infections comprised 94% of all cases. Cases of *Yersinia*, VTEC, and *Listeria* were considerably lower, with *Listeria* cases constituting only 0.9% of all cases. No long-term annual trends in cases over time were observed, except for *Listeria* cases which peaked in 2016 (96; 20.4%). However, all infections peaked in July/August (Figure 2.1). Overall, persons 40–49 and ≥60 years made up

45% of all cases. There were more reported infections in males (52.1%) than in females (47.9%). *Salmonella* (25.2%) and *Yersinia* (21.4%) had the most travel-related cases, while VTEC (15.8%) and *Listeria* (11.3%) had the most outbreak cases (Table 2.1).

The patterns of mean IRs overtime were similar to the patterns of cases (Figure 2.2). Overall, mean IRs for *Campylobacter*, *Salmonella*, *Yersinia*, and VTEC infections were highest in children 0-4 years old, while the mean IRs of *Listeria* infections were highest in older adults of ≥60 years old (Figure 2.3). Higher mean rates of *Campylobacter* were observed in males versus females (29.7 versus 23.4 per 100,000 person-years, respectively); no other differences by sex were statistically significant (Table 2.2, Figure 2.4).

Adjusting for season, age, sex, and the interaction between age and sex, the highest IR occurred in 2012 and 2013 for *Campylobacter*, 2012 for *Salmonella*, 2017 for *Yersinia*, 2011 for VTEC, and 2016 for *Listeria* infections. Infections caused by these five pathogens had the highest IRs in summer with the highest IRR (4.07) observed in VTEC. The lowest IRs were observed in winter for *Campylobacter*, VTEC, and *Listeria*, and in fall for *Salmonella* and *Yersinia*. Children 0–4 years old had the highest IRs for *Campylobacter*, *Salmonella*, *Yersinia*, and VTEC, and adults ≥60 years had the highest IR for *Listeria* (4.4 times the rate compared to children 0-4 years old). Overall, the IR was 0.7 times lower in females than males for *Campylobacter*; no other sex differences were significant. However, we found significant interactions between certain age groups and sex for *Campylobacter*, *Salmonella*, and VTEC infections. For example, among those 10–19 years old, the IRs of *Campylobacter* and *Salmonella* infections were significantly higher in males than females. The IRs of VTEC infection were significantly higher in females 30–39 and 40–59 years old

compared to males in the same age groups. No significant interaction was observed for *Yersinia* and *Listeria* infections (Table 2.2).

Discussion

The study describes and compares the incidence, seasonality, and demographic factors, of five major causes of enteric infections in Ontario. The distribution varied by pathogen, with *Campylobacter* and *Salmonella* infections making up the majority of cases, similar to other studies from Ontario (Drudge *et al*., 2019; Vrbova *et al*., 2012), other parts of Canada (Thomas *et al*., 2013; Valcour *et al*., 2016), and other countries (OzFoodNet Working Group, 2018; Scallan *et al*., 2011).

Although there were no annual trends in cases over time, there were observed differences in annual infection rates which can be explained by climatic variations and fluctuations in regional temperature and precipitation (Arsenault *et al*., 2012; Lal *et al*., 2013), different demographics (Arsenault *et al*., 2012; Chang *et al*., 2009; Varga *et al*., 2013b), immigration and travel (Kendall *et al*., 2012; Tighe *et al*., 2012), or disease outbreaks (Hanson *et al*., 2019; Self *et al*., 2019). All five infections in our study were elevated in summer, consistent with other studies (Valcour *et al*., 2016; Varga *et al*., 2013b; Vrbova *et al*., 2012). This may be due to the increased outdoor activities such as travel (Kendall *et al*., 2012; Tighe *et al*., 2012), and the higher proliferation of pathogens in food products and farm environments in warm weather, which can result in disease outbreaks (Kozak *et al*., 2014; Stein and Katz, 2017). Our results showed that some cases were linked to outbreak events for all the infections, with *Salmonella*, VTEC, and *Listeria* having the

highest proportions of outbreak-related cases, in line with a previous study in Ontario (Vrbova *et al*., 2012).

We observed higher rates of enteric infections in children 0–4 years old and adults ≥60 years old, consistent with other studies from Ontario (Majowicz *et al*., 2007; Varga *et al*., 2013b; Vrbova *et al*., 2012), the United States (Barkley *et al*., 2016; Chang *et al*., 2009), and the United Kingdom (Gillepsie *et al*., 2008). This was expected given that these age groups are more susceptible to infections due to their inherent vulnerabilities resulting from developing or weakened immune systems (Barkley *et al*., 2016). Poor hygiene practices (e.g., lack of hand-washing before eating or after visiting the toilet) are also important factors for the higher rates of enteric infections in children 0–4 years old (Karambu *et al*., 2013).

Our analysis showed age-dependent sex differences in infection rates for *Campylobacter, Salmonella*, and VTEC, but not for *Yersinia* or *Listeria*. There were higher rates of *Campylobacter* and *Salmonella* infections in young males (10–19 years) than in young females and higher rates in women (≥20 years) than in men. Similar to our findings, Sodha *et al*. (2015) determined that VTEC infection rates were higher in women aged 20-29 years and older in the United States. Researchers in England and Wales (Gillepsie *et al.*, 2008) also reported higher *Campylobacter* infection rates in women between 20 and 36 years old. The higher rates of these infections in women (compared to men) may be due to greater person-to-person contact with young children in the household. Women are also more likely to be exposed to these pathogens during food preparation given that these pathogens are mostly foodborne (Thomas *et al*., 2013), and women are generally more engaged in food preparation activities than men in Canada (Moyser and Burlock, 2018). Different sources of

infections and different transmission routes (Butler *et al*., 2015), age (Gillepsie *et al*., 2008), existing health conditions (Barkley *et al*., 2016), and medical care-seeking behaviours (Blackwell *et al*., 2009) have also been proposed as explanations for these sex-related health disparities, and we hypothesized that these factors influenced the results observed in our study.

In contrast to our findings, a meta-analysis of population data on reported cases of *Campylobacter* infections obtained from seven countries, including Canada, determined that infection rates were higher in males than females of all ages (Green *et al*., 2020). Several factors could be responsible for the contrast in this finding and our results. The effects of under-reporting and variations in laboratory test methods on infection rates across different regions are well known (Amaku *et al*., 2017; Majowicz *et al*., 2005). Exposure sources, behavioural, cultural, and socioeconomic factors (Butler *et al*., 2015; Gillespie *et al*., 2008; Shaw *et al*., 2016) as well as biological factors (van Lunzen and Altfeld, 2014) are all important determinants of age- and sex-specific infection rates. While other researchers in Canada and the United States observed no significant sex differences for *Salmonella* infections (Varga *et al*., 2013b; Vrbova *et al*., 2012; Younus *et al*., 2006), it was interesting to observe in our study that only infants and young children (<10 years old) have the same rate of *Salmonella* and *Campylobacter* infections regardless of sex, suggesting that factors apart from biological or genetic ones might play a role in the manifestations of these infections.

Strengths and Limitations

We detected demographic and seasonal variations among the major enteric infections in Ontario. There are several individual-level factors such as personal hygiene, food-handling practices and high-risk food consumption behaviours that might explain the higher rates in specific groups of individuals, and during specific periods such as in summer. Knowing the demographic factors and seasonal patterns of infections caused by the five major pathogens in Ontario, might inform community-focused policy-making initiatives. Our study will also aid public health authorities in the evaluation and implementation of disease prevention and control measures to mitigate the health burden of enteric infections in Ontario.

Findings from our study should be interpreted in light of the limitations inherent to the use of passive surveillance data which do not represent the true burden of diseases in the general population due to factors such as under-reporting and under-diagnosis in different populations, different regions, and across times. These can be due to differences in healthcare-seeking behaviour, accessibility to healthcare, failure to obtain stool samples by physicians, inadequate or lack of diagnostic tools, inaccurate diagnosis, or rate of reporting along the administrative chain (Amaku *et al*., 2017; Majowicz *et al*., 2005), which could result in underestimation of the number of cases in our study. Despite the limitations, our study provides a retrospective depiction of the epidemiology of the major enteric infections in Ontario, especially *Yersinia* and *Listeria* infections that had not been previously studied in Ontario or Canada.

Conclusion

This study investigated the incidence, seasonality, and demographic factors of *Campylobacter*, *Salmonella*, *Yersinia,* VTEC*,* and *Listeria* infections, in Ontario, Canada. Overall, we identified higher infection rates in young children and older adults known for their vulnerabilities to many infectious diseases. We noticed significant age- and sex-specific differences in infection rates for *Campylobacter, Salmonella,* (higher in young and older women compared to men in the same age groups), and VTEC (higher in young women than in young men), and none for *Yersinia* or *Listeria*. To our knowledge, the age- and sex-specific differences (or lack thereof) in incidence rates of *Salmonella, Yersinia,* and *Listeria* infections observed in our study have not been previously identified in Ontario. Infections from these five major pathogens peaked in the summer months, which may have been driven by disease outbreaks during this period. Further research is required to determine the local environmental and socioeconomic factors that may be responsible for the pathogen-specific disease distributions we observed in our study. Public health interventions should focus on these factors to significantly reduce infection risks.

Tables

Table 2.1: Annual, seasonal, and demographic distributions, and the proportion related to travel and outbreaks, of the 54,853 cases of five enteric diseases reported in Ontario, Canada (2010-2017)

	Campylobacter spp. n (%)	*Salmonella spp.* n (%)	*Yersinia spp.* n (%)	Verotoxin-producing *Escherichia coli* n (%)	*Listeria monocytogenes* n (%)	Total n (%)
Annual						
2010	3,371 (11.7)	2,730 (12.1)	205 (12.2)	153 (11.4)	60 (12.7)	6,519 (11.9)
2011	3,511 (12.2)	2,577 (11.4)	211 (12.6)	232 (17.3)	57 (12.1)	6,588 (12.0)
2012	3,900 (13.6)	3,038 (13.4)	162 (9.7)	209 (15.6)	43 (9.1)	7,352 (13.4)
2013	3,948 (13.7)	2,506 (11.1)	178 (10.6)	143 (10.7)	44 (9.3)	6,819 (12.4)
2014	3,790 (13.2)	3,054 (13.5)	149 (8.9)	126 (9.4)	51 (10.8)	7,170 (13.1)
2015	3,299 (11.5)	2,899 (12.8)	229 (13.7)	173 (12.9)	65 (13.8)	6,665 (12.2)
2016	3,443 (12.0)	3,102 (13.7)	260 (15.5)	175 (13.1)	96 (20.4)	7,076 (12.9)
2017	3,466 (12.1)	2,734 (12.1)	280 (16.7)	129 (9.6)	55 (11.7)	6,664 (12.1)
N (Total from 2010-2017)	28,728 (52.4)	22,640 (41.3)	1,674 (3.1)	1,340 (2.4)	471 (0.9)	54,853 (100.0)
Season						
Winter	4,799 (16.7)	5,311 (23.5)	450 (26.9)	161 (12.0)	80 (17.0)	10,801 (19.7)
Spring	6,663 (23.2)	5,580 (24.6)	445 (26.6)	295 (22.0)	118 (25.1)	13,101 (23.9)
Summer	10,841 (37.7)	7,195 (31.8)	477 (28.5)	657 (49.0)	168 (35.7)	19,338 (35.3)
Fall	6,425 (22.4)	4,554 (20.1)	302 (18.0)	227 (16.9)	105 (22.3)	11,613 (21.2)
Age Category (years)						
0-4	1,970 (6.9)	3,381 (14.9)	414 (24.7)	280 (20.9)	19 (4.0)	6,064 (11.1)
5-9	1,125 (3.9)	1,839 (8.1)	190 (11.4)	160 (11.9)	1 (0.2)	3,315 (6.0)
10-19	2,508 (8.7)	2,609 (11.5)	202 (12.1)	235 (17.5)	5 (1.1)	5,559 (10.1)
20-29	5,035 (17.5)	3,424 (15.1)	249 (14.9)	222 (16.6)	13 (2.8)	8,943 (16.3)
30-39	3,672 (12.8)	2,332 (10.3)	154 (9.2)	110 (8.2)	16 (3.4)	6,284 (11.5)
40-59	7,777 (27.1)	5,041 (22.3)	248 (14.8)	138 (10.3)	77 (16.3)	13,281 (24.2)
≥60	6,641 (23.1)	4,014 (17.7)	217 (13.0)	195 (14.6)	340 (72.2)	11,407 (20.8)
Sex						
Female	12,895 (44.9)	11,596 (51.2)	797 (47.6)	716 (53.4)	244 (51.8)	26,248 (47.9)
Male	15,821 (55.1)	11,022 (48.7)	876 (52.3)	624 (46.6)	227 (48.2)	28,570 (52.1)
Transgender[1]	2 (0.0)	3 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.0)
Unknown[1]	7 (0.0)	15 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	23 (0.0)
Other[1]	3 (0.0)	4 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.0)

Travel Status						
Not Applicable[2]	33,71 (11.7)	2,730 (12.1)	205 (12.2)	153 (11.4)	60 (12.7)	6,519 (11.9)
Not Reported	10,255 (35.7)	4,861 (21.5)	454 (27.1)	245 (18.3)	98 (20.8)	15,913 (29.0)
Unknown	121 (0.4)	150 (0.7)	9 (0.5)	3 (0.2)	2 (0.4)	285 (0.5)
Travel-related	4,982 (17.3)	5,700 (25.2)	359 (21.4)	154 (11.5)	33 (7.0)	11,228 (20.5)
Non-Travel-related	9,999 (34.8)	9,199 (40.6)	647 (38.6)	785 (58.6)	278 (59.0)	20,908 (38.1)
Linked to Outbreak						
Yes	46 (0.2)	1,790 (7.9)	15 (0.9)	212 (15.8)	53 (11.3)	2,116 (3.9)
No	28,682 (99.8)	20,850 (92.1)	1,659 (99.1)	1,128 (84.2)	418 (88.7)	52,737 (96.1)

[1]Cases excluded from sex-specific IR determinations.

[2]Indicates that travel information was not available for reporting in iPHIS (applies to cases reported in 2010).

Table 2.2: Incidence rate ratios (IRRs) from the multivariable models with 95% confidence intervals (CIs), by factor, for five enteric diseases in Ontario, Canada, 2010-2017 (N = 54,853 cases); significant values are shown in bold

Independent Variable		*Campylobacter spp.*[1] (n=28716)		*Salmonella spp.*[1] (n=22618)		*Yersinia spp.*[1] (n=1673)		Verotoxin-producing *Escherichia coli*[1] (n=1340)		*Listeria monocytogenes*[2] (n=471)	
		IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Year	2010	--	--	--	--	--	--	--	--	--	--
	2011	1.03	0.97-1.09	**0.93**	**0.87-0.99**	1.04	0.84-1.28	**1.51**	**1.22-1.88**	0.93	0.65-1.33
	2012	**1.13**	**1.07-1.19**	**1.09**	**1.02-1.16**	**0.79**	**0.63-0.99**	**1.35**	**1.08-1.68**	0.68	0.46-1.01
	2013	**1.13**	**1.07-1.19**	**0.89**	**0.84-0.95**	0.86	0.69-1.07	0.92	0.73-1.17	0.68	0.46-1.01
	2014	**1.07**	**1.01-1.13**	**1.08**	**1.01-1.15**	**0.72**	**0.57-0.90**	0.80	0.63-1.03	0.77	0.53-1.12
	2015	**0.93**	**0.88-0.98**	1.02	0.95-1.08	1.11	0.90-1.37	1.10	0.88-1.38	0.96	0.68-1.37
	2016	0.95	0.89-1.00	**1.07**	**1.01-1.14**	1.25	**1.02-1.53**	1.09	0.87-1.37	**1.39**	**1.01-1.92**
	2017	**0.94**	**0.89-0.99**	**0.93**	**0.87-0.99**	1.31	**1.07-1.60**	0.81	0.63-1.03	0.77	0.54-1.12
Season	Winter	--	--	--	--	--	--	--	--	--	--
	Spring	**1.39**	**1.33-1.45**	**1.06**	**1.01-1.10**	0.98	0.85-1.14	**1.83**	**1.50-2.23**	**1.48**	**1.11-1.96**
	Summer	**2.27**	**2.18-2.36**	**1.37**	**1.31-1.43**	1.05	0.91-1.21	**4.07**	**3.40-4.86**	**2.10**	**1.61-2.74**
	Fall	**1.33**	**1.27-1.39**	**0.86**	**0.82-0.90**	0.67	**0.57-0.79**	**1.41**	**1.15-1.73**	1.31	0.98-1.76
Age (years)	0-4	--	--	--	--	--	--	--	--	--	--
	5-9	**0.54**	**0.48-0.59**	**0.53**	**0.48-0.58**	0.44	**0.37-0.53**	**0.48**	**0.36-0.64**	**0.05**	**0.01-0.38**
	10-19	**0.59**	**0.54-0.64**	**0.37**	**0.34-0.40**	0.21	**0.18-0.26**	**0.36**	**0.28-0.46**	**0.12**	**0.04-0.31**
	20-29	**0.83**	**0.77-0.90**	**0.35**	**0.32-0.38**	0.23	**0.19-0.28**	**0.28**	**0.22-0.37**	**0.26**	**0.13-0.53**
	30-39	**0.69**	**0.64-0.75**	**0.25**	**0.23-0.28**	0.15	**0.12-0.18**	**0.12**	**0.09-0.17**	**0.34**	**0.17-0.66**
	40-59	**0.67**	**0.62-0.72**	**0.24**	**0.22-0.26**	0.11	**0.09-0.13**	**0.06**	**0.04-0.08**	0.74	0.45-1.22
	60+	**0.79**	**0.73-0.85**	**0.28**	**0.25-0.30**	0.13	**0.11-0.15**	**0.15**	**0.11-0.19**	**4.44**	**2.79-7.04**
Sex	Male	--	--	--	--	--	--	--	--	--	--
	Female	**0.66**	**0.60-0.73**	0.93	0.86-1.01	0.91	0.82-1.01	0.90	0.70-1.16	0.95	0.79-1.14
Age* Sex	0-4*Female	--	--	--	--	n/a	n/a	--	--	n/a	n/a
	5-9*Female	1.08	0.92-1.26	0.98	0.86-1.12	n/a	n/a	1.35	0.90-2.04	n/a	n/a
	10-19*Female	**0.85**	**0.75-0.97**	**0.85**	**0.75-0.96**	n/a	n/a	1.09	0.75-1.58	n/a	n/a
	20-29*Female	**1.47**	**1.31-1.66**	**1.26**	**1.13-1.42**	n/a	n/a	1.20	0.82-1.74	n/a	n/a
	30-39*Female	**1.22**	**1.08-1.38**	**1.19**	**1.05-1.35**	n/a	n/a	**1.65**	**1.03-2.63**	n/a	n/a
	40-59*Female	**1.21**	**1.09-1.36**	**1.25**	**1.12-1.40**	n/a	n/a	**2.12**	**1.36-3.30**	n/a	n/a
	60+*Female	**1.19**	**1.07-1.34**	**1.14**	**1.02-1.28**	n/a	n/a	1.41	0.95-2.08	n/a	n/a
Intercept		0.00007	0.00006-0.00007	0.00014 23	0.0001319-0.0001536	0.000 02	0.00002-0.00003	5.74e-06	4.36e-06-7.55e-06	6.42e-07	3.70e-07-1.11e-06

[1]Negative binomial model
[2]Poisson model
--Reference group
n/a: Not applicable; interaction terms excluded from models

Figures

Figure 2.1: Monthly raw and smoothed (a), and average (b) incidence per100,000 person-months, of five enteric diseases in Ontario, Canada (2010-2017)

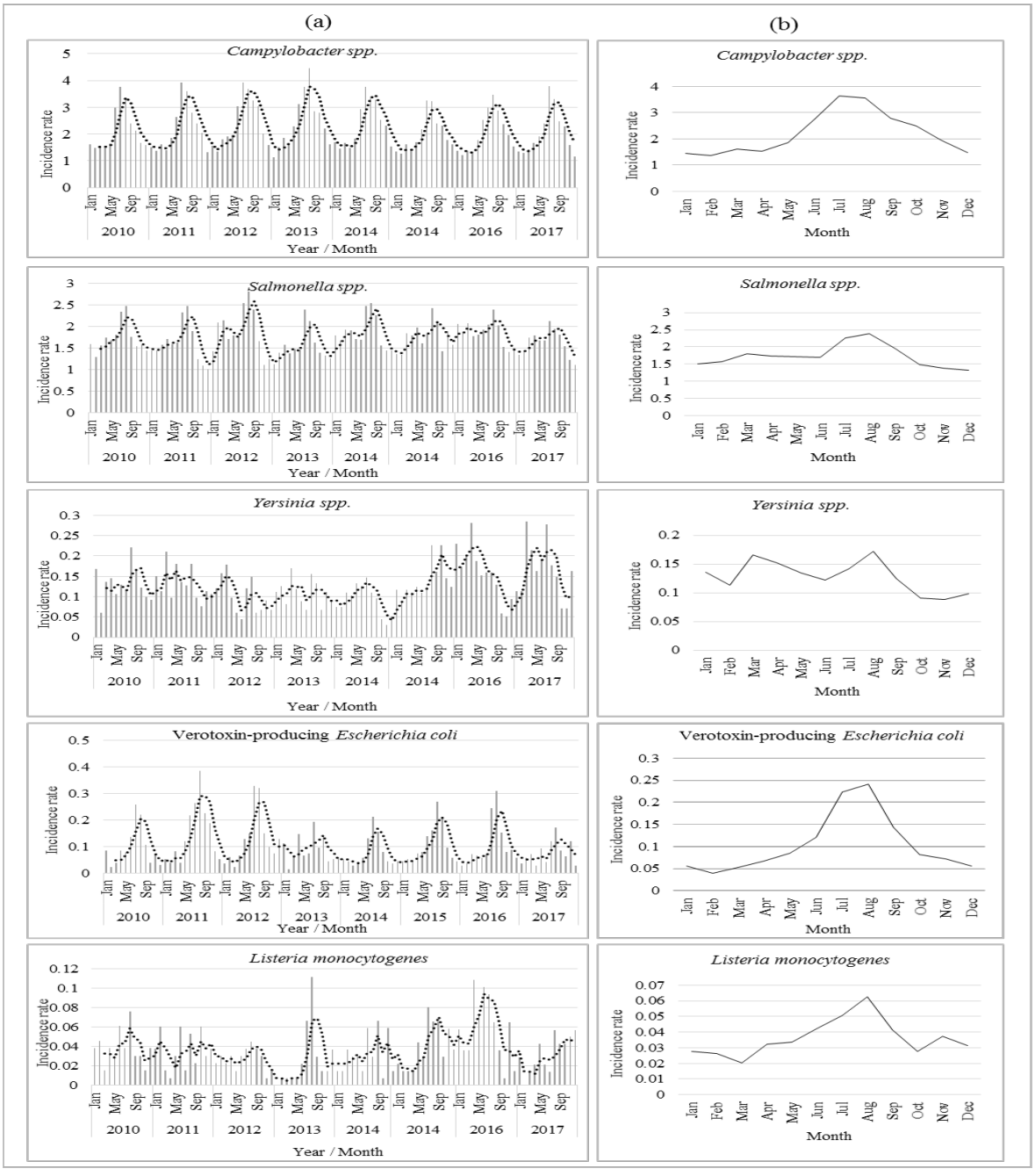


Figure 2.2: Annual and mean incidence rates, in 100,000 cases per person-year, of major enteric diseases in Ontario, Canada (2010-2017)

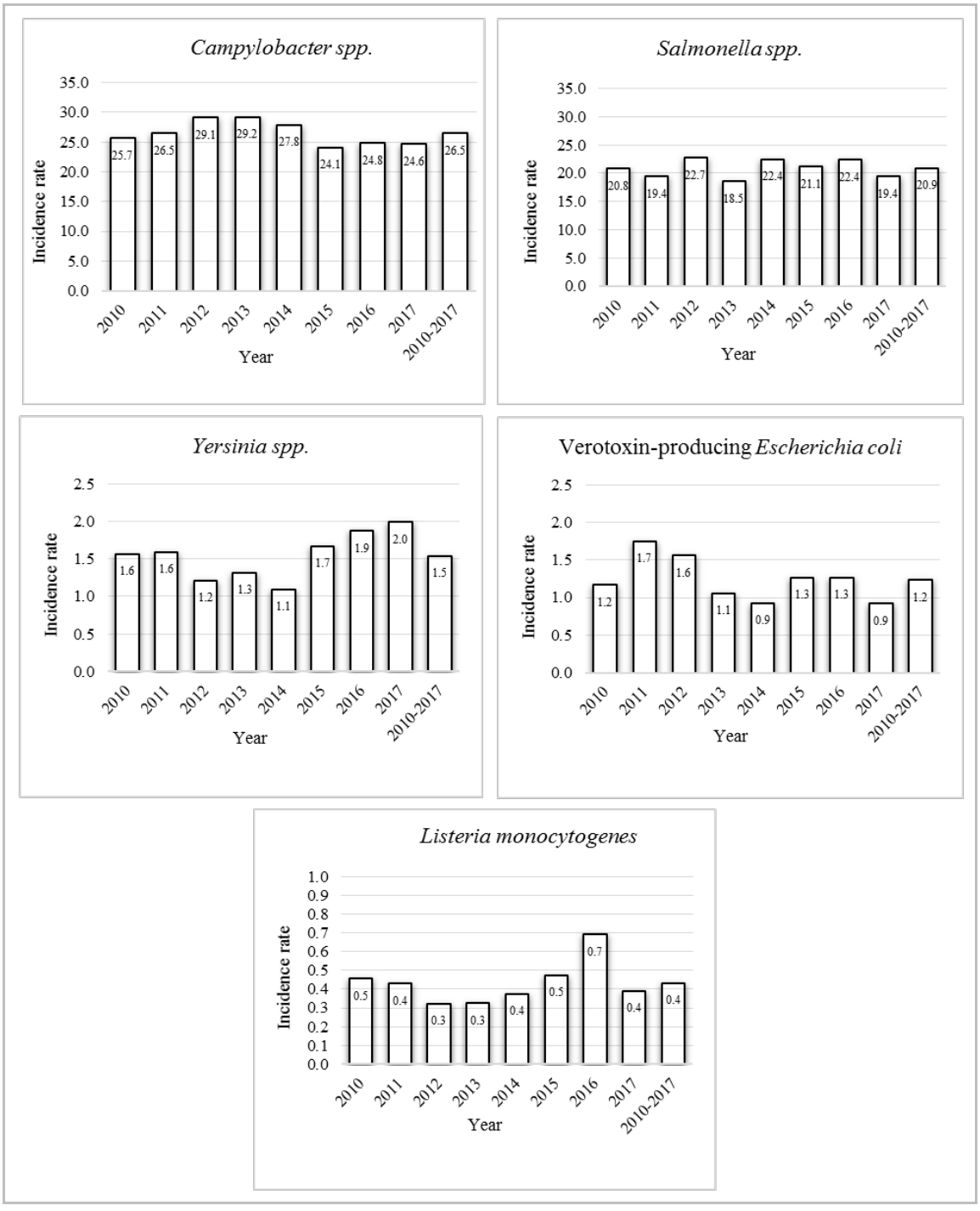


Figure 2.3: Age-specific mean incidence rates, in 100,000 cases per person-year, of major enteric diseases in Ontario, Canada (2010-2017)

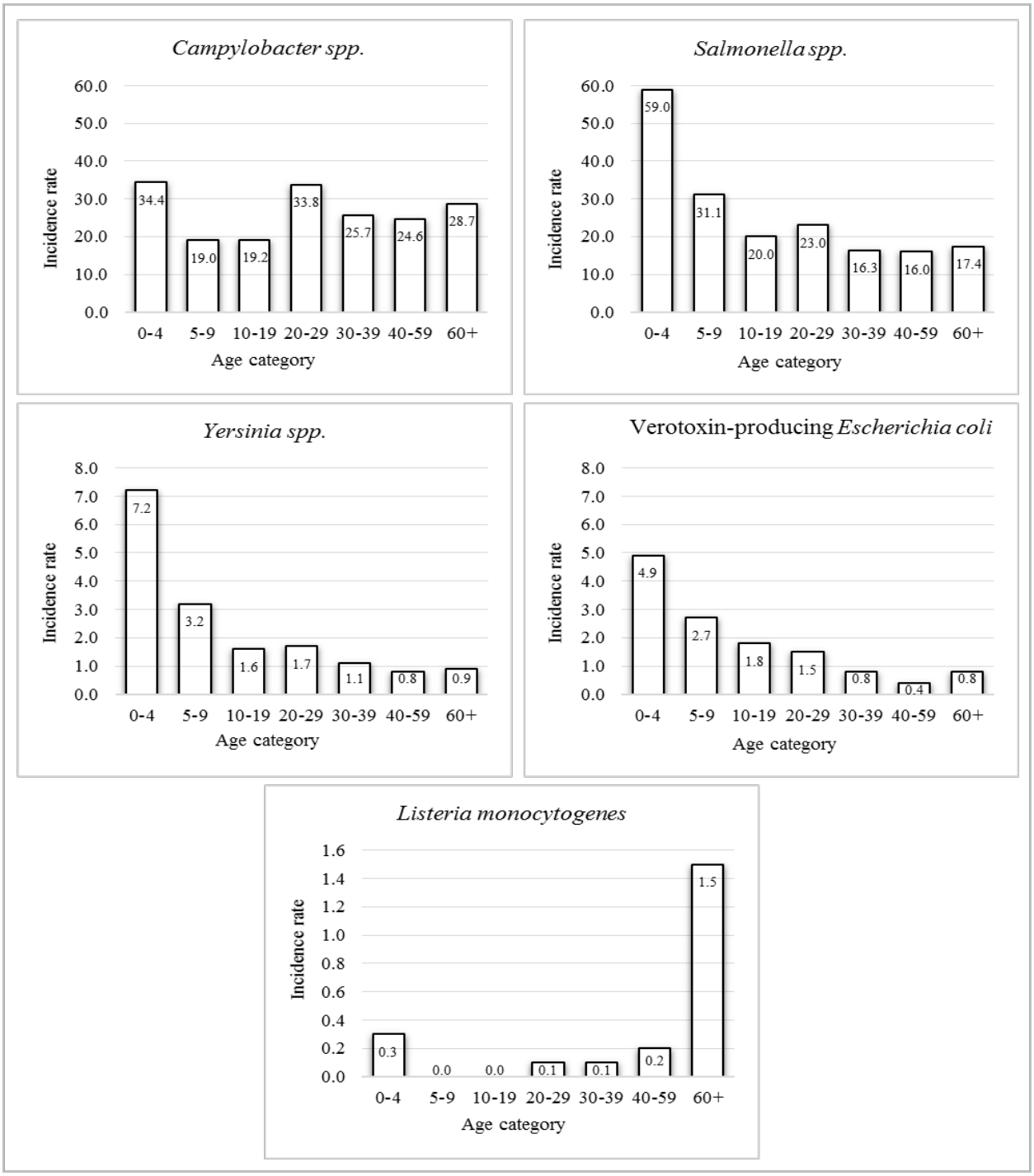
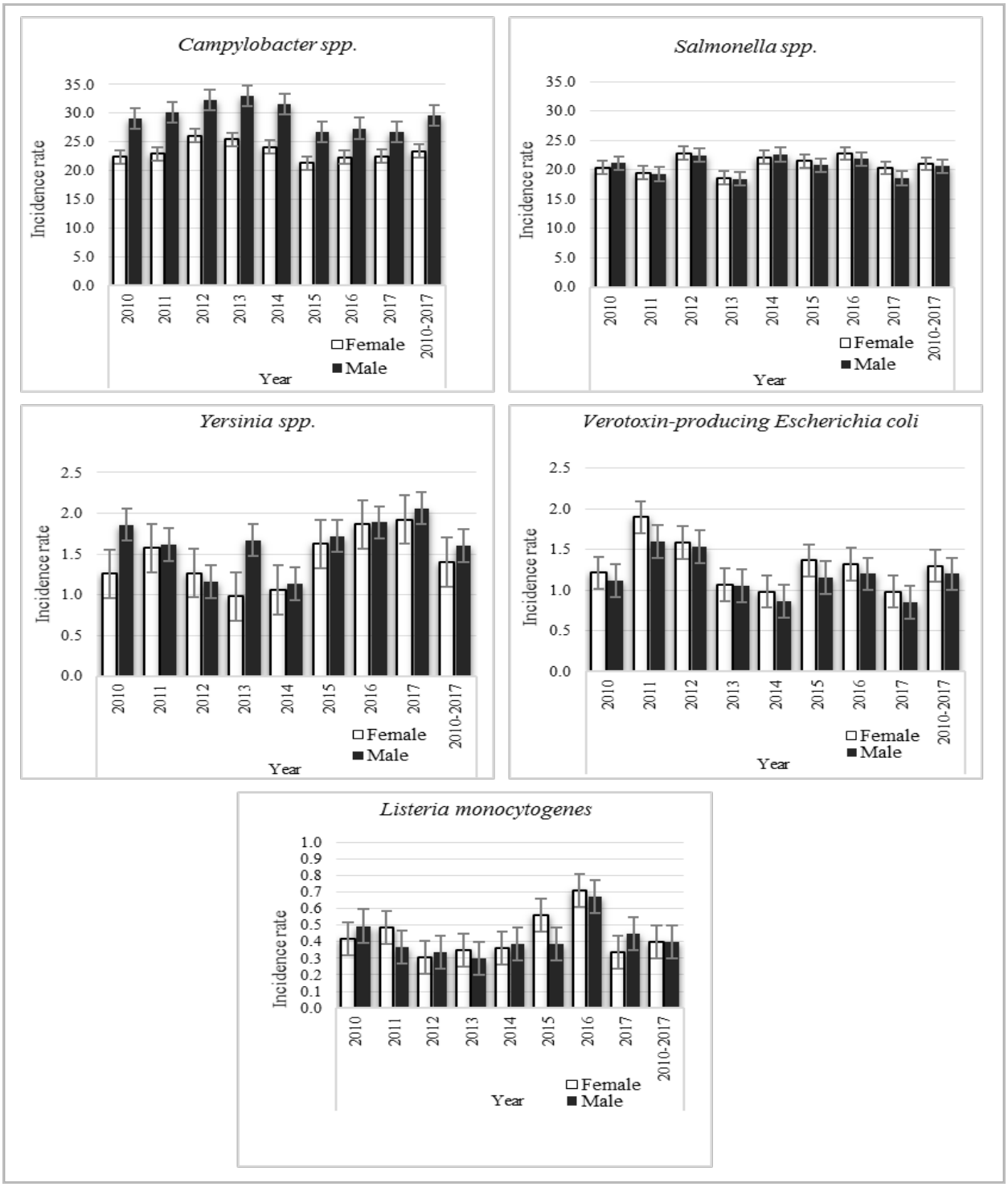


Figure 2.4: Sex-specific annual and mean incidence rates, in 100,000 cases per person-year, of major enteric diseases in Ontario, Canada (2010-2017), with 95% confidence interval error bars



Chapter 3

Temporal, spatial, and space-time distribution of infections caused by five major enteric pathogens, Ontario, Canada, 2010-2017

Manuscript as prepared for Foodborne Pathogens and Disease.
Formatting, inclucing referencing and citations, follows journal standards.

Abstract

In Canada and its provinces, enteric diseases pose substantial health and economic burdens. The distribution of these diseases is uneven across both geography and time, and understanding these patterns is therefore important for prevention of future outbreaks. We evaluated temporal, spatial, and space-time clustering of laboratory-confirmed cases of *Campylobacter spp*. (n=28,728), non-typhoidal *Salmonella spp*. (n=22,640), Verotoxin-producing *Escherichia coli* (VTEC; n=1,340), *Yersinia spp*. (n=1,674), and *Listeria monocytogenes* (n=471) infections, reported between 2010 and 2017 inclusive in Ontario, the most populous province in Canada (population ~13,500,000). For each enteric pathogen we calculated the mean incidence rates (IRs) for Ontario's 35 public health unit (PHU) areas and visualized them using choropleth maps. We examined temporal, spatial, and space-time high infection rate clustering using retrospective Poisson scan statistics. *Campylobacter* and *Salmonella* infections had the highest IRs while *Listeria* infections had the lowest IRs. *Campylobacter*, *Salmonella*, VTEC, and *Listeria* mostly clustered temporally in the spring/summer and sometimes extended into fall, while *Yersinia* showed a less clear seasonal pattern. The IR visualizations, and spatial and space-time scan statistics results showed geographic heterogeneity of infection rates with high infection rate clusters detected mainly in PHUs across the southwestern and central-western regions of Ontario for *Campylobacter*, *Salmonella*, and VTEC infections, and mainly in PHUs located in the central-eastern regions for *Yersinia* and *Listeria*. A high proportion of cases in some of the significant *Salmonella*, VTEC, and *Listeria* infection clusters were linked to disease outbreaks. Further research is needed to determine the pathogen-specific socioeconomic, environmental, and agricultural risk factors that may be related to the temporal and spatial disease patterns we observed in our study.

Introduction

Enteric diseases remain a significant global public health problem (Kirk *et al*., 2015a; Kirk *et al*., 2015b). An estimated 4 million domestically-acquired cases, 11,600 hospitalizations, and 238 deaths occur annually in Canada (Thomas *et al*., 2013; Thomas *et al*., 2015). *Campylobacter spp*., non-typhoidal *Salmonella spp*., *Yersinia spp*., Verotoxin-producing *Escherichia coli* (VTEC), and *Listeria monocytogenes*, are amongst the major causes of enteric diseases in Canada and Ontario (Drudge *et al*., 2019; Thomas *et al*., 2013; Thomas *et al*., 2015). However, regional differences in the distribution of enteric diseases across time and space are known to occur due to variations in individual- and area-level risk factors such as socio-demographic, environmental, and neighborhood characteristics (Arsenault *et al*., 2012; Chang *et al*., 2009; Daoud *et al*., 2017).

Spatial epidemiology has advanced considerably in recent years, along with geographic information systems (GIS) and mapping technologies, tools for analyzing the temporal and geographical distributions, and determinants of disease incidence (Kirby *et al.*, 2017). These tools have been previously used by researchers in and outside of Canada to identify disease clusters and risk sources in time and space, and to detect disease outbreaks (Desjardins *et al.*, 2020; Kirby *et al.*, 2017; Nwosu *et al.*, 2019; Paphitis *et al*., 2020; Pearl *et al*., 2006).

Canadian studies examining temporal and spatial distributions, and clusters of enteric diseases in Manitoba (Green *et al*., 2006), the Northwest Territories (Pardhan-Ali *et al*., 2012), Alberta (Pearl *et al*., 2006), and New Brunswick (Valcour *et al*., 2016), have shown temporal, regional, seasonal, and demographic differences in infection rates. In Ontario, researchers have explored the spatial distribution and clustering of infections caused by *Salmonella* Enteriditis (Varga *et al*., 2013a; Varga *et al*., 2013b; Varga *et al*., 2015a; Varga *et al*., 2015b; Varga *et al*.,

2020), *Salmonella* Heidelberg, *Salmonella* Typhimurium (Paphitis *et al.*, 2020; Paphitis *et al*., 2021) and VTEC (Michel *et al*., 1999; Varga *et al*., 2021), and have reported temporal and geographical heterogeneities of these infections.

To our knowledge, the temporal and spatial distribution and clustering of other reported infections (e.g., *Campylobacter, Listeria,* and *Yersinia*) have not been investigated in Ontario. Therefore, this study aimed to: (i) examine and compare pathogen-specific, mean crude IR distributions across Ontario's public health units (PHU), (ii) detect pathogen-specific temporal, spatial, and space-time infection clusters, at the PHU level, of *Campylobacter*, *Salmonella*, VTEC, *Yersinia*, and *Listeria* infections in Ontario, Canada, reported from January 1, 2010, to December 31, 2017, inclusive. The results from this study will enhance our knowledge of the temporal and spatial patterns of infections caused by these major pathogens and provide a scientific basis for focused public health prevention and control strategies.

Methods

Study area and population

The study was conducted in Ontario, 1 of the 13 provinces and territories of Canada, located in east-central Canada. Ontario is Canada's most populous province (13,448,494 inhabitants; ~40% of the Canadian population; Statistics Canada, 2017) with the third-largest land area (917,741 km^2, Statistics Canada, 2020). Ontario's northern region has 88% of the total land area but contains only about 6% of Ontario's population, while southern Ontario is more densely populated (94% of Ontario's population; Statistics Canada, 2017; Statistics Canada, 2020). Ontario is divided into 35 local public health unit (PHU) areas, which are local government health agencies established by municipalities to deliver health programs (Ontario Ministry of Health and Long-term Care, MOHLTC, 2020). Importantly, Ontario has the most

farms (including fruit and cash crops as well as poultry, dairy, and beef cattle) among Canadian provinces. About 95% of the cattle farms in Ontario are located in southern Ontario (Ontario Ministry of Agriculture, Food and Rural Affairs, OMAFRA, 2021a), mostly concentrated in the southwestern region with some in central and eastern Ontario (Government of Ontario, 2019).

Case Data

Under Ontario's *Health Protection and Promotion Act* (Government of Ontario, 2020), private and public health laboratories are required to report several infectious diseases, including the five pathogens being examined, to local PHUs for investigation. Disease data are managed in Ontario's Ministry of Health and Long-term Care's (MOHLTC) integrated Public Health Information System (iPHIS) surveillance database using standard case definitions (MOHLTC, 2019).

We obtained data on all cases of *Campylobacter, Salmonella*, VTEC, *Yersinia*, and *Listeria*, reported in Ontario with episode dates from January 1, 2010, to December 31, 2017, inclusive, via a request to Public Health Ontario (the provincial public health organization). This study was approved by a University of Waterloo Research Ethics Committee (ORE # 40133).

Each case record included the date of disease onset, five-year age category, sex, PHU of residence, and whether the case was domestic versus travel-acquired, and sporadic versus outbreak-associated. A case is considered travel-related if the case travelled outside Ontario or Canada during the disease incubation period (MOHLTC, 2018). In these data, the month and calendar year of occurrence was used as the disease onset date. When they were not available, the earliest of the sample collection date or the date the case was reported was used as a proxy.

Analysis

Data were compiled in Excel 2013 (Microsoft Corporation, One Microsoft Way, Redmond, Washington, USA), and checked for missing observations. Pathogen-specific mean crude IRs per 100,000 person-years in each PHU were calculated by dividing the eight-year total number of cases per PHU by the eight-year total population estimates (Dohoo *et al*., 2012) from the 2016 Census (Statistics Canada, 2019). Using Statistics Canada's PHU cartographical boundary files (Statistics Canada, 2018), and natural breaks (Jenks, 1967) to classify IRs into six categories, the mean crude IRs were visualized in choropleth maps in ArcGIS 10.7.1 (Environmental Systems Research Institute, ESRI, Inc., Redlands, California, USA). The map depicting the names and labels of each PHU was created in ArcGIS 10.7.1.

Scan statistic was used to detect purely temporal, purely spatial, and space-time high infection rate clusters across PHUs, for each pathogen in SaTScan software, version 9.6 (available online at https://www.satscan.org/). Scan statistic uses a maximum likelihood function that detects disease clusters that are least likely to occur by random chance alone. It uses a scanning window across time and/or space comparing IRs (Poisson model) inside the window to the IRs outside the window at each location (Kulldorff, 2018). A statistically significant high infection rate cluster is identified when the IR inside the window, compared to the IR outside the window, is higher than expected by random chance alone. The cluster with the highest likelihood (the cluster least likely to be due to chance) is denoted as the primary cluster. Secondary non-overlapping clusters are also identified and ranked based on their likelihood ratios. Monte Carlo hypothesis testing is used to estimate the significance levels of these clusters (Kulldorff, 2018).

We used retrospective Poisson models to detect temporal, spatial, and space-time infection rate clusters for the total eight-year period. Poisson models were also used to detect

temporal and space-time clusters for each year of the study period. A circular spatial scanning window was selected and set to detect a maximum cluster size of 50% of the population at risk in space or time. A circular-shaped window is optimal when analyzing aggregate data (Kulldorff *et al*., 2006). The lowest spatial scale was the PHU, represented in the data by the PHUs' centroids. The minimum and maximum temporal units were set at one month and 50% of the study period, respectively. We scanned only for high infection rate clusters and used 999 Monte Carlo replications to estimate the significance of each cluster at $p<0.05$ (Kulldorf, 2018). The latitude and longitude for each PHU centroid was identified, and significant ($p<0.05$) spatial and space-time clusters were mapped using ArcGIS. The outbreak status of cases included in significant clusters was evaluated to determine if the clusters were linked to reported outbreaks.

To address the non-uniformity of relative risks (RRs) throughout each significant spatial or space-time cluster for the Poisson models, we also presented the RR of each PHU inside the clusters. The RR for each PHU inside a significant cluster is obtained from the equation below:

$$RR = \frac{c/e}{(C-c)/(C-e)}$$

Where c is the total number of observed cases in each PHU, e is the total number of expected cases in the PHU, and C is the total number of observed cases in Ontario. A RR>1 indicates a higher risk of infection within that PHU compared to the other PHUs.

Results

Descriptive analysis

A total of 54,853 laboratory-confirmed cases of *Campylobacter* (28,728; 52.4%), *Salmonella* (22,640; 41.3%), VTEC (1,340; 2.4%), *Yersinia* (1,674; 3.1%), and *Listeria* (471; 0.9%) were reported in Ontario during the eight-year period. The annual total number of cases ranged from 6,519 (11.9%) in 2010 to 7,352 (13.4%) in 2012.

Incidence rate distributions

The PHU-level mean IRs (cases per 100,000 per person-time) of infections varied among pathogens and across locations. The highest IRs were observed in *Campylobacter*, *Salmonella*, and VTEC, with high mean IRs concentrating in the southwestern, central-western, and central-eastern regions of the province, and the lowest mean IRs in the northern region (Table 3.1, Figure 3.1). Additional information on the mean IR distribution in each PHU and the map depicting the names and labels of each PHU is given in the Appendices (Table A1 and Figure A1, respectively).

Temporal, spatial, and space-time clustering

The Poisson scan statistic analysis detected several significant ($p < 0.05$) temporal, spatial, and space-time high infection rate clusters, for all the enteric pathogens in our study (Table 3.2, Figure 3.2). *Campylobacter*, *Salmonella*, VTEC, and *Listeria* infections, showed similar temporal patterns, with most of the infection rates clustering in the spring/summer and sometimes extending into fall. Exceptions to this pattern were the two space-time infection clusters for *Salmonella* (March 2012 and January to June 2016) and the one space-time cluster (February to March 2017) for VTEC (Table 3.2). *Yersinia* infections, however, showed a less clear seasonal pattern and had a relatively long duration.

For the whole study period, *Campylobacter* and *Salmonella* infections were both spatially clustered in PHUs in the southwest, central west, and central east, while VTEC infections spatially clustered in PHUs in the southwest and central west. One of the spatial clusters for *Campylobacter*, and *Salmonella*, and four of the spatial clusters for VTEC, included the same four PHUs (Grey-Bruce, Wellington-Dufferin-Guelph, Huron, and Perth) in the southwest and central-west regions of Ontario. The spatial infection clusters in the central east for

Campylobacter and *Salmonella* included the PHUs, Toronto and York. *Yersinia* and *Listeria* infections spatially clustered in the central east only; in Toronto and York for *Yersinia*, and only in Toronto for *Listeria* (Table 3.2, Figure 3.2).

VTEC also spatially clustered in PHUs in the central east and eastern regions of Ontario, while *Yersinia* also spatially clustered in the southwest, central west and eastern regions (Table 3.2, Figure 3.3). VTEC and *Yersinia* were even more spatially-dispersed from the yearly space-time scan analysis, than those from the analysis of the whole study period, with infections spatially clustering in PHUs in the northeast and northwest (Table 3.2, data not mapped).

Many of the significant clusters for *Salmonella*, VTEC, and *Listeria* infections included outbreak-related cases. The highest proportions of outbreak-related cases occurred in a space-time cluster of *Salmonella* cases in Ottawa in the eastern region, occurring in March 2012 (82.6%); space-time clusters of VTEC cases in Kingston, Frontenac, Lennox & Addington in the eastern region, occurring in February to March 2017 (80%), and in Grey-Bruce, Wellington-Dufferin-Guelph, Huron, Perth, occurring in June to October 2011 (54.3%); and a temporal cluster of *Listeria* cases occurring in April to August 2016 (37.7%). In contrast, there were very low or no proportions of cases linked to outbreaks in the significant clusters for *Campylobacter* and *Yersinia* infections (Table 3.2). Additional information on the proportion of outbreak-related cases and travel-related cases, across the PHUs and regions in Ontario, is given in the Appendices (Table A2).

Discussion

This study describes and compares the distribution of incidence rates, and identifies temporal, spatial, and space-time clustering of the five major causes of reported enteric infections in Ontario's PHUs, using scan statistic models.

Campylobacter, *Salmonella*, VTEC, and *Listeria* infections showed seasonal patterns, in which most of the infections occurred in the warmer months (spring and summer). Other researchers have also observed higher rates of enteric infections in warmer weather (Lal *et al*., 2012; Valcour *et al*., 2016; Varga *et al*., 2021). Contaminated food plays a major role in the transmission of these pathogens to humans (Butler *et al.*, 2015; Thomas *et al*., 2013). The higher temperatures experienced in spring and summer increase the survival of pathogens and their proliferation in food products, leading to an increase in enteric disease outbreaks (Stein and Katz, 2017). Higher levels of seasonal activities in summer such as travel (Bramwell, 2016; Tighe *et al*., 2012), eating in restaurants (Lee & Middleton, 2003; Nygren *et al*., 2013; Todd *et al.*, 2007), or other activities that increase the contact between humans and animals (e. g., visiting zoos) (Butler *et al*., 2015; Vrbova *et al.*, 2018) are also important determinants of the higher rates of infections observed in warm weather (David *et al*., 2017).

The IR mapping in our study showed distinct spatial patterns for each enteric pathogen. The highest infection rates were observed primarily in PHUs in the southwest and central west (for *Campylobacter*, *Salmonella*, and VTEC), and in the central-east (for *Yersinia* and *Listeria*). The spatial and space-time scan statistic analysis detected significant high-infection rate clusters in these regions, indicating that the spatial heterogeneity of infections did not occur by chance alone.

In our study, a high infection-rate spatial cluster of VTEC infections was detected in PHUs in the southwest region of Ontario. This region was also identified by Varga *et al*., 2021, as an area with higher-than-expected VTEC infections. Ontario's southwestern region includes many rural areas characterized by an extensive and high densities of cattle, poultry, and other livestock farming operations (OMAFRA, 2021b), potentially resulting in the high infection rates

observed (Arsenault *et al*., 2012; Green *et al*., 2006; Klumb *et al*., 2020; Shaw *et al*., 2016). Farming operations can also lead to environmental contamination of groundwater wells and drinking water (Hrudey *et al*., 2003; Reynolds *et al*., 2020), and fresh produce (Bartz *et al*., 2017). The high rates and clusters observed in southwest Ontario concur with other previous studies where higher VTEC infection rates in Ontario (Michel *et al*., 1999) and high *Salmonella* infection rates in the United States (Shaw *et al*., 2016) were detected in rural areas.

The central-eastern regions of Ontario are home to many large cities (Statistics Canada, 2019). High population density (Arsenault *et al*., 2012) results in higher risk for person-to-person transmission due to close contact with infected persons (Butler *et al*., 2015) and frequent consumption of restaurant meals (Lee & Middleton, 2003; Nygren *et. al*., 2013; Todd *et al.*, 2007) that may explain the high infection rates observed in these regions. The spatial clusters in the central-eastern regions might also reflect urban travel as the clusters contain high proportions of travel-related cases.

We performed temporal and space-time scan statistics using shorter periods (for each year of the study period), and observed that these yearly scans were more sensitive in detecting significant high-rate clusters and more precise in the locations and durations of the significant clusters. This approach may be used to detect high IRs and infection rate clusters that occur in short periods, in localized areas, or smaller communities.

Our results showed that relatively high proportions of cases in the significant temporal, space, and space-time clusters, were linked to outbreak events for *Salmonella*, VTEC, and, *Listeria*, consistent with a previous study in Ontario (Vrbova *et al*., 2012) and Quebec, Canada (Gaulin *et al*., 2014). This is not surprising, as disease clusters help detect areas of disease outbreaks (Paphitis *et al*., 2020) and outbreak information has been used to interpret clustered

cases of diseases (Pearl *et al*., 2006). A large proportion (82.6%) of the space-time cluster of *Salmonella* cases in the City of Ottawa in March 2012 (cluster 2) was linked to outbreaks. Incidentally, several *Salmonella* outbreaks occurred in Ontario between 2012 and 2014. Notably, an outbreak of *S.* Typhimurium was reported in March 2012 at a school in Ottawa for which the source was traced to ground beef burger meat mix (Ontario Agency for Health Protection and Promotion, OAHPP, 2018; Vrbova *et al*., 2018).

A large proportion (35%-38%) of *Listeria* temporal and space-time clusters detected between April and August 2016 in the central east region was also linked to outbreaks in our study. These outbreaks were due, in part, to the consumption of contaminated packaged leafy green salads (Self *et al*., 2019) and pasteurized chocolate milk (Hanson *et al*., 2019), and were reflected in the increase in *Listeria* IRs observed in 2015 and 2016 (John *et al.,* 2022). In agreement with other studies that investigated disease outbreaks in Canada (Bélanger *et al*., 2015; John *et al*., 2022; Ravel *et al*., 2009), we observed relatively low proportions of cases of *Campylobacter* and *Yersinia* linked to outbreaks in the present study. This indicates that *Campylobacter* and *Yersinia* cause more sporadic cases than outbreak cases, which may be due to low viability and transmissibility of *Campylobacter* and *Yersinia*, or their low survival rate in the environment, compared to *Salmonella*, VTEC, and *Listeria* (Todd *et al*., 2009).

Strengths and Limitations

We identified temporal and spatial patterns of reported infections caused by five major enteric pathogens in Ontario, at the PHU level. We detected significant high-rate infection clusters mainly in the southwest, central west, and central east, which could be attributed to the proximity of high farm and population densities. Some of the disease clusters included outbreak-related cases, which may explain the high infection rates observed in spring and summer for

Campylobacter, *Salmonella*, VTEC, and *Listeria*. Assessing the temporal and spatial distributions of enteric infections enables the consideration of environmental and community-level risk factors, such as proximity to high densities of poultry and cattle operations as well as high population densities that may explain the higher infection rates and relative risks in specific areas (Pearl *et al*., 2006). Accurate cluster detection enables identifying at-risk populations and assists adequate public health interventions, for example, screening, surveillance, and prevention (Kirby *et al.,* 2017; Kulldorf, 2018). Therefore, our study will aid public health authorities in the evaluation and implementation of focused enteric disease prevention and control measures to mitigate the health burden of enteric infections.

Findings from our study are subject to the limitations inherent in passive surveillance data which do not represent the true burden of diseases in the general population. Factors such as under-reporting and under-diagnosis in different populations, different regions, and across times, due to differences in healthcare-seeking behavior, accessibility to healthcare, failure to obtain stool samples by physicians, inadequate or lack of diagnostic tools, inaccurate diagnosis, and rate of reporting along the administrative chain (Amaku *et al*., 2017; Majowicz *et al*., 2005), could result in underestimation of the number of cases in our study. Despite these limitations, our study provides an insight into the temporal and spatial distributions of infections caused by five major enteric pathogens in Ontario, especially *Yersinia* and *Listeria* infections that had not been previously studied in Ontario or Canada.

Conclusion

To our knowledge, our study was the first to investigate the temporal and spatial distributions of cases of *Campylobacter*, *Salmonella*, *Yersinia,* VTEC*,* and *Listeria* infections, in all 35 PHUs in Ontario, Canada. *Campylobacter*, *Salmonella*, VTEC, and *Listeria*, mainly

temporarily clustered in the spring and summer, whereas, *Yersinia* did not show a very clear temporal pattern. We identified areas with high infection rates and disease clusters mainly in the southwestern and central-western regions (for *Campylobacter*, *Salmonella*, and VTEC); and mainly in the central-eastern region (for *Yersinia* and *Listeria*). Our results help to bridge the knowledge gap in understanding the clustering of diseases caused by these five major pathogens in Ontario, in time and space, at the PHU level. Results from our study will aid in guiding further research to determine the agricultural, environmental and socioeconomic factors that may be related to the temporal and spatial disease patterns we observed in our study. Knowledge of these factors will significantly reduce infection risks by implementing control and preventive measures along the farm-to-fork continuum. As our analysis was at the PHU level, future research may also investigate the effect of different geographical scales (e.g., forward sortation area level) for data analysis especially for areas of low population densities.

Table 3.1: Public health units (PHUs) with the highest mean incidence rates (IRs) of infections, caused by five major enteric pathogens, in Ontario, Canada (2010-2017)

Pathogen	Mean IR[1, 2]	PHU	Region
Campylobacter spp.	59.6	Huron County	Southwest
	57.9	Perth District	Southwest
	45.8	Grey Bruce	Southwest
	39.8	Wellington-Dufferin-Guelph	Central west
	35.1	Haldimand-Norfolk	Central west
	31.5	York Region	Central east
	31.3	Toronto	Central east
	30.2	Haliburton, Kawartha, Pine Ridge	Central east
	30.1	Niagara Region	Central west
	28.1	Southwestern	Southwest
Salmonella spp.	28.8	Grey Bruce	Southwest
	25.1	Huron County	Southwest
	24.6	Perth District	Southwest
	24.2	York Region	Central east
	23.9	Wellington-Dufferin-Guelph	Central west
	23.9	Haldimand-Norfolk	Central west
	22.8	Durham Region	Central east
	22.4	Peel Region	Central east
	22.2	North Bay Parry Sound District	North east
	22.1	Toronto	Central east
Verotoxin-producing *Escherichia coli*	8.2	Perth District	Southwest
	7.6	Huron County	Southwest
	5.9	Grey Bruce	Southwest
	3.5	Wellington-Dufferin-Guelph	Central west
	2.4	Southwestern	Southwest
	2.1	Waterloo Region	Central west
	1.8	Haldimand-Norfolk	Central west
	1.6	Leeds, Grenville and Lanark District	Eastern
	1.5	Peterborough County-City	Central east
	1.5	Hastings & Prince Edward Counties	Eastern
	1.5	Middlesex-London	Southwest
	1.5	Eastern Ontario	Eastern
	1.4	Sudbury and District	North east
Yersinia spp.	3.3	York Region	Central east
	2.1	Toronto	Central east
	2.1	North Bay Parry Sound District	North east
	1.9	Halton Region	Central west

Pathogen	Mean IR[1, 2]	PHU	Region
	1.8	Wellington-Dufferin-Guelph	Central west
	1.7	Leeds, Grenville and Lanark District	Eastern
	1.7	Grey Bruce	Southwest
	1.6	Algoma District	North east
	1.5	Waterloo Region	Central west
	1.4	Perth District	Central east
	1.4	Peel Region	Central east
Listeria	1.0	Peterborough County-City	Central east
	0.8	Renfrew County and District	Eastern
	0.7	Southwestern	Southwest
	0.6	Algoma District	North east
	0.6	Toronto	Central east
	0.5	Simcoe Muskoka District	Central east
	0.5	Wellington-Dufferin-Guelph	Central west
	0.5	Chatham-Kent	Southwest
	0.5	Peel Region	Central east
	0.4	Haldimand-Norfolk	Central west
	0.4	Sudbury and District	North east
	0.4	Porcupine	North east
	0.4	Eastern Ontario	Eastern
	0.4	Huron County	Southwest
	0.4	Thunder Bay District	North west
	0.4	Grey Bruce	South west
	0.4	Windsor-Essex County	Southwest
	0.4	City of Hamilton	Central west
	0.4	York Region	Central east
	0.4	City of Ottawa	Eastern
	0.4	Halton Region	Central west

[1]Incidence rate (number of cases per 100,000 person-years)
[2]Mean incidence rate (total number of cases (N)/total population over 8 years

Table 3.2: Significant high-rate spatial, space-time, and temporal clusters of infections caused by five major enteric pathogens, at the local public health unit (PHU) level, in Ontario, Canada (2010-2017)

Cluster type[1]	Study period/year	Cluster #	# PHUs (n=35)	Cluster duration	Observed # cases (O)	RR [2]	p-value [3]	% Cases linked to outbreak
Campylobacter spp.								
Temporal	2010-2017	1	All	Jun 2013-Oct 2013	2297	1.58	0.001	0.0
	2010	1	All	Jun-Sep	1642	1.89	0.001	0.0
	2011	1	All	Jun-Oct	2035	1.91	0.001	0.3
	2012	1	All	Jun-Oct	2267	1.93	0.001	0.2
	2013	1	All	Jun-Oct	2297	1.93	0.001	0.0
	2014	1	All	Jun-Nov	2474	1.87	0.001	0.0
	2015	1	All	Jun-Oct	1832	1.73	0.001	0.1
	2016	1	All	Jun-Oct	1977	1.88	0.001	0.3
	2017	1	All	Jun-Oct	2006	1.90	0.001	0.4
Spatial	2010-2017	1	4	--	2150	1.79	<0.001	0.4
		2	2	--	9715	1.28	<0.001	0.2
		3	1	--	6928	1.24	<0.001	0.1
		4	1	--	2787	1.21	<0.001	0.4
		5	1	--	313	1.33	<0.001	0.0
		6	1	--	1083	1.14	0.003	0.0
Space-time	2010-2017	1	4	Jun 2011-Nov 2014	5691	1.40	<0.001	0.1
		2	4	Jun 2010-Nov 2013	1031	1.97	<0.001	0.6
	2010	1	16	Jun-Aug	644	2.03	<0.001	0.0
		2	9	Jun-Sep	685	1.52	<0.001	0.0
	2011	1	16	Jun-Sep	798	1.84	<0.001	0.8
		2	8	Jul-Sep	612	1.77	<0.001	0.0
	2012	1	5	Jun-Oct	1120	1.75	<0.001	0.0
	2013	1	7	Jun-Oct	1272	1.82	<0.001	0.0
		2	7	Jun-Oct	378	1.82	<0.001	0.0
	2014	1	9	Jun-Nov	1209	1.7	<0.001	0.0
		2	14	Jun-Sep	543	1.64	<0.001	0.0
	2015	1	21	Jul-Sep	661	1.78	<0.001	0.0
	2016	1	8	Jun-Oct	920	1.69	<0.001	0.5
		2	16	Jul-Sep	555	1.66	<0.001	0.0
	2017	1	5	Jun-Sep	839	1.8	<0.001	0.5
Salmonella spp.								
Temporal	2010-2017	1	All	July2012-Sep 2012	1036	1.50	0.001	12.4
	2010	1	All	Jul-Aug	632	1.47	0.001	10.9
	2011	1	All	Jul-Sep	887	1.56	0.001	3.8
	2012	1	All	Jul-Sep	1036	1.54	0.001	12.4
	2013	1	All	Jul-Aug	611	1.58	0.001	3.9
	2014	1	All	Jul-Sep	989	1.42	0.001	21.5
	2015	1	All	Aug-Sep	617	1.35	0.001	8.6
	2016	1	All	Jun-Sep	1164	1.20	0.001	8.3
	2017	1	All	Apr-Sep	1551	1.30	0.001	4.6
Spatial	2010-2017	1	4	--	10696	1.16	<0.001	8.1
		2	2	--	3327	1.16	<0.001	8.1

Cluster type[1]	Study period/year	Cluster #	# PHUs (n=35)	Cluster duration	Observed # cases (O)	RR [2]	p-value [3]	% Cases linked to outbreak
		3	6	--	4620	1.13	<0.001	6.8
		4	1	--	4881	1.07	0.001	8.3
Space-time	2010-2017	1	5	Jul 2012-Sep 2012	546	1.76	<0.001	14.3
		2	1	Mar 2012	69	4.24	<0.001	82.6
	2010	1	7	Jul-Sep	468	1.46	<0.001	9.4
	2011	1	7	Jul-Sep	469	1.56	<0.001	2.3
	2012	1	5	Jul-Sep	546	1.73	<0.001	14.3
		2	1	Mar-Mar	69	3.96	<0.001	82.6
	2013	1	7	Jul-Aug	342	1.71	<0.001	3.8
	2014	1	6	Jul-Sep	552	1.57	<0.001	22.3
	2015	1	5	Jul-Sep	495	1.51	<0.001	7.7
	2016	1	10	Aug-Aug	134	2.11	<0.001	20.9
		2	5	Jan-Jun	428	1.5	<0.001	8.4
	2017	1	6	Apr-Sep	814	1.41	<0.001	5.8
	2015	1	2	Jan-Oct	43	2.98	<0.001	0.0
	2016	1	2	Apr-Sep	71	2.25	<0.001	0.0
	2017	1	16	Mar-Aug	72	2.08	0.0018	0.0
Verotoxin-producing *Escherichia coli*								
Temporal	2010-2017	1	All	Jun 2011-Oct 2011	170	2.69	0.001	21.2
	2010	1	All	Jun-Aug	81	3.34	0.001	12.3
	2011	1	All	Jun-Oct	170	3.80	0.001	21.2
	2012	1	All	Jul-Aug	87	3.50	0.001	10.3
	2013	1	All	Apr-Sep	97	2.10	0.001	24.7
	2014	1	All	Jun-Aug	68	3.48	0.001	11.8
	2015	1	All	Jun-Sep	106	3.15	0.001	25.5
	2016	1	All	Jul-Sep	98	3.79	0.001	18.4
	2017	1	All	Jul-Nov	79	2.19	0.001	7.6
Spatial	2010-2017	1	4	--	245	4.96	<0.001	14.3
		2	2	--	88	6.81	<0.001	3.4
		3	1	--	77	4.97	<0.001	24.7
		4	1	--	80	2.98	<0.001	16.3
		5	2	--	54	1.78	0.015	11.1
Space-time	2010-2017	1	4	Jun 2014-Sep 2017	125	5.51	<0.001	4.0
		2	9	Jun 2011-Sep 2011	60	2.63	<0.001	8.3
	2010	1	7	Jun-Aug	32	7.67	<0.001	6.3
	2011	1	4	Jun-Oct	46	13.39	<0.001	54.3
		2	7	Aug-Sep	37	2.6	0.0055	8.1
	2012	1	5	Jun-Sep	42	8.89	<0.001	28.6
		2	3	Aug-Aug	8	13.05	0.0018	0.0
		3	1	Jul-Aug	7	13.34	0.0061	0.0
	2013	1	7	Jul-Oct	27	5.03	<0.001	14.8
		2	3	Jul-Sep	13	5.48	0.012	15.4
	2014	1	16	Jun-Aug	36	5.18	<0.001	13.9
	2015	1	6	May-Oct	50	6.52	<0.001	12.0
	2016	1	4	Jul-Aug	21	18.5	<0.001	14.3
		2	11	Jul-Sep	34	2.71	0.0067	14.7
	2017	1	4	Apr-Sep	24	10.31	<0.001	0.0
		2	1	Feb-Mar	5	17.31	0.026	80.0
Yersinia spp.								

Cluster type[1]	Study period/year	Cluster #	# PHUs (n=35)	Cluster duration	Observed # cases (O)	RR [2]	p-value [3]	% Cases linked to outbreak
Temporal	2010-2017	1	All	Aug 2015-Sep 2017	618	1.52	0.001	1.6
	2012	1	All	Feb-Mar	45	1.96	0.003	0.0
	2014	1	All	Mar-Aug	99	1.95	0.002	0.0
	2015	1	All	Aug-Oct	84	1.72	0.001	0.0
	2016	1	All	Jan-May	149	1.89	0.001	6.7
	2017	1	All	Mar-Aug	184	1.89	0.001	0.0
Spatial	2010-2017	1	2	--	765	2.11	<0.001	0.0
		2	1	--	295	2.41	<0.001	0.0
		3	1	--	470	1.52	<0.001	0.0
Space-time	2010-2017	1	2	Apr 2014-Sep 2017	368	1.93	<0.001	0.0
		2	13	Jul 2017-Jul 2017	21	4.28	0.006	0.0
	2010	1	2	Apr-Sep	70	3.13	<0.001	0.0
	2011	1	4	Mar-Aug	91	2.79	<0.001	0.0
	2012	1	6	Jan-Apr	58	2.91	<0.001	0.0
	2014	1	2	Apr-Sep	57	3.7	<0.001	0.0
	2015	1	2	Jan-Oct	43	2.98	<0.001	0.0
	2016	1	2	Apr-Sep	71	2.25	<0.001	0.0
	2017	1	16	Mar-Aug	72	2.08	0.0018	0.0
Listeria monocytogenes								
Temporal	2010-2017	1	All	Jul 2015-Aug 2016	125	2.06	0.001	30.4
	2013	1	All	Jul-Aug	24	5.86	0.001	8.3
	2015	1	All	Jul-Nov	41	2.37	0.012	4.9
	2016	1	All	Apr-Aug	61	2.43	0.001	37.7
	2017	1	All	Aug-Dec	35	2.42	0.018	5.7
Spatial	2010-2017	1	1	--	140	1.65	<0.001	7.1
Space-time	2010-2017	1	7	Apr 2016-Aug 2016	38	3.19	<0.001	31.6
	2012	1	3	Jul-Sep	5	15.65	0.043	0.0
	2013	1	21	Aug-Aug	11	7.7	0.0025	9.1
	2016	1	5	Apr-Jul	31	2.7	0.031	35.5

[1]Discreet Poisson model
[2]Relative risk
[3]Statistical significance at $p<0.05$

Figure 3.1: Mean incidence rates per 100,000 person-years of infections caused by five major enteric pathogens, by public health unit, in Ontario, Canada (2010-2017)

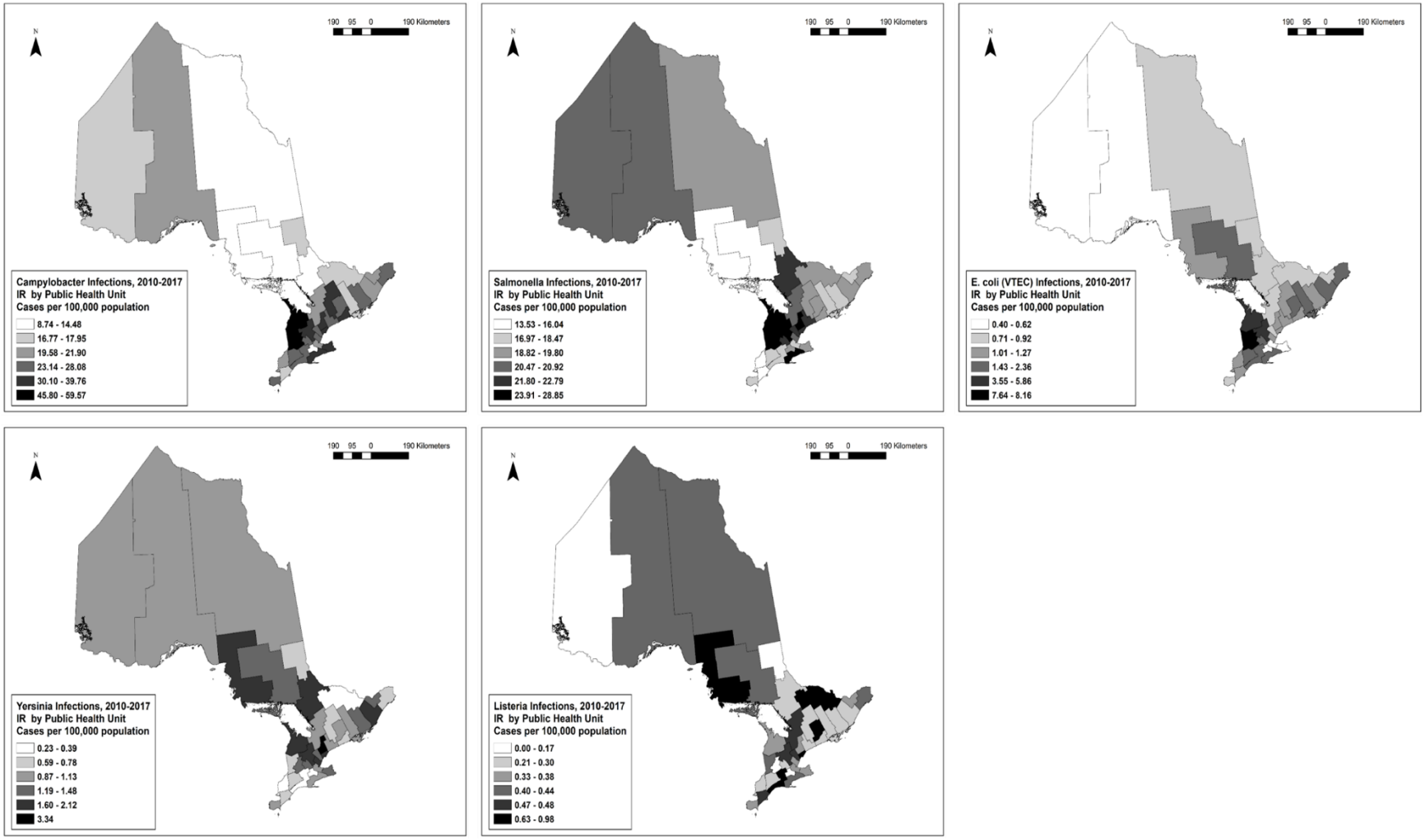


Figure 3.2: Significant spatial clusters of infections caused by five major enteric pathogens, at the public health unit level, in Ontario, Canada (2010-2017)

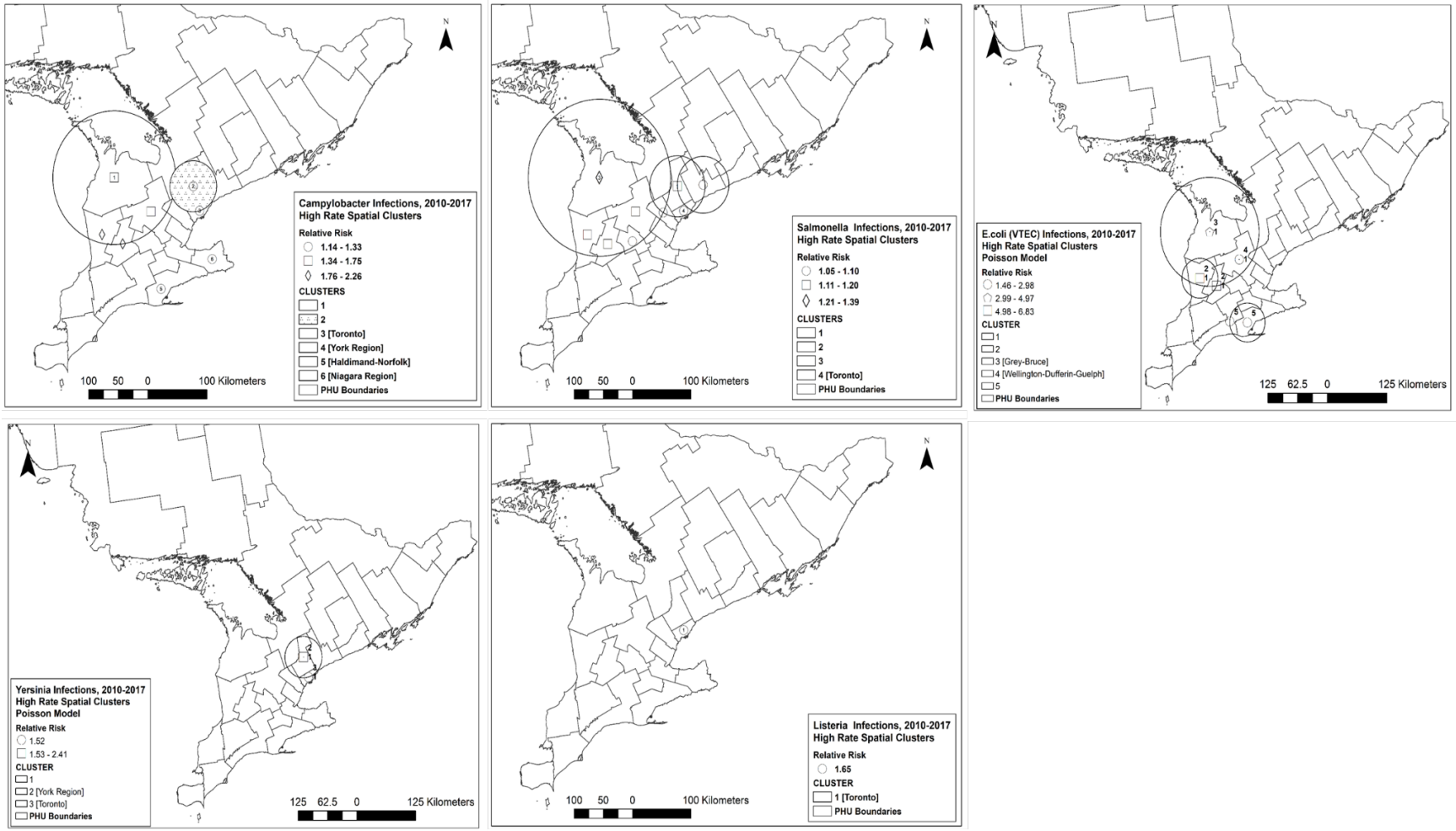
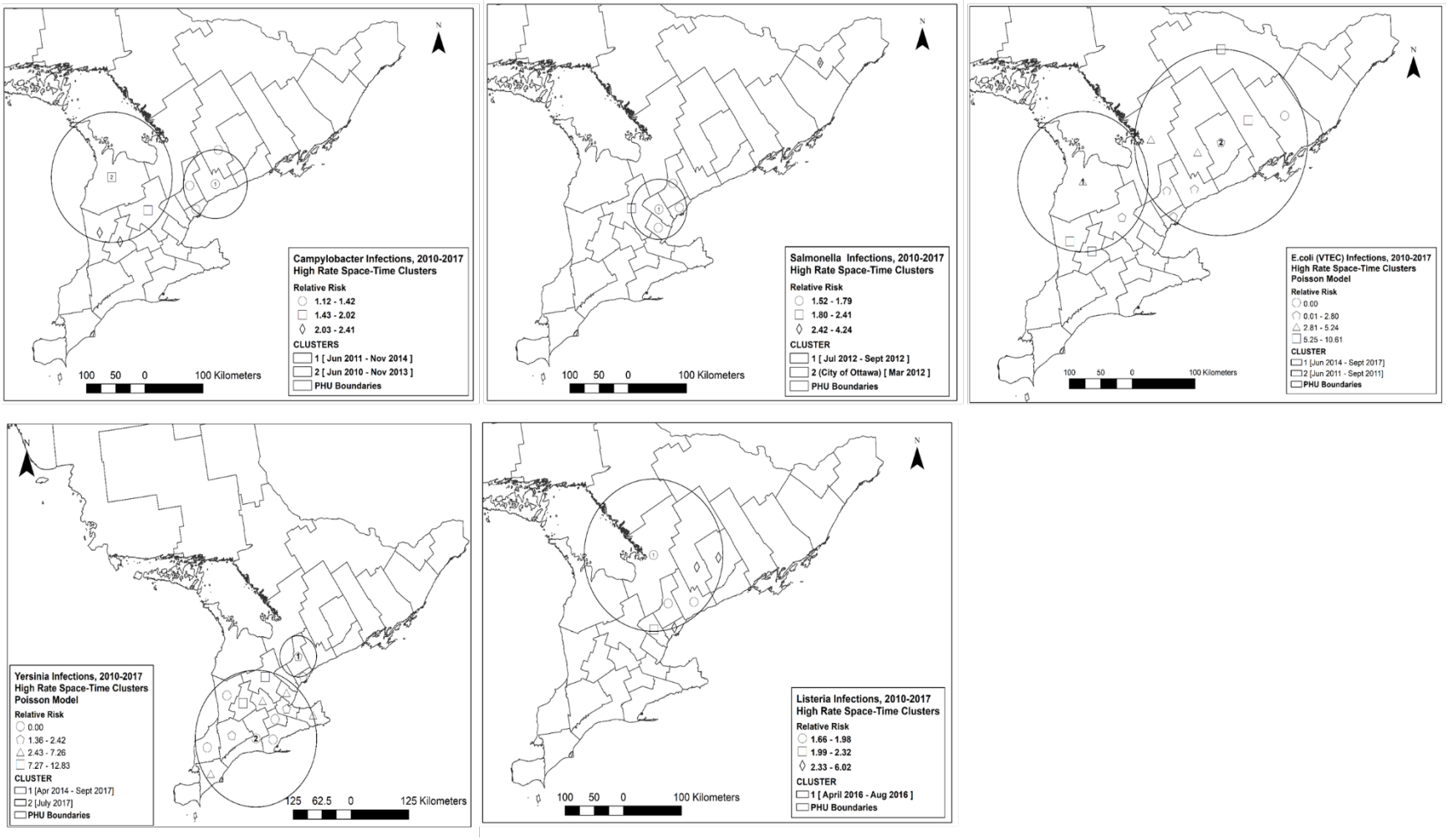


Figure 3.3: Significant space-time clusters of infections caused by five major enteric pathogens, at the public health unit level, in Ontario, Canada (2010-2017)



Chapter 4

Socioeconomic determinants of *Campylobacter* and non-typhoidal *Salmonella* infections in Ontario, Canada, 2015-2017: an ecological study

Manuscript as prepared for Epidemiology & Infection.
Formatting, including referencing and citations, follow journal standards.

Summary

Campylobacter sp. and non-typhoidal *Salmonella* sp. are major causes of enteric diseases in Ontario, Canada, and worldwide**.** Although low socioeconomic status is generally associated with poor health outcomes, its relationship with enteric diseases in Ontario is not well known. Using negative binomial regression models, we examined the association between age- and sex-adjusted incidence rates (IRs) of laboratory-confirmed cases of *Campylobacter* and *Salmonella* (aggregated to the forward sortation [FSA] area level), and FSA-level socioeconomic factors (median household income; percent population with bachelor degree or higher; unemployment rate; and percent visible minorities, Aboriginals (as defined by Statistics Canada), total immigrants, recent immigrants, and lone-parent families), adjusting for the population of the FSA from the 2016 Census. After controlling for the other variables in the final multivariable models, percent population with bachelor degree or higher and percent total immigrants were significant risk factors for *Campylobacter* IRs*,* while median income and percent total immigrants were significant risk factors for *Salmonella* IRs. Further investigation of these socioeconomic factors and the mechanisms through which they affect infection rates in different communities, are needed in future studies.

Introduction

Enteric diseases remain a significant public health issue in Ontario, Canada, and worldwide, causing great health and economic burden [1]. About 4 million domestically-acquired cases (1 in 8 Canadians) of foodborne enteric infections are estimated to occur annually in Canada, with about 11,600 hospitalizations and 238 deaths [2, 3], and an estimated annual cost of CAN$3.7 billion [4, 5]. Of the pathogens known to cause enteric infections, *Campylobacter* sp. and *Salmonella* sp. are amongst the top ranking pathogens that cause the greatest number of infections, hospitalizations, and death in Canada [2, 3]. *Campylobacter* and *Salmonella* infections are among the infectious diseases that are reportable in Ontario, under Ontario's *Health Protection and Promotion Act* [6], and are the most frequently reported causes of enteric illness in Ontario [7, 8], resulting in mean annual incidence rates (IRs) of 26.5 and 20.9 cases per 100,000 person-years, respectively [8].

Campylobacter infections are primarily associated with handling or consumption of fresh or undercooked poultry [9, 10], while *Salmonella* infections often result from handling or consumption of contaminated chicken, processed poultry, or raw eggs [9, 11]. The clinical presentations of enteric diseases vary and are relatively mild, but can result in hospitalization and even death, especially in children, the elderly, and the immuno-compromised persons [1, 12].

While there are several traditional risk factors for enteric infections, such as personal hygiene [11, 13], inadequate food handling practices and behaviours [14], travel [15, 16], and eating outside of home [17, 18], socioeconomic status (SES) is increasingly being investigated as a risk factor for enteric infections worldwide [19-23]. Many studies on SES and infectious

diseases generally show higher rates of diseases among populations of low SES in both developing [21, 24-26], and developed countries [20, 27], with highest rates observed in the most deprived areas [19]. However, the association between SES and infections generally show inconsistent results, due to the complex nature of transmission mechanisms and pathways, and differences in pathogen virulence and host factors [28].

Given that infectious diseases distribution vary with population dynamics and across different geographical regions [16, 29-32], it is important to understand the SES risk factors for infections in different communities. A review of literature revealed that only three studies have been conducted in Ontario, and three in the rest of Canada, to investigate SES risk factors for enteric diseases (Table B1 in the Appendices [22, 33-37]). One of the three studies in Ontario, a retrospective, cross-sectional telephone survey in two selected communiities, reported a higher risk of acute gastrointestinal illness in low income females than in males of the same income category [34]. The other two studies in Ontario used surveillance data to investigate SES risk factors for *Salmonella* Enteriditis in the greater Toronto area [22] and for VTEC across Ontario [37]. These studies found that high average number of children per census family, and high and low (compared to medium) average median family income were risk factors for *Salmonella* Enteriditis infection [22]; while low median family income was a risk factor for VTEC [37]. Therefore, the relationships between *Campylobacter* and *Salmonella* infections and the various SES risk factors in our study have not been investigated across Ontario; more investigations into the nature of the SES risk factors for enteric diseases, in Ontario are needed.

Thus, the overall goal of this study was to investigate the area-level SES risk factors for the incidence rates of reported enteric infections caused by non-typhoidal *Salmonella* sp. and *Campylobacter* sp., commonly transmitted by food, in Ontario, Canada (2010-2017). The specific objective was to determine the association between pathogen-specific age- and sex-adjusted IRs of reported infections due to these two pathogens, and each of the forward sortation area (FSA)-level SES risk factors in Table 4.1.

Methods

Study Area and Population

Our study area was the province of Ontario, Canada's most populated province (13,448,494 inhabitants; ~40% of the Canadian population [38], consisting of 513 forward sortation areas, FSAs [39, 40]). A FSA is a geographical unit (a postal delivery area) representing the first three digits in a Canadian postal code [40]. Cases (508 cases of *Campylobacter* and 458 cases of *Salmonella*) with no FSA information were excluded from analysis. To avoid using unstable rates for FSAs with small populations, we also excluded data for 9 FSAs (K1P, K1X, K6T, K8B, L4V, L9J, N3E, N6N, and P0Y) with zero population and those below 1000 (total population of 3730), resulting in the exclusion of 4 additional cases (1 case of *Campylobacter* and 3 cases of *Salmonella*). The annual FSA population, for the 504 FSAs included in our study, ranged from 1090 to 111,370 with a mean of 26,673, based on the 2016 Canada Census [37].

Data and Sources

We obtained and analyzed de-identified disease surveillance data on cases of *Campylobacter* sp. and non-typhoidal *Salmonella* sp., reported in Ontario's 513 forward sortation areas (FSAs), between January 1, 2015 and December 31, 2017, inclusive, via a request to Public Health Ontario (the provincial public health organization), from Ontario's Ministry of Health and Long-term Care's (MOHLTC) integrated Public Health Information System (iPHIS) surveillance database, using standard case definitions [41]. This study was approved by a University of Waterloo Research Ethics Committee (ORE # 40133).

Each case record included disease onset date, sample collection date, or the date the case was reported (month and calendar year); sex; five-year age category; and FSA of residence. Data were compiled in Excel 2013 (Microsoft Corporation, One Microsoft Way, Redmond, Washington, USA), and checked for missing observations. Data for year and age were 100% complete. Observations with missing sex information (11 cases, 0.06%) were excluded from analysis.

The total number of laboratory-confirmed cases of *Campylobacter* and *Salmonella* reported in Ontario over the study period (3 years), were aggregated at the FSA level and used as the response variables. The FSA-level population from the 2016 Census was used as the offset variable to account for background population. FSA-specific socioeconomic data collected by Statistics Canada from the 2016 Canada population census [38] were used as the predictor variables (Table 4.1).

Data Analysis

Data were analysed in Excel 2013 and Stata software, version 14.2 (StataCorp LLC, College Station, Texas, USA). FSA-specific IRs per 100,000 persons for *Campylobacter* and *Salmonella* infections were calculated as the sum of the annual pathogen-specific cases reported between 2015 and 2017, divided by three times the FSA-level population obtained from the 2016 Census [38, 42].

Using the maximum likelihood estimation and the least squares method, we conducted separate Poisson univariable analysis, for each pathogen, to examine the relationship between the age- and sex-adjusted, FSA-specific, 3-year IRs and each of the continuous FSA-level socioeconomic variables in Table 4.1. The overall fit of the model was assessed for over-dispersion of data using the Deviance and Pearson χ^2 goodness-of-fit (gof) test statistics [42] by using the *estat gof* command in Stata. Because the Poisson model was deemed inadequate for the analysis, since the χ^2 was significant at $p<0.05$ (indicating over-dispersion of the case data), we used the negative binomial model to analyze the data.

To choose the final multivariable model for each pathogen, all the main effects were tested for significance ($p<0.05$) based on the likelihood ratio test, in a backward stepwise selection process. Variables that were not statistically significant ($p\geq0.05$) were sequentially removed from the model. To check whether any of the variables in the final models were subject to confounding by any variable that were excluded from the final model, we re-introduced the excluded variable individually into the model. We examined the change in the strength, direction, and significance of the coefficient at $p<0.05$. A change from significant to non-

significant (or vice versa), a change in sign, or change of 20% or higher to the coefficient of a statistically significant variable, would indicate a confounding effect, and should be retained the variable in the final model [42]. We estimated age- and sex-adjusted incident rate ratios (IRRs) and their corresponding p-values and 95% confidence intervals, and graphed the statistics from the final fitted models by using the *margins* and *marginsplot* commands in Stata.

Results

Descriptive analysis

From 2015 to 2017, a total of 9691 laboratory-confirmed cases of *Campylobacter* and 8273 cases of *Salmonella* were reported in Ontario. The number of cases in each FSA ranged from 0 to 179 for *Campylobacter*, and 0 to 87 for *Salmonella*. Of the 504 FSAs included in our study, 13 (2.6%) FSAs reported no cases of *Campylobacter* or *Salmonella*; 22 (4.6%) and 15 (3.0%) FSAs, respectively, reported more than 50 cases of *Campylobacter* and *Salmonella*. For the FSAs that reported at least one case during the study period, the FSA-level crude IR ranged from 1.5 to 95.0 cases per 100,000 persons for *Campylobacter*, and from 1.5 to 68.6 cases per 100,000 persons for *Salmonella* (Table B2 in the Appendices). There were higher rates (>50 cases per 100,000 persons) for *Campylobacter* and *Salmonella* in FSAs located in the southwestern and central east regions of the province than in the northern region.

Univariable analysis

Results of the univariable analysis are shown in Table 4.2. *Campylobacter* and *Salmonella* rates were significantly higher with an increase in median income, percent population with bachelor's degree or higher, recent immigrants, and total immigrants; and

significantly lower with an increase in percent Aboriginals. For example, an increase in the percent population with a bachelor degree or higher increased infection rates by a factor of 1.0083 (0.8%) and 1.0047 (0.5%), respectively, for *Campylobacter* and *Salmonella*. On the other hand, an increase in the percent Aboriginals within the FSA decreased infection rates by a factor of 0.9482 (5.2%) and 0.9729 (2.7%), respectively, for *Campylobacter* and *Salmonella*.

Multivariable analysis

The results of the final multivariable models are shown in Table 4.3. The relationships between the IRs and socioeconomic variables in the final multivariable models are shown in Figures 4.1 to 4.11. Re-introduction of the variables that were removed from the models did not change the magnitude, sign, or significance of any of the coefficients for the variables included in the final multivariable models.

Campylobacter

Even after controlling for the other covariates in the final multivariable model, and similar to the results from the univariable analysis, the rate of *Campylobacter* infection significantly increased with an increase in percent population with bachelor degree or higher and percent total immigrants; and significantly decreased with percent unemployment persons, Aboriginals, and lone-parent families. In the multivariable analysis, and in contrast to the results from the univariable analysis, *Campylobacter* infection rates significantly decreased with an increase in median household income and percent visible minorities. There was no significant association with percent recent immigrants. Specifically, *Campylobacter* infection rates increased by a factor of 1.0034 (0.3%) and 1.0118 (1.2%), respectively, with an increase in

percent population with bachelor degree or higher and percent total immigrants. On the other hand, *Campylobacter* rates decreased by 4.4%, 0.8%, 3.9%, and 3.1%, respectively, with an increase in percent unemployed persons, visible minorities, Aboriginals, and lone-parent families. The negative association with median household income was very negligible; IRR was approximately 1 (Table 4.3, Figures 4.1 to 4.7).

Salmonella

Similar to the results from the univarible analysis, and after controlling for other covariates in the final multivariable model, *Salmonella* infection rates increased with an increase in median household income and percent total immigrants; and decreased with an increase in percent Aboriginals. In contrast to the results from the univariable analysis, *Salmonella* rates decreased with an increase in percent visible minorities. There was no significant association with percent population with bachelor degree or higher, recent immigrants, or lone-parent families. Specifically, *Salmonella* rates increased by a factor of 1.0145 (1.5%) with an increase in percent total immigrants; and decreased by a factor of 0.9934 (0.7%) and 0.9892 (1.1%), respectively, with an increase in percent visible minorities and Aboriginals. The positive association with median household income was also very negligible; IRR was approximately 1 (Table 4.3, Figures 4.8 to 4.11).

Discussion

FSAs in the southern and central eastern regions of Ontario experienced higher rates of reported infections caused by both pathogens. These findings align with results from other studies on the distribution of enteric infections in Ontario, Canada, and the U.S. [7-8, 43-44].

Southern Ontario is known for its animal agriculture, including cattle, livestock, and poultry farms and operations [45, 46]. Exposures to farm settings or farm animals are significantly correlated to high rates of enteric infections, including *Campylobacter* and *Salmonella* infections [9, 27]. A prospective epidemiological study conducted between 2012 and 2016 in Minnesota in the U.S., to determine the exposure risks to food production animals or their environments among cases of domestically-acquired enteric infections, found that 23% of the cases reported exposure to animal agriculture, including 28% of *Campylobacter* cases and 10% of *Salmonella* cases [9]. The eastern part of Ontario is an urban region, characterized by dense population [38]. In these areas, person-to-person contact, contaminated environment, or contact with pets are potential routes of disease transmission [47, 48].

However, exposures to risk factors for enteric diseases are determined by complex interactions among pathogen characteristics, individual behavior, geographical factors, and environmental and cultural characteristics, as well as demographic and SES factors. [8, 13, 21, 29, 32, 49-51]. Therefore, we examined the association between the *Campylobacter* and *Salmonella* IRs, and various FSA-level SES risk factors. It is worthy to note that, although this study was a group-level study, some inferences about individual-level risk factors were made in the subsequent discussions below, potentially resulting in ecologic fallacy.

Median household income

Income is an indicator of SES that can impact various aspects of material resources with direct implications for health [52]. In the univariable analysis, we observed that both

Campylobacter and *Salmonella* infection rates were higher in FSAs with higher median household incomes. The inverse was the case in the multivariable analysis for *Campylobacter*, where infection rates decreased in FSA's with an increase in median household income. This indicates that the relationship between *Campylobacter* IRs and median household income was influenced by other covariates in the final multivariable model, indicating that the relationship between median household income and *Campylobacter* IRs were confounded by the other variables in the model.

In this study, the risk of *Campylobacter* infection decreased, while the risk of *Salmonella* infection increased, in FSAs with higher median household income. However, the relationship between *Campylobacter* and *Salmonella* rates and median household income was minimal. In agreement with our findings, in Connecticut, U.S., the risk of *Salmonella* infection was higher in census tracts with lower proportion of persons living below poverty level [23], whereas in Denmark, the rates of *Campylobacter*, *Salmonella* Enteriditis, and *Shigella* infections in adults increased significantly with income group [28]. A possible explanation for the results observed here may be that other socioeconomic factors have a stronger influence on infection rates than does income. The differences between these results and the ones observed here may be due to the complex relationhip between *Campylobacter* and *Salmonella* infection risks, and behavioural patterns [51, 53], seasonal factors [8, 30, living and environmental conditions [19, 35], and other sociodemographic factors [8, 22, 23, 34]. For example, in Northwest Territories, Canada, the risk of *Salmonella* infection was higher in communities with higher proportion of households in

core needs up to 42% after which the risk decreased [35]. In Toronto, Canada, the highest risk of *Salmonella* Enteriditis infection was observed in FSAs with high average number of children per census family [22].

Percent bachelor degree or higher

We observed that *Campylobacter* IRs significantly increased with an increase in percent FSA population with bachelor degree or higher. *Campylobacter* IRs was also shown to increase with increased educational attainment, in Manitoba, Canada [33] and in Denmark [28]. Although, this may be illogical since education increases the knowledge necessary to make healthy decisions [52, 54], food safetly knowledge may be low even among educated persons [55]. As well, knowledge of proper safe food handling methods is not necessarily a predictor of actual practice [56. 57]. For example, in Canada, the prevalence of consuming undercooked egg increases with increasing educational level [53]. Similarly, a multistate survey to study the prevalence of foodborne disease relating to food consumption and handling practices in the U.S., found that consumption of undercooked hamburger was common among persons with higher education [51], significantly increasing risk of infections in this group. Therefore, some underlying individual-level factors, such as improper food handing behaviour or high-risk food consumption behaviour among persons with higher educational level, that may explain our findings.

Our findings may also be due to better healthcare seeking behaviour exhibited by persons with higher educational attainment. Educated persons may be more able to understand their

health needs, communicate more effectively with healthcare providers, and have the capacity to obtain and understand basic health information and services required to make appropriate health decisions [54], such as seeking medical care for enteric infections. For example, in Kenya, caretakers with formal education were more likely to seek medical care for pediatric enteric infections, than those without formal education [58]. In this regard, episodes of infection in this group will be highly represented in the surveillance system due to increased detection rate.

Persons with higher education with higher discretionary income are more inclined to eat outside of home than their counterparts [59], which could increase the risk for infections in populations with high proportions of highly educated persons. Eating in restaurants and other food facilities increases the risk of infection [17, 60] due to factors such as non-compliance [61] and improper food handling practices [62] these facilities. In Canada, eating in food service establishments was an important risk factor for the foodborne disease outbreaks reported between 2008 and 2014 [63]. Travel activity also tend to be higher among population with higher education due to more discretionary income, which would increase the risks of travel-related infections in this population [16, 64].

We did not find any significant association between *Salmonella* IRs and percent FSA population with bachelor degree or higher in the final multivariable model. In contrast, in Denmark, Simonsen and colleagues [28] reported a decrease in the rate of *Salmonella* Typhimurium with high educational level, while studies in the U.S. reported higher *Salmonella* infection rates in areas with higher educational levels [59, 65]. The difference between these findings and our results may be due to the different food preferences in different populations.

The risk of foodborne infection depends, in part, on the specific type of food or food exposure route [66, 67]. For example, a food source attribution study across different regions determined that, in the European subregions, poultry meat, eggs, and pork, are important risk factors for *Salmonella* infections; whereas in the American subregions (U.S. and Canada), pork was of lesser importance compared to poultry meat and eggs [67]. The variations in results may also be due to differences in travel destinations since the risk of exposure to a specific infection depends on the travel destinations [64].

Unemployment rate

We observed lower rates of *Campylobacter* in FSAs with higher unemployment rates. An ecological study to evaluate the socioeconomic risk factors for foodborne disease outbreaks in Catalona, Spain, also reported that communities with high proportions of unemployment had fewer outbreaks of foodborne diseases [68]. High unemployment rate typically results in poor health outcomes and high mortality rates, due to limited access to income and choices that can support healthy living [69-71]. However, Ontario has a universal and free basic healthcare system, irrespective of employment status. Therefore, unemployment would not present a barrier to medical care access that would explain the lower rates of *Campylobacter* infections observed in FSAs with higher unemployement rates. Therefore, other factors such as reduced international travel and other leisure activities, may be at play here. Reduced ability to travel, resulting from decreased income, would minimize the risk of exposures to enteric infections. Travel is an important risk factor for many enteric infections, including those due to *Campylobacter* and

Salmonella [16, 64]. In the U.S., *Campylobacter* (42%) and *Salmonella* (32%) were the most common pathogens identified in travel-associated enteric infections [64]. Decreased income from unemployment may also result in less probability of eating outside of home [55], resulting in lesser risk of foodborne diseases associated with eating out.

Percent visible minorities

We observed lower rates of *Campylobacter* and *Salmonella* in FSAs with a higher percent of visible minorities. This could be a reflection of poor healthcare utilization among the visible minority population due to fear of discrimination or negative perception of health care providers. Fear of racism or being treated poorly due to one's cultural background is a significant predictor of low health care utilization [72]. Another possible explanation may be the use of traditional medicines such as herb use (versus use of orthodox medication) among visible minorities, especially for mild symptoms like those that are mostly encountered with enteric diseases. For example, a systematic review of the prevalence of herb use among minority groups in the U.S., reported that the prevalence of herb ranged from 17% to 30%. "Treatment of an ailment" was the most frequently reported reason for the herb usage. Where a medical condition was specified, chronic health conditions, such as diabetes, cancer, and human immunodeficiency viruses-related diseases, were the ones resulting in the herb usage [73]. However, it is conceivable to hypothesize that herbs are also used to treat symptoms of enteric diseases among visible minorities, due to cultural reasons or the belief that traditional or herbal medicines are safer than orthodox medicines [73].

Similar to our results, a study in Toronto reported that FSAs with higher population (51.9-93.4%) of visible minorities had a lower risk for *Salmonella* Enteriditis infection than FSAs with lower population (29.5-51.8%) of visible minorities [22]. In another Ontatio sudy, the risk of VTEC infection rates was also lower in FSAs with higher proportions of visible minorities [37]. Being that visible minorities are concentrated in urban areas, and farming operations, with which *Campylobacter* and *Salmonella* infections are often associated [9, 27], are mainly in rural areas [45, 46], the authors postulated that the lower infection rate observed in FSAs with high proportions of visible minorities, was likely due to reduced exposure to farm-related infection risks [37]. In a study to determine the burden of enteric infections in Ontario, Canada, the authors reported that *Campylobacter* and *Salmonella* infections were the most common enteric infections in cases who only had exposures to animals [48].

Percent Aboriginals

We observed that *Campylobacter* and *Salmonella* infection rates were lower in FSAs with higher percent Aboriginals, defined by Statistics Canada as persons that "have ancestry associated with the Aboriginal peoples of Canada, i.e., First Nations (North American Indian), Métis, and Inuit" (Statistics Canada, 2018), in the population. Compared to southern Ontario, a high proportion of Indigenous peoples resides in northern Ontario [38] that is known for its long and sever cold weather conditions [74], under which the proliferation of pathogens in the environment would be minimized [8, 16, 32]. Lower rates of enteric infections in the north (compared to the south) were also reported in a recent Ontario study [8]. Therefore, the lower

rates of *Campylobacter* and *Salmonella* infections in FSAs with higher Aboriginals observed in the present study may be reflective of the actual infection rates due to the cold weather condition in northern Ontario, where a high proportion of Indigenous peoples are concentrated. Residents in northern Ontario may also have reduced risk of *Campylobacter* and *Salmonella* infections from animal exposure as fewer farms are located in northern Ontario than in Southern Ontario [46].

Lower healthcare use among Indigenous peoples may also explain the lower rates of diseases in FSAs with higher population of Aboriginals. Only 4.8% and 16.9% of people with enteric infections, respectively, in Rigolet and Iqaluit (two Inuit communities in Canada) used healthcare services, despite the high rate of self-reported incidence of enteric infections in these communities [75]. This may be due to language barriers, challenges and cost involved in travelling from the rural community to the healthcare facility, cultural differences, or lack of trust for the quality of healthcare services [75]. Limited accessiblitiy to healthcare services across many regions in Indigenous communities may be responsible for the lower health care use in these communites [76]. Although Healthcare Canada has a universal healthcare system, inequitable access to healthcare services are experienced by Indigenous peoples in Canada [76, 77].

Percent Total Immigrants

We observed higher rates of *Campylobacter* and *Salmonella* infections in FSAs with higher percent total immigrants. Immigrants are identified as a vulnerable group due to factors such low SES, language barriers, living environment, marginalization, and government policies

[78], and are more likely to have food of poor microbial quality available to them than non-immigrants (79, 80]. Studies into the quality of retail foods available to persons of different SES in the U.S., reported food of low microbial quality in areas of lower SES, compared to higher SES areas [79, 80]. This poses increased risks for enteric infections in low SES populations.

In contrast to our findings, a study in Toronto, Canada, did not find any significant relationship between *Salmonella* Enteriditis infection rate and immigrant population [22]. One explanation for this may be because the study in Toronto pertained only to one strain of *Salmonella* while our study made no differentiation between strains but included all *Salmonella* strains. Another explanation is the differences in distribution and IRs of *Salmonella* across different regions [8], and among *Salmonella* strains and phage types [8, 16, 81] as well as their associations with various demographicrisk factors in influencing disease outcome [16]. For example, *Salmonella* Enteriditis (57.6%), *Salmonella* Typhimurium (18.4%), and *Salmonella* Heidelberg (16.1%), were the most frequently reported causes of *Salmonella* infections reported between 2010 and 2017 in Ontario [8]. As well, children 0-9 years old had the highest risk of *S.* Typhimurium infection, while adults 20-29 years old had the highest risk of *S.* Heidelberg infection.

The differences between the Toronto study [22] and the present study may also be due differences in health statuses, cultural and sociodemographical characteristics, as well as differences in food handling and consumption behaviours, of the immigrant population in Toronto, compared to the rest of Ontario. Thus infection rates could be different across

immigration communities. For example, in the U.S., *Salmonella* infection rates were higher in communities with more African American populations than in communities with more Hispanic populations [65].

Percent lone-parent families

We observed that *Campylobacter* IRs were lower in FSAs with higher population of lone-parent families. Similarly, Varga and colleagues in 2021 [37] reported that VTEC cases in high-rate spatial disease clusters were more likely to originate from areas with low proportions of lone-parent families. Of all Census families in Canada, 13.7% and 3.3%, respectively, are lone-mothers and lone-fathers, and in Ontario, 80% of lone-parent families are lone-mothers [38]. Lone mothers are significantly less likely to be employed and to have lower income, compared to mothers in two-parent families [82, 83]. Due to economic reasons, we propose that lone parents will most likely not engage in leisure activities such as travel or visiting the zoo, thereby reducing their exposure to infections related to travel [15-16, 64], or direct contact with animals [9, 48, 66]. The lower *Campylobacter* IR in FSAs with higher lone-parent families may also result from low healthcare seeking behaviour in these FSAs due to lower educational attainment in populations of lone-parent families [83]. The frequency of healthcare use may be higher in communities with more educated persons who are more equipped to seek, process, and understand the various medical services available in the community [54].

At the individual level, our results might also be explained by the dietary choices in lone-parent homes. A survey conducted in 2014 in Newfoundland, Canada, determined that 40% of

lone parents always consumed basic foods such as meat, pasta, fruits, and vegetables. In addition, approximately 70% of lone parents purchase food requiring no cooking [82]. Since most cases of *Campylobacter* and *Salmonella* infections result from the handling or consumption of fresh poultry, eggs, chicken [11, 17], the risk of contracting these infections may be lower in FSAs with higher population of lone-parent families, compared to FSAs with lower population of lone-parent families (or with higher two-parent families).

Limitations

Our findings are subject to some limitations. We used surveillance case data, which is known to underestimate true case numbers. To be included in a surveillance system, a case must access the healthcare system, and the healthcare provider must request a stool sample, which must be provided for laboratory testing to confirm diagnosis [1, 84-85]. In Ontario, it is estimated that for every case of enteric infection reported, the number of cases in the community ranges from 105 to 1,389, with a mean of 313 [85]. Specifically, for every case of *Campylobacter* and *Salmonella* infection reported in Canada, there were estimated 23 to 49 cases and 13 to 37 cases, respectively, occurring annually in the Canadian community [86].

The case data in our study spanned three years, from 2015 to 2017, while the population data we used for our analysis was from the Census 2016, to approximate a mid-point between the years of study. While this could have minimized the effect of population change that occurred over the study period, we do not think this would have changed the results from our study since the estimated population growth in Ontario, from 2015 to 2017, was only 2.6% [87]. However,

there could have been a differential population change in different FSAs or regions of Ontario during the study period. For example, a substantial population growth in the urban areas or a considerable decline in population in the rural areas [88]. would have biased our results such that the IRs in the urban areas would have been over-estimated, and IRs in the rural areas under-estimated.

We aggregated our case data and used FSA as the unit of analyses. It is possible that studies based on other geographical levels will produce different results due to the Modifiable Area Unit problem [89]. For example, in Quebec, Canada, the number of predictor variables significantly associated with the risk of *Campylobacter* infection decreased as the geographical level of aggregation increased [29]. In addition to the limitations above, any variation within each FSA are not apparent (as in any group-level analysis). Therefore, inferences to individual-level association may lead to biased interpretations (ecologic fallacy) [42]. However, we believe that this bias is reduced in our study since data were analyzed at a low geographical scale, the FSA level, with more population homogeneity, compared to analysis at a higher geographical scale [90]. As well, ecological studies can be used to identify community-level risk factors for health outcomes, the knowledge of which can inform policies affecting communities and help inform preventive programs for diseases [42, 90], especially when individual-level data are not available or in cases where there is need to investigate health risks in the context of the environment where people live or work [90].

Conclusions

Our study examined the relationship between *Campylobacter* and *Salmonella* IRs, and select SES factors at the FSA level in Ontario, Canada. To the best of our knowledge, this was the first study to investigate area-level SES risk factors for reported infections due to these pathogens across Ontario.

Generally, low SES status results in poorer health outcomes or increased risk for diseases. Our study showed that the effect of SES on *Campylobacter* and *Salmonella* infection rates is pathogen-specific, and dependent upon the SES factor. For example, we saw that the risk of *Campylobacter* infections increased significantly with increasing percent population with bachelor degree and higher in an FSA, whereas the risk of *Salmonella* infections was not predicted by this SES factor in the final multivariable model. On the other hand, *Campylobacter* and *Salmonella* infections were similar in their associations with percent visible minorities, Aboriginals, and total immigrants. Incidence rates of infections caused by both pathogens had an inverse relationship with percent visible minorities and Aboriginals, and a direct relationship with percent total immigrants.

Our results are not contrary to the current evidence in the literature concerning SES risk factors for infectious diseases, which show variabilities in the relationship between socioeconomic risk factors and enteric diseases. However, an important contribution to current literature is the finding that, in Ontario, the risk of *Campylobacter* infection is higher in FSAs with higher population of persons with bachelor degree or higher, and in FSAs with higher population of total immigrants; while the risk of *Salmonella* infection is higher in FSAs with

higher median household income, and higher population of total immigrants. Other SES variables (percent unemployed persons, visible minorities, Aboriginals, percent recent immigrants, and lone-parent families) were not identified as risk factors of *Campylobacter* or *Salmonella* infections, at the FSA level. These findings give more insight into the role the various SES factors in our study play in enteric infection risks in Ontario. This will aid public health authorities to design effective public health protection and prevention programs that would, for example, help in: improving safe food handling and consumption practices in populations with a high number of people with bachelor degree or higher; and in reducing the risk of exposure to infection in communities with higher percentage of immigrant populations.

Table 4.1: Forward Sortation Area-specific socioeconomic characteristics from the 2016 Canada Census used as predictor variables in the study

Variable	Definition[1]
Median household income	Median income of families in a household is the amount that divides the income distribution of that household into two halves.
% Population with a bachelor's degree or higher	The number of persons between 25 and 64 years of age with a university degree or higher divided by the total population between 25 and 64 years of age.
% Unemployed persons (unemployment rate)	The number of unemployed persons 15 years of age and older divided by the number of persons 15 of age older in the labour force.
% Visible minorities	The total number of visible minorities divided by the total population. Visible minorities are "persons other than Aboriginal peoples, who are non-Caucasian in race or non-White in colour".
% Aboriginal persons	The total number of Aboriginal peoples divided by the total population. Aboriginal persons are persons that "have ancestry associated with the Aboriginal peoples of Canada, i.e., First Nations (North American Indian), Métis, and Inuit".
% Total immigrants	The total number of immigrants divided by the total population. Immigrants are "persons who are, or who have ever been, landed immigrants or permanent residents".
% Recent immigrants	The total number of recent immigrants divided by the total population. Recent immigrants are "persons who are, or who have ever been, landed immigrants or permanent residents, who arrived in Canada in the previous five years".
% Lone-parent families in a household	The total number of lone-parent families divided by total number of census families in households. A lone-parent family is a "lone parent of any marital status with at least one child living in the same dwelling as that child or those children".

[1] Statistics Canada (2018)

Table 4.2: Age- and sex-adjusted incidence rate ratios (IRR), p-values, and 95% confidence intervals (CI), from the univariable models of the relationship between *Campylobacter* and non-typhoidal *Salmonella* infections and their socioeconomic risk factors, in Ontario, Canada, 2010-2017; non-significant values are shown in bold

Variable	*Campylobacter spp.*				*Salmonella spp.*			
	IRR	Assoc.	*p*-value*	CI	IRR	Assoc.	*p*-value*	CI
Median income	1.000005	+	<0.001	1.000003-1.000006	1.000004	+	<0.001	1.000003 - 1.000006
% Bachelor degree	1.008324	+	<0.001	1.00677-1.009881	1.004798	+	<0.001	1.003091-1.006508
% Unemployed persons	0. 9119651	-	<0.001	0.8995117-0.9245909	**0. 9876708**	**-**	**0.088**	0.9736929-1.001849
% Visible minorities	**1.000428**	**+**	**0.83**	0.9994123-1.001445	1.004108	+	<0.001	1.003047-1.005172
% Aboriginals	0.948201	-	<0.001	0.9404203-0.9560461	0.9728673	-	<0.001	0.9661836-0.9795972
% Total immigrants	1.002803	+	<0.001	1.001404-1.004204	1.007166	+	<0.001	1.005678-1.008656
% Recent immigrants	1.012363	+	0.002	1.004441-1.020347	1.029143	+	<0.001	1.020669-1.037688
% Lone-parent families	0.9711203	-	<0.001	0.9664631-0.9758	**0. 9986192**	**-**	**0.579**	0.9937611-1.003501

*$p<0.05$

Table 4.3: Age- and sex-adjusted incidence rate ratios (IRR), p-values, and 95% confidence intervals (CI), from the final multivariable model of the relationship between *Campylobacter* and non-typhoidal *Salmonella* infections, and their socioeconomic risk factors, in Ontario, Canada, 2010-2017

Variable	IRR	*p*-value*	CI
Campylobacter			
Median income	0.9999918	<0.001	0.9999896 - 0.999994
% Bachelor degree	1.0034	0.001	1.001469 - 1.005336
% Unemployed persons	0. 9563671	<0.001	0.9337878 - 0.9794924
% Visible minorities	0.9924863	<0.001	0.9892665 - 0.9957166
% Aboriginals	0.9607908	<0.001	0.9505596 - 0.9711321
% Total immigrants	1.011872	<0.001	1.007142 - 1.016625
% Lone-parent families	0.9691822	<0.001	0.9617852 - 0.9766361
Intercept	0.0008623	<0.001	0.000657 - 0.0011319
Salmonella			
Median income	1.000003	0.001	1.000001 - 1.000005
% Visible minorities	0. 9933967	<0.001	0. 9901068 - 9966976
% Aboriginals	0. 9891847	0.003	0.9820224 - 0.9963993
% Total immigrants	1.014495	<0.001	1.009637 - 1.019377
Intercept	0.0001442	<0.001	0.0001248 - 0.0001665

*$p<0.05$

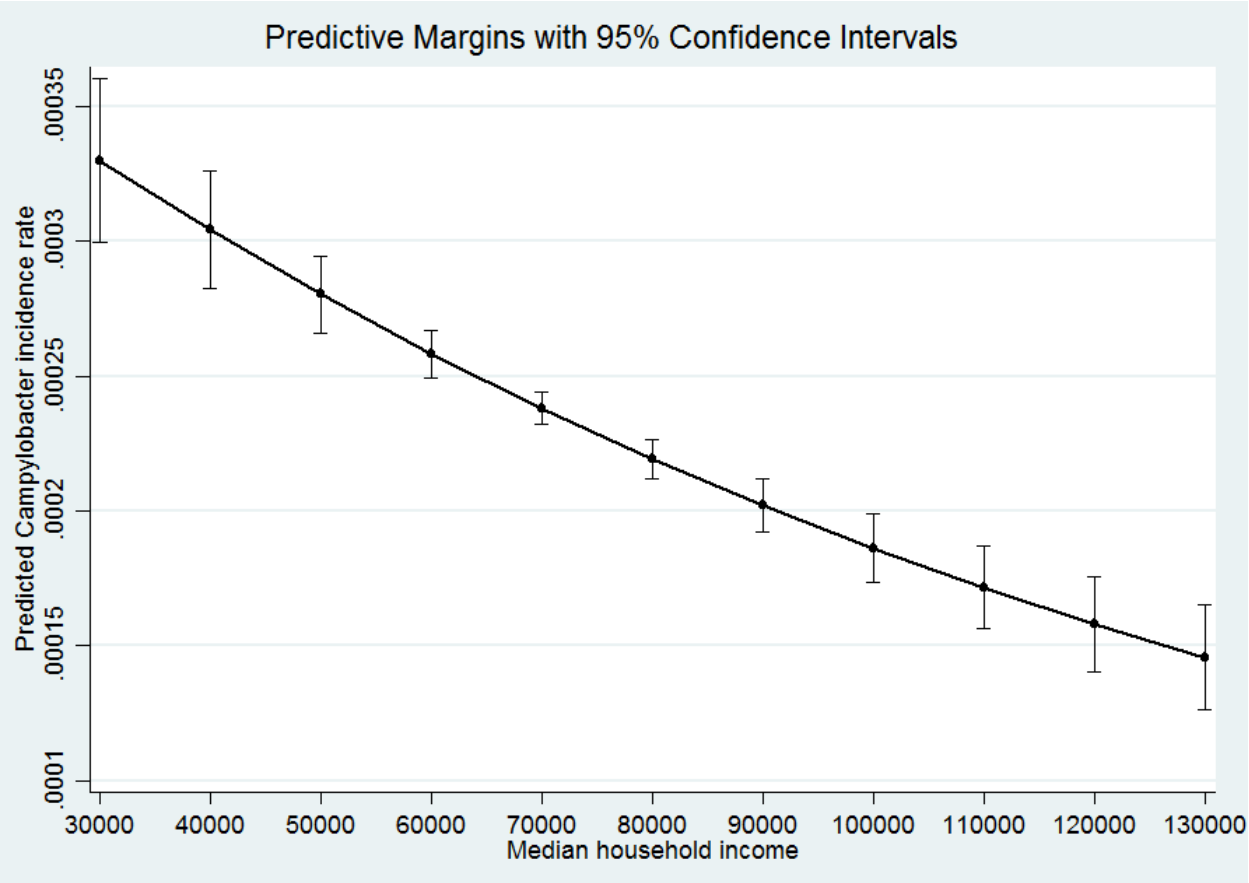


Figure 4.1: The relationship between age- and sex- adjusted incidence rate (per person-years) of *Campylobacter* infections and median household income in each FSA, holding all other variables in the final multivariable regression model constant. Median household income is in Canadian dollars.

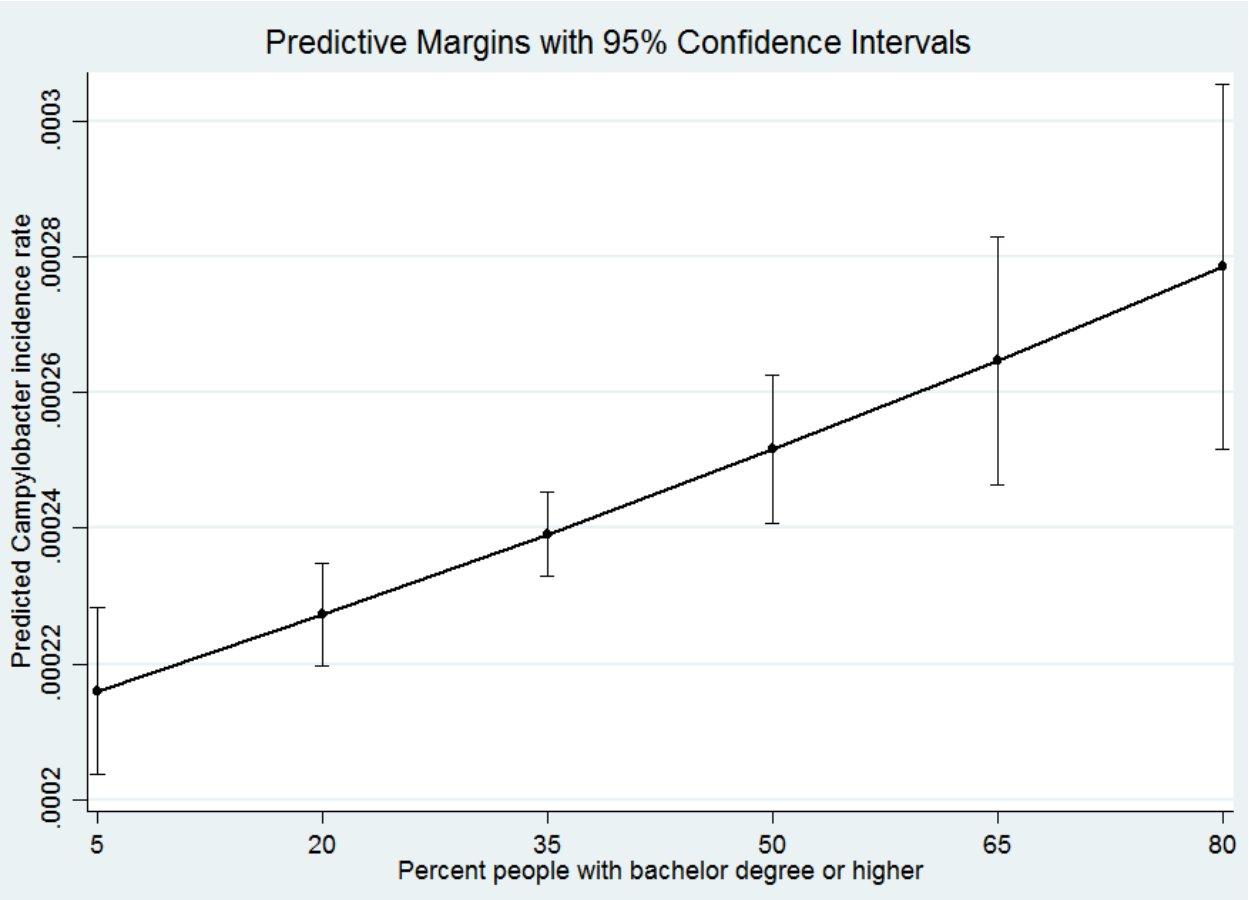


Figure 4.2: The relationship between age- and sex- adjusted incidence rate (per person-years) of *Campylobacter* infections and percent people with bachelor degree or higher in each FSA, holding all other variables in the final multivariable regression model constant.

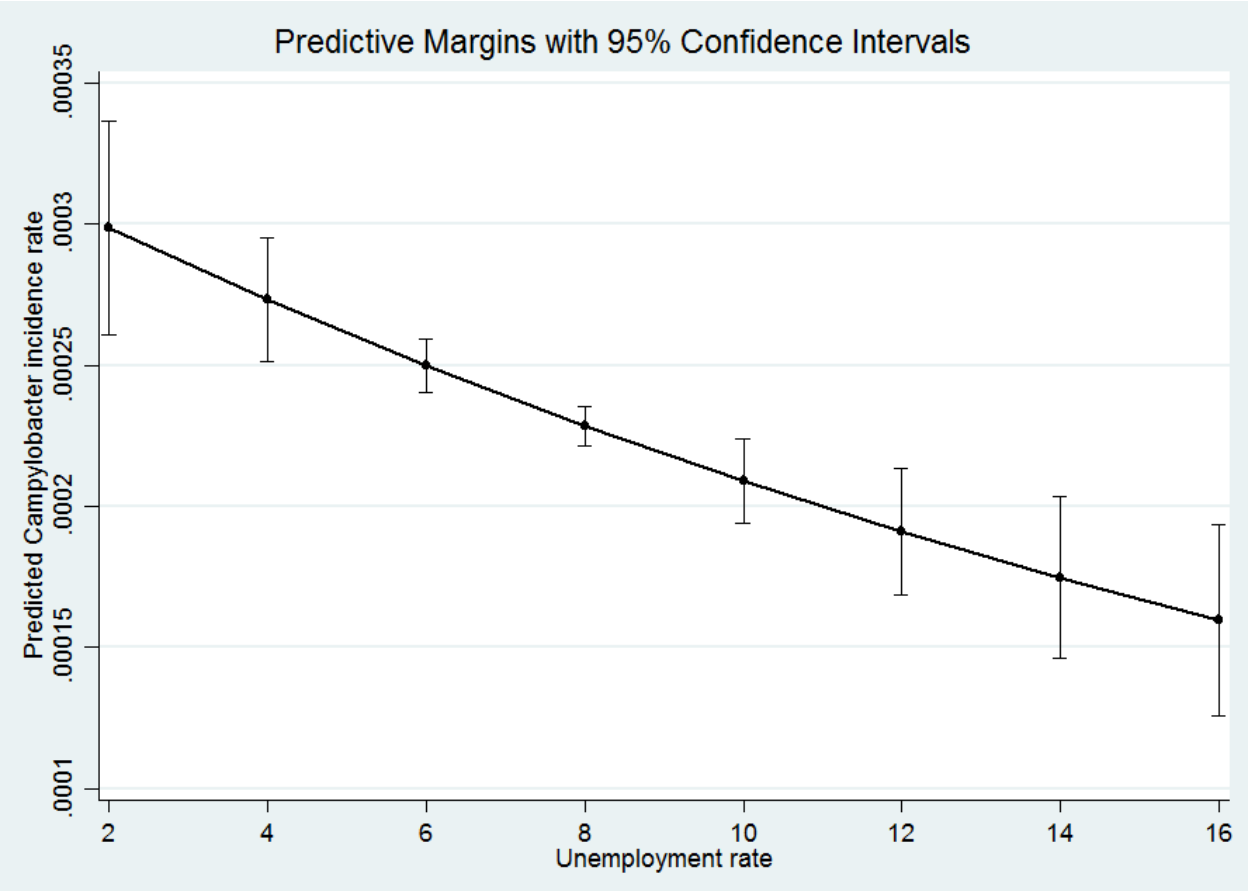


Figure 4.3: The relationship between age- and sex- adjusted incidence rate (per person-years) of *Campylobacter* infections and unemployment rate in each FSA, holding all other variables in the final multivariable regression model constant.

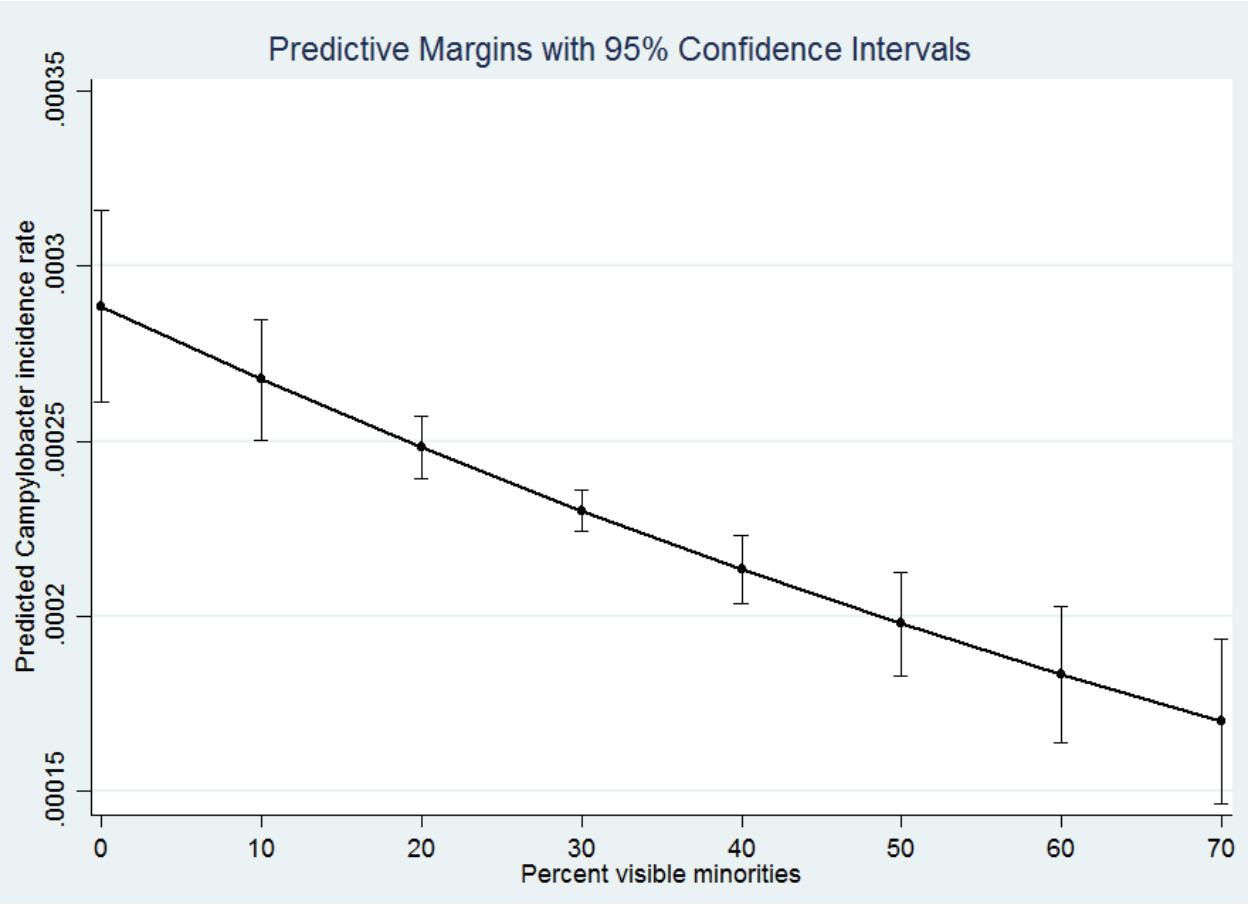


Figure 4.4: The relationship between age- and sex- adjusted incidence rate (per person-years) of *Campylobacter* infections and percent visible minorities in each FSA, holding all other variables in the final multivariable regression model constant.

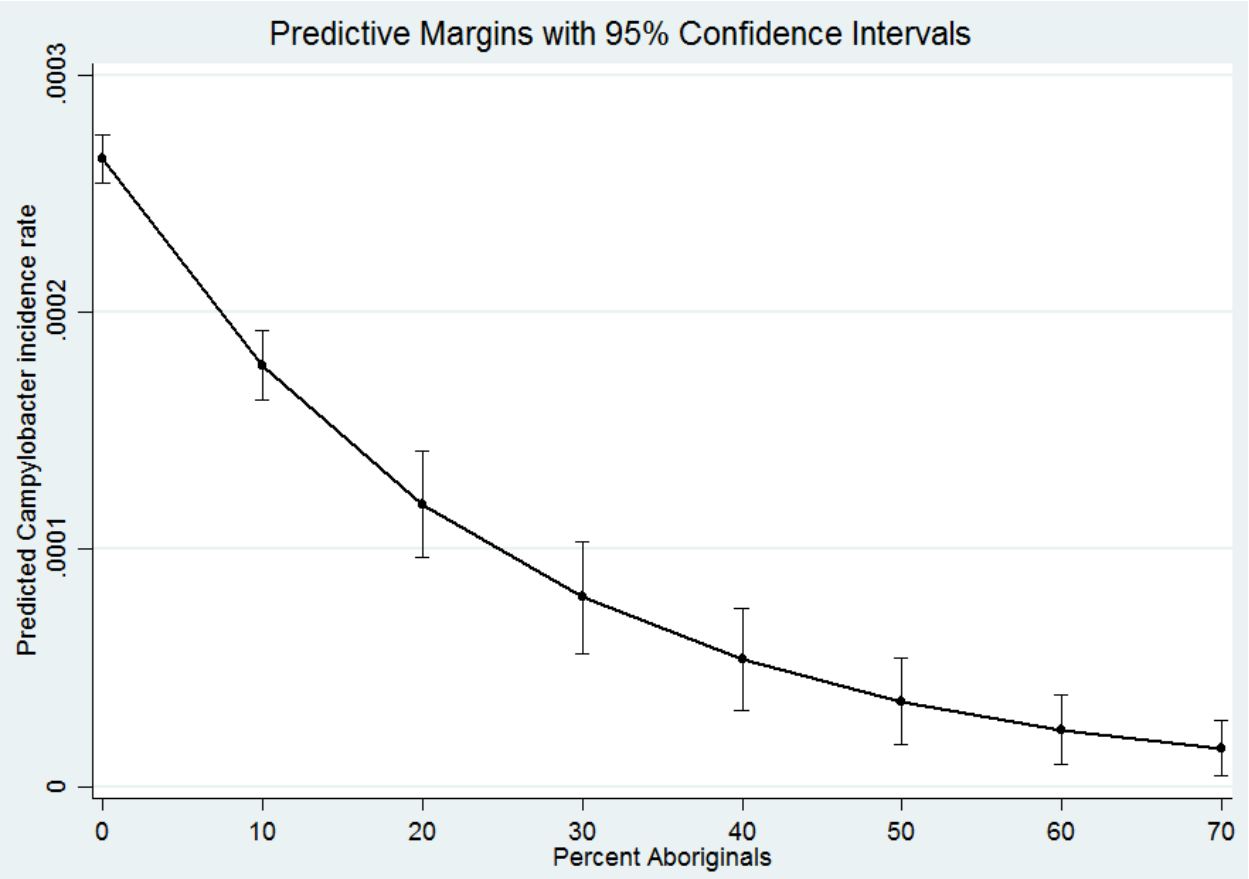


Figure 4.5: The relationship between age- and sex- adjusted incidence rate (per person-years) of *Campylobacter* infections and percent Aboriginal peoples in each FSA, holding all other variables in the final multivariable regression model constant.

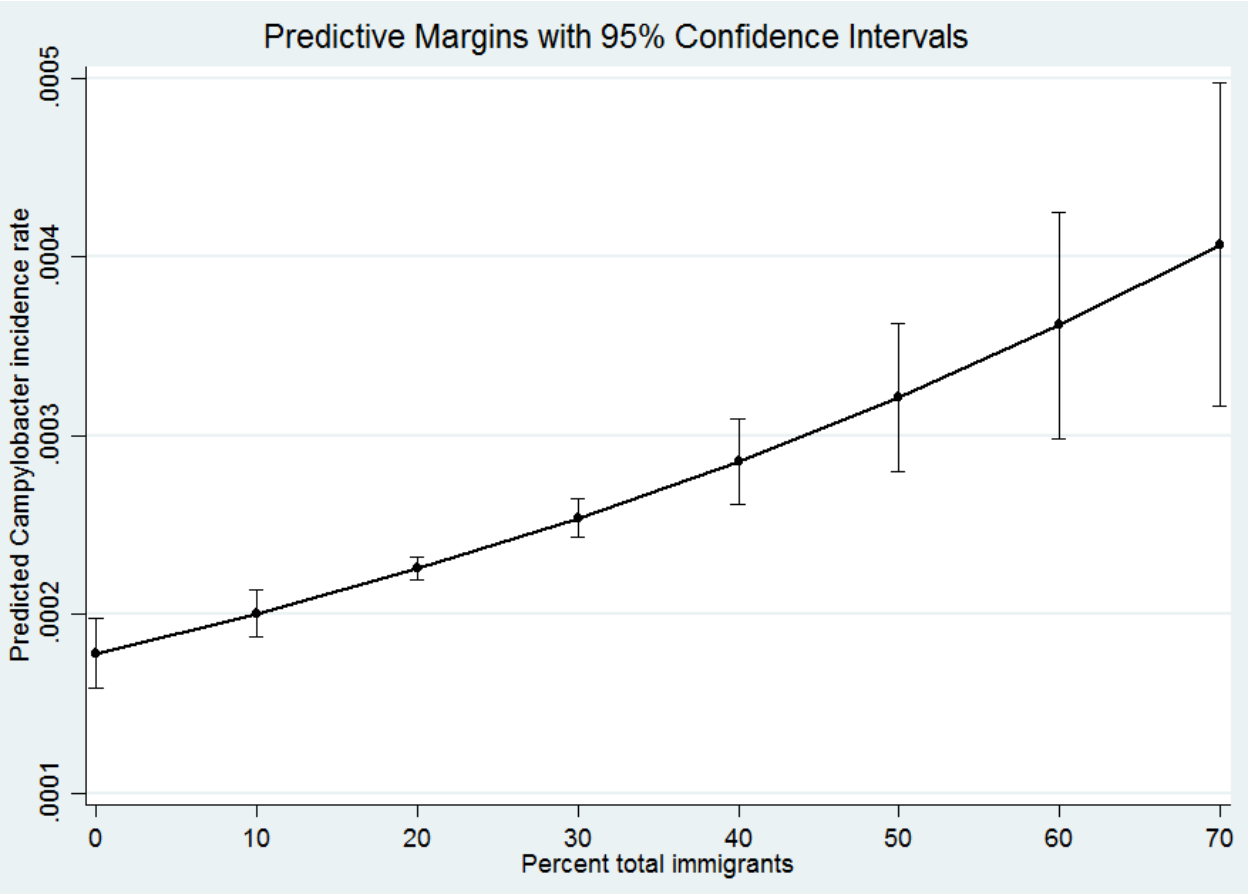


Figure 4.6: The relationship between age- and sex- adjusted incidence rate (per person-years) of *Campylobacter* infections and percent total immigrants in each FSA, holding all other variables in the final multivariable regression model constant.

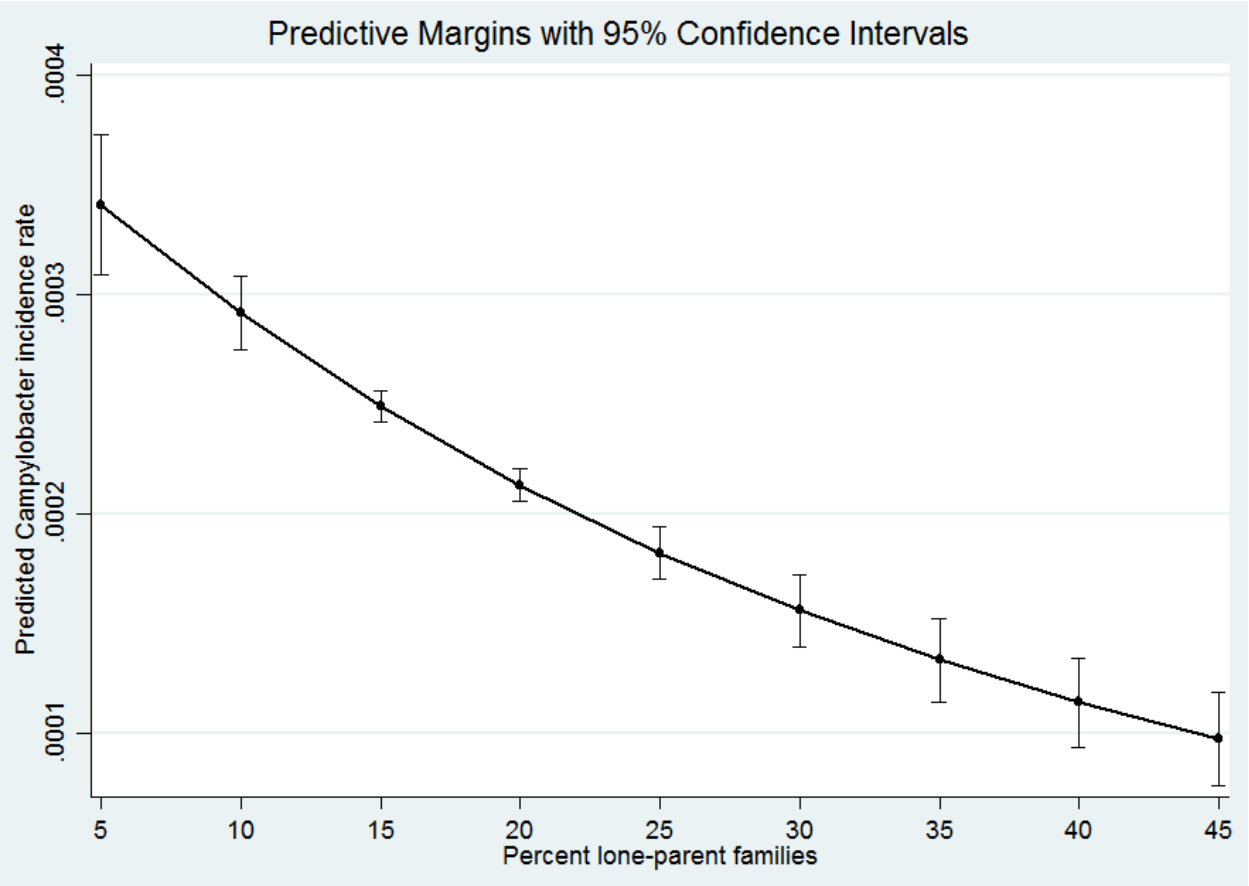


Figure 4.7: The relationship between age- and sex- adjusted incidence rate (per person-years) of *Campylobacter* infections and percent lone-parent families in each FSA, holding all other variables in the final multivariable regression model constant.

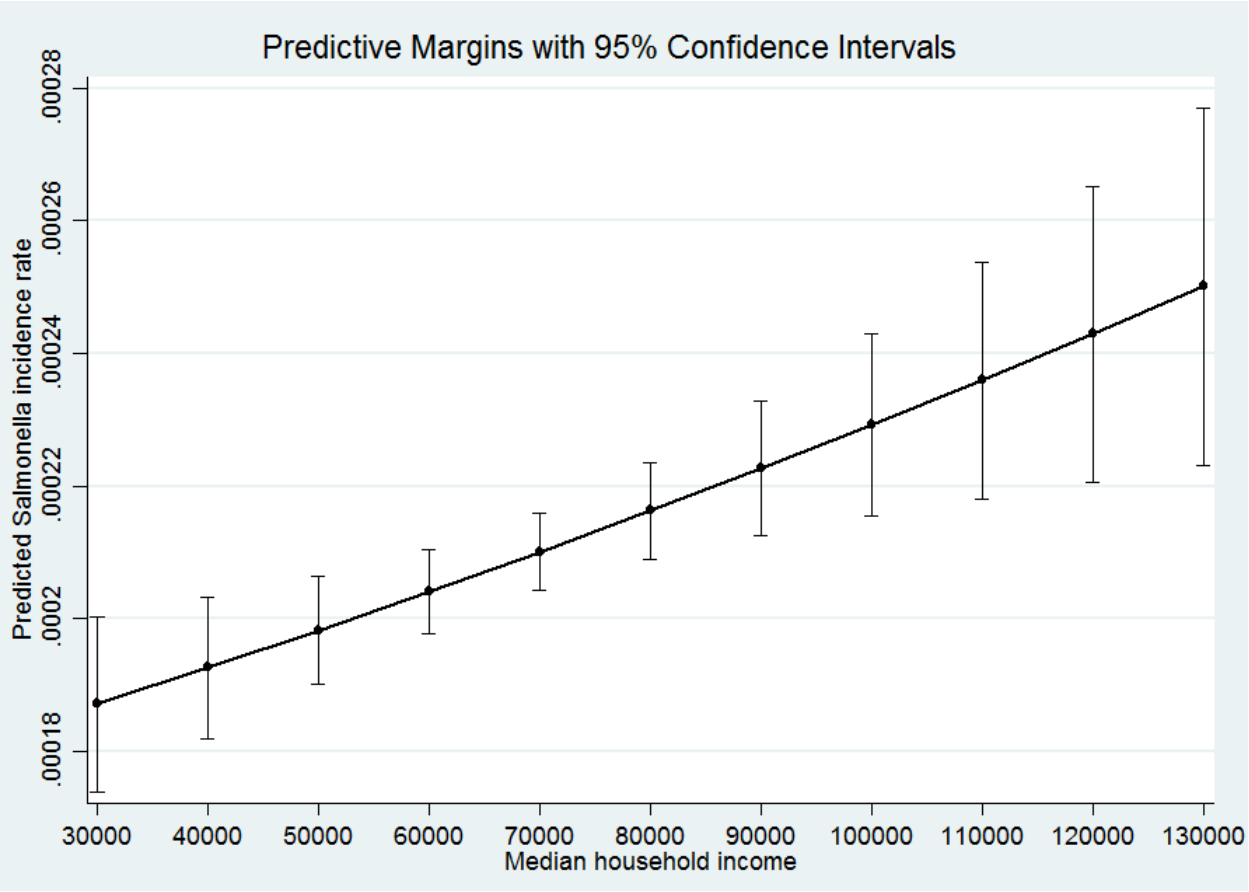


Figure 4.8: The relationship between age- and sex- adjusted incidence rate (per person-years) of *Salmonella* infections and median household income in each FSA, holding all other variables in the final multivariable regression model constant. Median household income is in Canadian dollars.

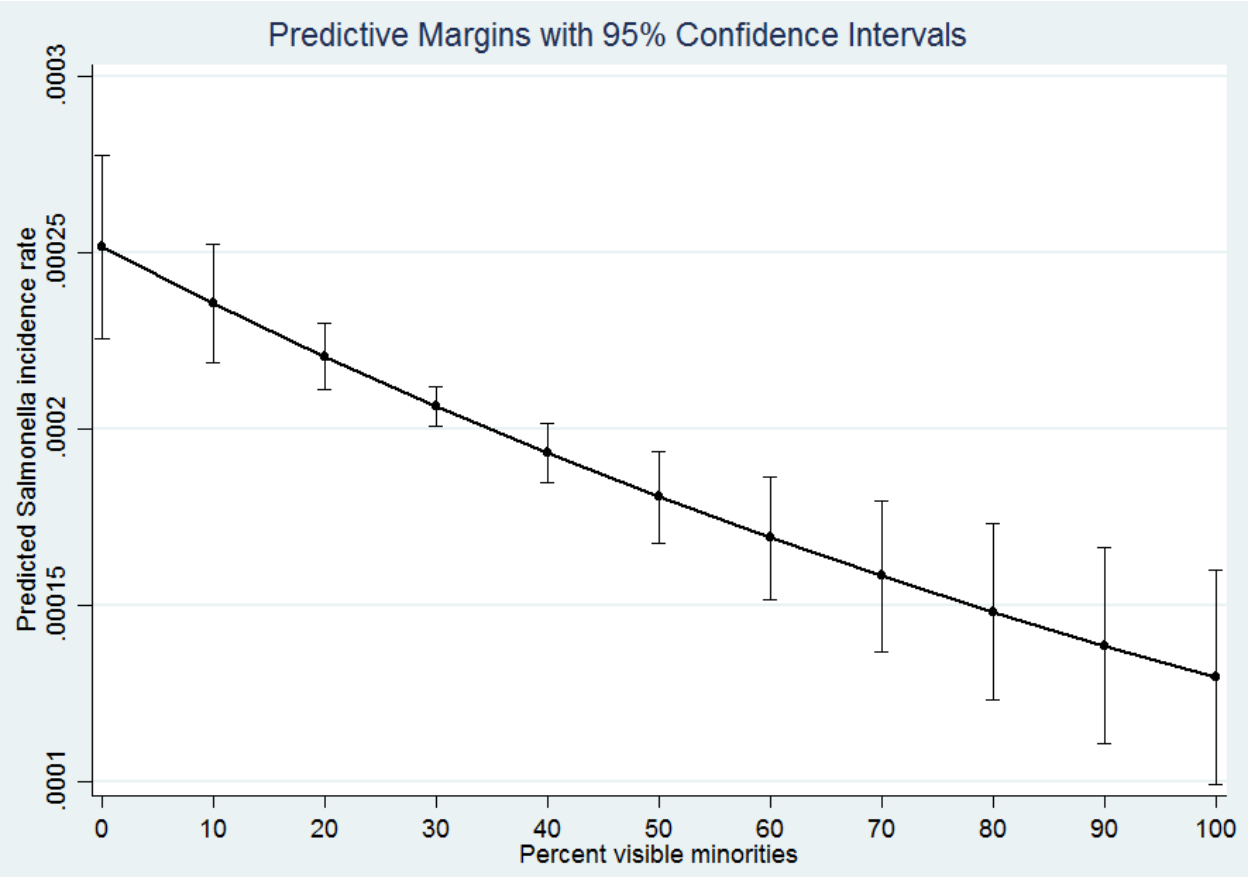


Figure 4.9: The relationship between age- and sex- adjusted incidence rate (per person-years) of *Salmonella* infections and percent visible minorities in each FSA, holding all other variables in the final multivariable regression model constant.

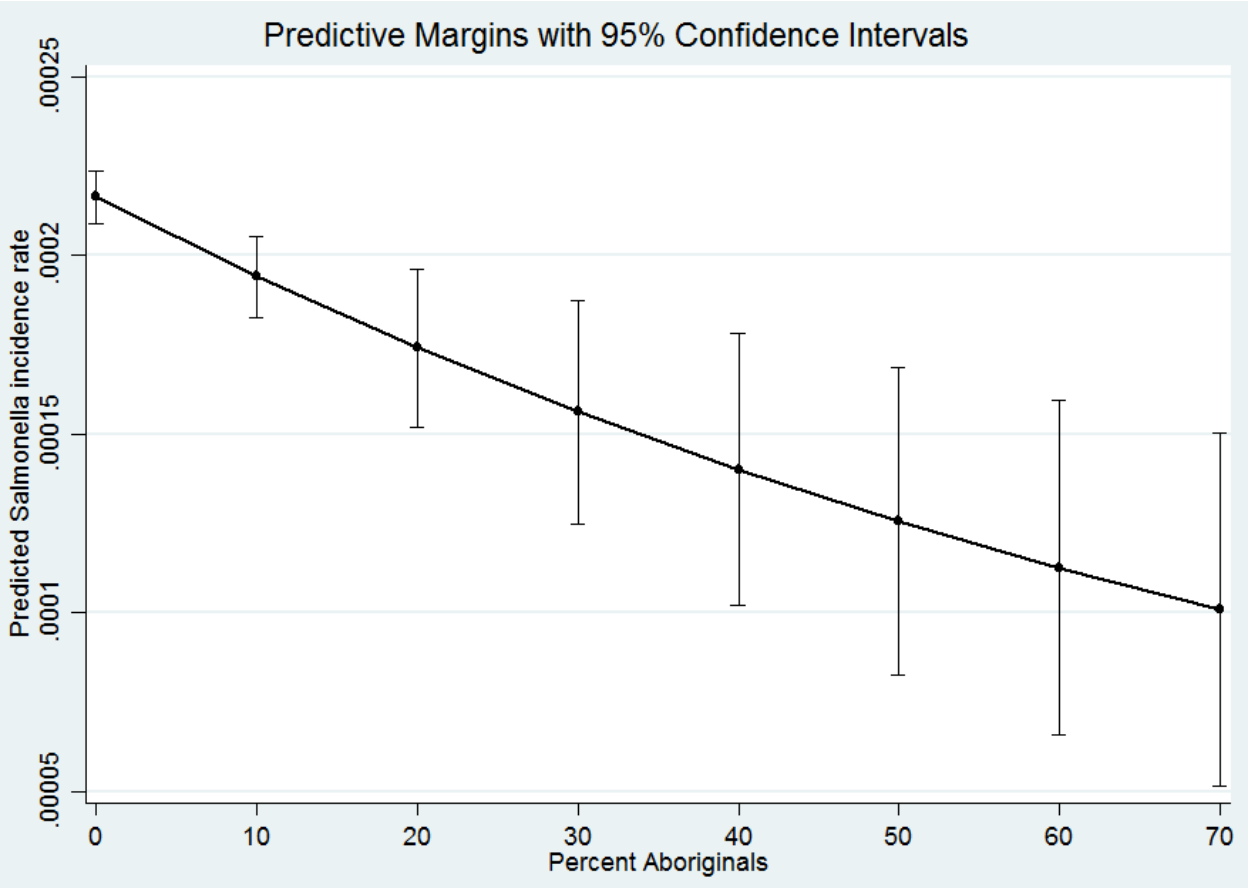


Figure 4.10: The relationship between age- and sex- adjusted incidence rate (per person-years) of *Salmonella* infections and percent Aboriginal peoples in each FSA, holding all other variables in the final multivariable regression model constant.

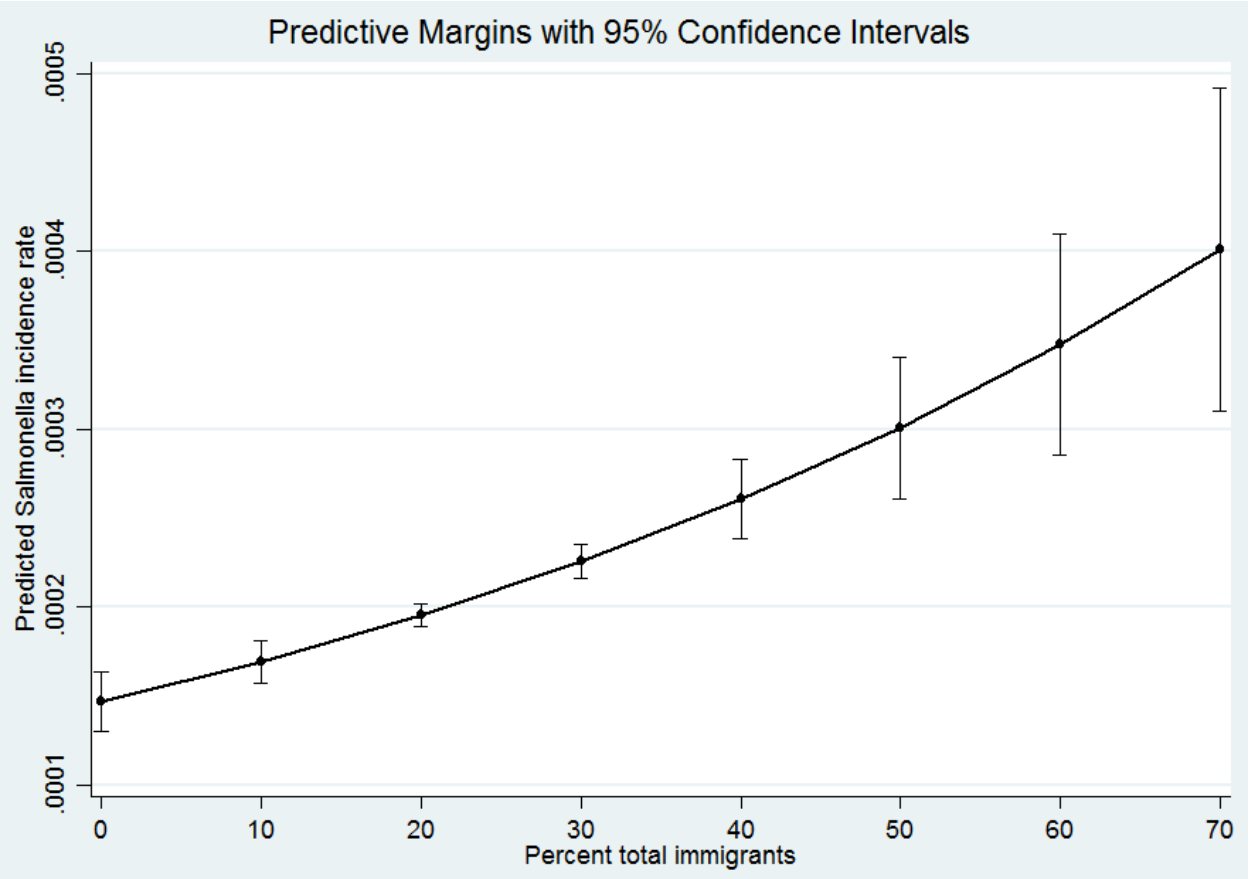


Figure 4.11: The relationship between age- and sex- adjusted incidence rate (per person-years) of *Salmonella* infections and percent total immigrants in each FSA, holding all other variables in the final multivariable regression model constant.

Chapter 5
General Discussion

Overview

Enteric diseases, caused by microorganisms such as viruses, bacteria, and parasites, remain a major public health concern, affecting millions of Canadian annually (Thomas *et al*., 2017). In Canada and Ontario, the bacteria *Campylobacter*, *Salmonella*, Verotoxin-producing *Escherichia coli* (VTEC), *Yersinia spp.*, and *Listeria monocytogenes* are among the most frequently reported causes of enteric infections (Drudge *et al*., 2019; Thomas *et al*., 2013) and are commonly transmitted by food (Butler *et al.*, 2015; Vrbova *et al*., 2012; Whitfield *et al*., 2017).

Several individual-level risk factors (e.g., poor hygiene, high-risk food consumption behaviour) are traditionally examined for contributing to the burden of enteric diseases. Current evidence, however, shows that area-level or community-level factors, such as socioeconomic status (SES), are important determinants of health inequalities, including the inequalities in enteric disease distribution, in various populations (Quinlan, 2013; WHO 2010). Therefore, the inherent nature of pathogenic microorganisms, the various complex pathways through which they can cause infections, and the effects of seasonal, environmental, and geographical factors, on disease transmission, make it important to examine the distribution and risk factors of infections in different populations.

Therefore, the overall goal of this thesis was to investigate the distributions of, and the risk factors for, major enteric infections in humans commonly transmitted by food, in Ontario,

Canada (2010-2017). To achieve this goal, this thesis (i) estimated the incidence, seasonal, and demographic risk factors of *Campylobacter spp*., non-typhoidal *Salmonella spp*., Verotoxin-producing *Escherichia coli* (VTEC), *Yersinia spp*., and *Listeria monocytogenes* reported infections (Chapter2); (ii) examined the temporal, spatial, and space-time clustering of these reported infections (Chapter 3); and, (iii) identified area-level socioeconomic risk factors for reported infections caused by *Campylobacter spp*. and non-typhoidal *Salmonella spp.* (Chapter 4).

Summary of key findings

Chapter 2 examined the incidence, demographic, and seasonal risk factors of infections caused by five major enteric pathogens (*Campylobacter*, *Salmonella*, VTEC, *Yersinia spp*., and *Listeria*), in Ontario, at the public health unit level. Incidence rates (IRs) varied by pathogen, with the highest annual mean rates observed in *Campylobacter* and *Salmonella*, and the lowest mean rate in *Listeria*, VTEC and *Yersinia* (in that order). This was not surprising as *Campylobacter* and *Salmonella* are the most frequent enteric bacteria implicated in enteric illness and disease outbreaks in many countries, including Canada and the U.S (Angelo *et al*., 2021; Bélanger *et al*., 2015; Self *et al*., 2019). The differences in IRs among these pathogens allude to the differences in the pathogenesis of diseases, including differences in pathogen virulence factors, host factors, different risk factors that determine exposure risks and transmissibility of infection (van Seventer and Hochberg, 2017).

The study also observed variations in the demographic risk factors for infections caused by the pathogens studied. IRs for *Campylobacter*, *Salmonella*, VTEC, and *Yersinia*, infections

were significantly higher in children 0-4 years of age, while *Listeria* IR was clearly highest in older adults 60 years and over. The higher IRs among these age groups may be due to their vulnerabilities to many infectious diseases resulting from weakened immune system (Barkley *et al*., 2016), and poor hygiene practices in children 0-4 years old (Karambu *et al*., 2013).

Age- and sex-specific differences in IRs were also observed for *Campylobacter*, *Salmonella*, and VTEC, but not for *Yersinia* or *Listeria*. For example, *Campylobacter* rates were significantly higher in young males of 10-19 years old than in females of the same age group, and were significantly higher in adult females of 20 years and over than males of the same age group. These findings are in alignment with studies conducted in other parts of the world, in the U.S., where the risk of VTEC infections was higher in women 20-29 years and older (Sodha *et al*., 2015), and in England and Wales, where the risk of *Campylobacter* infections was higher in women 20 and 36 years old (Gillespie *et al.*, 2008). A possible factor is their increased exposure to foodborne pathogens during food preparation activities (Moyser and Burlock, 2018; Thomas *et al*., 2013). Sex-specific differences in infection rates may also be a result of biological differences in the immune responses against infectious diseases in males versus females (van Lunzen and Altfeld, 2014).

The highest rates were observed in summer for all the five pathogens studied in this thesis. Similar studies in Ontario and other parts of Canada (Valcour *et al*., 2016; Varga *et al*., 2013a; Vrbova *et al*., 2012) also observed highest enteric infection rates in warmer months, when pathogens proliferate at a faster rate due to more suitable environmental growth factors (Lukacsovics *et al*., 2014), more social engagements amongst persons, travel (Kendall *et al*.,

2012), and eating outside the home such as in the restaurant and other food services (Lee & Middleton, 2003; Vrbova *et al*., 2012).

Chapter 3 illustrates the temporal, spatial, and space time clustering of reported infections caused by *Campylobacter*, *Salmonella*, VTEC, *Yersinia*, and *Listeria*, across Ontario. Once again, variations in disease clustering patterns were observed among the pathogens. *Campylobacter*, *Salmonella*, VTEC, and *Listeria*, mainly temporarily clustered in the spring and summer, whereas, *Yersinia* did not show a very clear temporal pattern. It is possible that *Yersinia* is less affected by seasonal variations than the other pathogens in this thesis. The survival of pathogenic microorganisms and their transmission, depends on the pathogen, the transmission route, the contact surface (transmission vehicle), and environmental factors such as temperature and humidity (Todd *et al*., 2009).

In terms of spatial clustering, *Campylobacte*r, *Salmonella*, and VTEC, showed similar geographical pattern and mainly clustered in southwestern and central-western regions (rural areas) of Ontario. The high farm densities in these regions may be responsible, in part, for the high-rate clusters (Green *et al*., 2006; OMAFRA, 2021). For example, proximity to farm environments or farm animals are risk factors for many enteric infections such as those due to *Campylobacter*, *Salmonella*, and VTEC (Butler *et al*., 2016; Klumb *et al*., 2020). On the other hand, *Yersinia* and *Listeria* spatially clustered in the central-eastern (urban) region known for its high-density population (Arsenault *et al*., 2012). Due to the high population density in the urban region, person-to-person contact (Butler *et al*., 2015) as well as contact with household pets (Whitfield *et al*., 2017), would be risk factors for the spread of enteric infections.

In agreement with other studies in Ontario and Quebec (Gaulin *et al*., 2014; Vrbova *et al*., 2012), relatively high proportions of cases in some of the significant clusters were linked to outbreaks for *Salmonella*, VTEC, and *Listeria*, but not for *Campylobacter* or *Yersinia*. This finding also aligns with other studies from Canada, which reported very low proportions of *Campylobacter* and *Yersinia* cases linked to outbreak cases, compared to the other major enteric bacteria in the studies (Bélanger *et al*., 2015; Ravel *et al*., 2009). This may be related to the differences in the rates of survival of these pathogens. *Campylobacter* has a lower survival rate in the environment than *Salmonella* (Todd *et al*., 2009). The pathogen-specific differences in infection rates and variations in clustering patterns, further highlight distinctions in exposure sources and in the risk factors (environmental, demographic, and socioeconomic) of infections caused by the pathogens in our study.

Chapter 4 examined the relationship between *Campylobacter* and *Salmonella* IRs, and eight FSA-level SES factors (median household income; percent population with bachelor degree or higher; unemployment rate; and percent visible minorities, Aboriginals, total immigrants, recent immigrants, and lone-parent families), in Ontario. After adjusting for the other covariates in the final multivariable model, *Campylobacter* rates increased in FSAs with higher percent population with bachelor degree or higher, and in FSAs with higher percent total immigrants. *Salmonella* rates increased in FSAs with higher median household income (although the relationship with median household income was minimal), and in FSAs with higher total immigrants.

Median income and education can mediate their impacts on enteric disease outcomes through mechanisms such as increased travel (Kendall *et al*., 2012; Varga *et al*., 2020), consumption of undercooked food (Shiferaw *et al*., 2000), eating outside of home (Todd *et al*., 2007), and contact with pet animals (Whitfield *et al*., 2017). It was interesting to observe that percent total immigrants in the population was a risk factor for both *Campylobacter* and *Salmonella* infections. This may be due to the poor living environment or access to food of low microbial quality, which are normally associated with vulnerable populations or those of low socioeconomic status, such as immigrants (Derose *et al*., 2007; Koro *et al*. 2010; Signs *et al*., 2011). High travel activity may also account for the higher risks of *Campylobacter* and *Salmonella* infections observed in communities with higher population of immigrants. International travel is a risk factor for many infectious diseases (Kendall *et al*., 2012; Tighe *et al*., 2012; Varga *et al*., 2020), and a high number of people with different ethnic backgrounds may travel back to their countries of origin to visit families and friends (Kendall *et al*., 2012).

Contributions to enteric disease literature

This thesis addresses some current gaps relating to the distribution of enteric diseases caused by the five major pathogens (*Campylobacter*, *Salmonella*, VTEC, *Yersinia*, and *Listeria*) in this study, and their demographic, seasonal, and socioeconomic risk factors, in Ontario.

Chapter 2 identified demographic and seasonal patterns of reported infections, which bear similarities to the reports from other researchers (Barkley *et al*., 2016; Gillepsie *et al*., 2008; Majowicz *et al*., 2007; Valcour *et al*., 2016; Varga *et al*., 2013a). Obtaining similar outcome as other studies facilitates the generalizability of research results and enables the adoption of the

same or similar control measures, especially where the same patterns and risks are identified. Furthermore, the thesis emphasizes the elevated risks for enteric diseases in children 0-4 years of age and older adults of 60 years and over, and prompts the need to increase every effort in ensuring the control and prevention of disease transmission to these vulnerable populations, especially in summer when the risk for enteric disease outbreaks are generally at its peak (Heiman *et al*., 2015; Stein and Katz, 2017).

Additionally, this thesis presents the epidemiology of infections (e.g., *Yersinia* and *Listeria* infections) which, to the author's knowledge, had not been previously reported in research studies in Ontario or Canada. This particularly addresses a significant gap in the literature as *Yersinia* ranks the fifth top bacterial pathogen causing foodborne enteric illness in Canada (Thomas *et al*., 2013), while *Listeria* has a very high case fatality rate (Choi *et al*., 2018a; Choi *et al*., 2018b; Scallan *et al*., 2011). Therefore, knowledge of their distributions and the risk factors that promote infections due to these pathogens is an important initial step in identifying at-risk populations and potential public health interventions.

This thesis also determined age- and sex-specific differences in IRs of *Campylobacter*, *Salmonella* (higher in young and older women compared to men in the same age groups), and VTEC (higher in young women than in young men), adjusting for year, season, age, and sex. There were no significant age- and sex-based differneces observed for *Yersinia*, or *Listeria* IRs. To our knowledge, the age- and sex-specific differences (or lack thereof) in IRs of *Salmonella, Yersinia,* and *Listeria* infections observed in our study have not been previously reported in Ontario. This finding addresses a significant gap in the literature as knowledge of age- and sex-

specific risk factors for infections aid in directing focus-based public health interventions to specific sub-populations.

Chapter 3 provides information on the temporal and spatial clustering of reported infections caused by *Campylobacter*, *Salmonella*, VTEC, *Yersinia* and *Listeria* in Ontario. Identifying areas of high disease rates and cluster patterns (in space and time) is of public health significance as it is the first step in elucidating potential causes for the high rates in specific areas, for adequate public health interventions (Kirby *et al.,* 2017; Kulldorf, 2018). Previous studies that have examined the temporal and spatial clustering of enteric infections in Ontario are limited and only investigated cases of *Salmonella* and VTEC (for example, Paphitis *et al*., 2020; Paphitis *et al*., 2021; Varga *et al*., 2013b; Varga *et al*., 2021). To the author's knowledge, this thesis is the first known research to examine the disease clustering of pathogens such as *Campylobacter*, *Yersinia*, and *Listeria*, in Ontario.

Using scan statistic, significant high-rate temporal clusters of infections were detected in spring/summer for all the pathogens in the study, except for *Yersinia*, which showed no clear temporal pattern. This finding aligns with the results in Chapter 4, where high rates of infections were also observed during warmer months. This is of a significant public health importance as it highlights the elevated risks of potential disease outbreaks when the environmental temperature is higher (Heiman *et al*., 2015; Stein and Katz, 2017), and emphasizes the need for proper infection control and prevention in summer season, to mitigate potential outbreaks.

Spatially, significant high-rate clusters of infections for *Campylobacter*, *Salmonella*, and, VTEC, were detected mainly in the southwest and central-western Ontario, that is characterized

by high-density farm operations (OMAFRA, 2021); and for *Yersinia* and *Listeria* infections, in the central eastern region, known for its high population density (Arsenault *et al*., 2012). The distinct clustering patterns illustrate areas and populations at high risk for potential disease outbreaks (Paphitis *et al*., 2020; Paphitis *et al*., 2021). This finding may form the basis for determining community-level or individual-level risk factors that may be responsible for these clusters, to inform (pathogen-specific) public health control and prevention measures. Examples of such measures may include education on avoding contact with potentially contaminated surfaces, personal hygiene (especially hand hygiene), proper food handling techniques, and direct contact with animals.

Consequently, the results in Chapter 3 add to the current body of knowledge on the temporal and spatial distribution, and clustering of enteric infections in Ontario and other parts of Canada, in Manitoba (Green *et al*., 2006), the Northwest Territories (Pardhan-Ali *et al*., 2012), Alberta (Pearl *et al*., 2006), and New Brunswick (Valcour *et al*., 2016), and enhance our knowledge of the temporal and spatial patterns of infections caused by these major pathogens, which provide a scientific basis for focused public health prevention and control strategies, focused on minimizing the spread of these pathogens, especially in high-risk areas or populations.

Research has also shown that SES has a strong influence on societal stratification and health inequalities (WHO, 2010). However, the association of SES with enteric infections has not been extensively studied in Ontario or Canada. Therefore, Chapter 4 assessed the effect of eight FSA-level SES factors (median household income; percent population with bachelor

degree or higher; unemployment rate; and percent visible minorities, Aboriginals, total immigrants, recent immigrants, and lone-parent families), on the IRs of *Campylobacter* and *Salmonella*, across Ontario.

There was an obvious trend for *Salmonella* IR to increase with an increase in median household income and percent total immigrants. While low SES is generally known to be a predictor of poorer health outcome (Gillespie *et al*., 2010; Quinlan 2013), the findings from this thesis, as in similar studies (Newman *et al*., 2015; Simonsen *et al*., 2008), show that this cannot be presumed, especially in the context of the complex and variable pathways through which infectious pathogens can influence health (van Seventer and Hochberg, 2017).

Some of the mechanisms through which income can affect enteric illness are, better access to material resources and services such as health care and leisure travel (Lebrun and Dubay, 2010; WHO, 2010). The use of healthcare services can improve health directly in terms of having access to regular medical treatment. However, it may lead to a higher representation of high income earners in the infectious diseases surveillance system, compared to lower income earners. Engaging in activities such as travel has been linked to higher risk of exposure to infections (Tighe *et al*., 2012; Varga *et al*., 2020). In addition, people who earn higher are more likely to engage in high-risk food consumption behavior and improper food handling practices than their counterparts (Nesbitt *et al*., 2009; Patil *et al*., 2005; Shiferaw *et al*., 2000). These factors may explain the positive relationship median household income has with *Salmonella* IR.

This thesis also reveals the health disparities in FSAs with high percentage of the population who are immigrants. Immigrants, who leave their country of origin to seek a better

life in a different country, are often identified as vulnerable group in the context of health inequity (Vacková and Brabcová, 2015). They tend to suffer several barriers to material resources such as reasonable income, employment and good healthcare services (Derose *et al*., 2007; Lebrun and Dubay, 2010; Quesnel-Vallée *et al*., 2011), and even access to healthy food (Koro *et al*., 2010; Signs *et al*., 2011). International travel to home countries by immigrants may be another explanation for the higher risks of *Campylobacter* and *Salmonella* infections observed in communities with higher population of immigrants (Kendall *et al*., 2012; Tighe *et al*., 2012). These factors contribute to increased risk to poor health outcomes (Derose *et al*., 2007) and may help explain the health disparities in FSAs with higher percentage of immigrants in the present study.

The thesis also showed FSAs with higher percentage of persons with bachelor degree or higher, are at an increased risk of *Campylobacter* infection, but not *Salmonella* infection. Research show that enteric disease outcomes are pathogen-specific, and also dependent upon several factors such as host factors, transmission pathways, environmental conditions (Lukacsovics *et al*., 2014; van Seventer and Hochberg, 2017), food and animal sources (Butler *et al*., 2015; Vrbova *et al*., 2012; Whitfield *et al*., 2017), and behavioural factors (Shiferaw *et al*., 2000; Todd *et al*., 2007). Therefore it is not surprising that *Campylobacter* and *Salmonella* infection rates differ in the context of their SES indicators.Therefore, the increased *Campylobacter* IR observed with higher education in this study may be a result of behavioural risk factors such as the consumption of undercooked food and poor food handling practices, which have been associated with persons with higher educational level (Shiferaw *et al*., 2000).

Implications for public health practice

Enteric symptoms resulting from infections due to the five major pathogens (*Campylobacter*, *Salmonella*, VTEC, *Yersinia*, and *Listeria*) in this thesis are frequently reported in Ontario (Drudge *et al*., 2019). The control and prevention of these infections rely on a comprehensive understanding of the burden of disease and the risk factors for transmission in a population. Therefore, this thesis provides evidence about the inequality in the distribution and clustering of enteric infection rates (in time, space, and person), influenced by seasonal, demographic, and socioeconomic risk factors that will inform public health stakeholders within the health care system (for example, public health units, Ontario Ministry of Health and Long-Term Care, and decision makers in the health care delivery sector) and in the community (for example, schools, workplaces, and food service facilities) in the control and mitigation of enteric diseases in Ontario.

The identification of high-rate clusters of infections in the southern part of the province that are dominated by farms and farming processes, will encourage active surveillance and monitoring for enteric pathogens in the animal population (by the Ontario Ministry of Agriculture, Food and Rural Affairs, OMAFRA, for example), to prevent their transmission into the human populations. Such preventive measures can include barriers to fecal-oral pathway, through which enteric pathogens are typically transmitted in high-risk areas. Similarly, the high IRs and infection clusters of *Listeria* and *Yersinia* in the central eastern region, characterized by dense population, will inform heightened surveillance, and prevention and control programs, in

that region, such as proper faecal waste disposal, pest control, minimizing contact with animals, good personal hygiene, and good disinfection practices.

This thesis identified some demographic groups such as infants and young children (0-4 years old) and older adults (60 years old and older), as high-risk populations for enteric diseases. Public health interventions should target these vulnerable groups to prevent the spread of infections. Control of disease transmission in high-risk areas and populations can focus on preventing human-to-human transmission, by promoting behaviors such as proper personal hygiene practices (e.g., frequent hand-washing), and frequent cleaning and sanitation of public areas and facilities, such as restaurants, daycare centers, long-term care homes, and healthcare settings, where transmission and outbreaks are likely to occur.

Measures promoted by the various public health units to support breastfeeding among women will also play a significant role in protecting infants and young children from enteric diseases, especially in populations of low SES. According to current evidence, breastfeeding is protective against multiple illnesses, including enteric diseases, in infants (Frank *et al*., 2019). There should be increased surveillance (by Ministry of Health and Long-Term Care, for example) in high-risk populations to enable early and rapid detection and treatment, that will decrease the duration and risk of transmission of enteric diseases.

The seasonal profiles exhibited by *Campylobacter*, *Salmonella*, VTEC, and *Listeria* infection rates in summer will enable public health officials to focus on interventions that will prevent or reduce the potential for exposure to infections in warmer seasons. This can include

advisories from public health authorities on taking precautions during international travel (e.g., avoidance of eating or drinking potentially contaminated food or water), and proper handling and storage of food. Knowledge of increased infection rates in summer will also form the basis of establishing control measures for early detection and elimination of disease outbreaks, including outbreak management procedures and infection control.

SES factors, such as median household income, percent people with bachelor degree or higher, and percent immigrant population should be considered as risk factors for *Campylobacter* and *Salmonella* infections. Among populations of high median household income and higher education, public health control efforts should be directed at reducing or eliminating behaviors or lifestyles, such as the consumption of raw or undercooked food; and promoting those behaviors, such as handwashing after touching potentially contaminated surfaces or after direct contact with animals (e.g., those found in petting zoos). This may involve continuous training and counseling of caregivers and other stakeholders on the significance of these behaviors in enteric disease epidemiology.

This thesis also provides evidence that FSAs with higher percentage of immigrants may be disadvantaged in the context of having a disproportionally higher rates of *Campylobacter* and *Salmonella* infections in the population. This finding can form the basis for public health control measures focused on ensuring food safety compliance in food facilities located in populations of low SES (e.g., immigrants). This can reduce the risk of exposure to food of poor microbial quality in this population. Interventions that foster ease of immigrant resettlement and successful

integration can reduce resettlement stress among immigrants, thereby reducing their susceptibility to diseases, including enteric diseases.

Limitations of the thesis

The overall limitation of this thesis is the constraints inherent in the use of passive surveillance case data. Evidence show that surveillance data represents only a small fraction of the true disease burden, due to problems of under-reporting, under-diagnosis, and differential access to medical care (Flint *et al*., 2004; Majowicz *et al*., 2005). Consequently, this thesis presents an under-estimation of the number of cases and potentially biased IRs (lower IRs than actual), in place, time, and person. However, the findings in the studies correspond to other reports of the relative number of cases and IRs of infections caused by the pathogens in this thesis (Drudge *et al*., 2019; Scallan *et al*., 2011; Thomas *et al*., 2013).

Another limitation of this thesis is that the case data did not include risk factor information, such as food, water, and animal contact. Thus, a specific exposure source could not be assigned to each case. However, estimates of pathogen-specific cases attributable to different exposure sources have been published in the literature (Butler *et al*., 2015; Thomas *et al*., 2013; Whitfield *et al*., 2017).

Interpretation of the results in Chapter 4 should be made with caution as the thesis used population data from the 2016 Census, when the study spanned three years, from 2015-2017. This was to approximate a mid-point between the years of study but may have obscured the effect of change in population during the study period. However, a population growth of 2.6%,

from 2015-2017 (Statistics Canada, 2022), would likely not have changed the conclusions from the study.

Additionally, the case data was aggregated at the FSA level which was used as the unit of analyses. Research based on different geographical scales may product different results. As well, inferences to individual-level associations between infection rates and SES factors may lead to ecologic fallacy (Dohoo *et al*., 2012). Ecologic fallacy is a faulty thinking that occurs when the relationship observed in a group is applied to individuals who make up that group. The reason is because group-level characteristics do not always reflect individual-level characteristics (Demissie *et al*., 2000; Dohoo *et al*., 2012). In this thesis, for example, the fact that populations with higher percentage of immigrants are at higher risks of *Campylobacter* and *Salmonella* infections, does not necessarily mean that immigrants have a higher risks of these infections than non-immigrants. The higher IRs of infections in these populations may result from the type of retail food stores available in these areas that can be accessed by anyone. Although applying group-level characteristics to individuals in that group may be correct, it is not supported by aggregate or group-level data (Ontario Agency for Health Protection and Promotion [OAHPP], 2013).

Nevertheless, the thesis presents the incidence rates distribution of reported infections caused by five major enteric pathogens in Ontario, identified areas of high infection rates and disease clustering, and determined seasonal, demographic, and area-level socioeconomic risk factors for infections.

Implications for future research

There is need to assess the local environmental, agricultural, and socioeconomic risk factors in sub-communities that may contribute to the high IRs and disease clustering in areas of high infection rates, and the mechanisms through which they affect infection rates. These studies may be performed at different geographical scales (e.g., public health unit, census tract, regions) to either validate or complement the results from this thesis. Considerations for future studies should also investigate the socioeconomic risk factors for infections caused by VTEC, *Yersinia*, and *Listeria*, across Ontario.

Evidence show that the pathogens included in this thesis are commonly transmitted by food (Butler *et al.*, 2015; Vrbova *et al*., 2012; Whitfield *et al*., 2017). Similar to studies in the U.S. (Koro *et al*., 2010; Signs *et al*., 2011), investigation into the quality of food available to different populations (low and high SES) in the community will help in ascertaining the contribution of food quality to infection rates. Examination of food safety compliance and factors that affect compliance to food safety, in food retail facilities and restaurants in different communities, will also determine the extent of non-compliance (if any) in these facilities.

Studies to determine the individual-level behavioral risk factors for infections in populations of high SES (e.g., those with high income or educational level) are needed to better understand their impacts on the burden of enteric diseases in Ontario, especially in areas of high IRs. Future research could also explore the risk factors for enteric disease among the immigrant populations in Ontario, taking into account their diversity in the country of origin, cultural

backgrounds, underlying illness, genetic, and biological factors, as well as other variables (e.g., age, sex, education level, and language fluency).

Results from these studies would be valuable in informing future public health interventions to reduce the rate of infections in different communities, especially, in high-risk areas and among the high-risk groups identified in this thesis.

References

This section includes the references from all earlier chapters, presented by chapter. Where relevant, the formatting of the references for each chapter matches the journals to which the manuscript was submitted, or for which it was prepared.

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Appendix A: Additional Tables and Figures – Chapter 3

Table A1: Mean incidence rates of infections caused by five major enteric pathogens, at the local public health unit (PHU) level, in Ontario, Canada (2010-2017)[1]

Public Health Unit [2]	*Campylobacter spp.*	*Salmonella spp.*	Verotoxin-producing *Escherichia coli*	*Yersinia spp.*	*Listeria monocytogenes*
Algoma District	13.8	13.5	1.3	1.6	0.6
Brant County	14.5	19.1	0.6	0.3	0.2
Chatham-Kent	18.0	15.3	1.1	0.6	0.5
City of Hamilton	19.9	17.0	0.4	1.0	0.4
City of Ottawa	21.9	18.3	0.8	1.2	0.4
Durham Region	24.8	22.8	1.2	1.0	0.3
Eastern Ontario	26.6	18.8	1.5	0.8	0.4
Grey Bruce	45.8	28.8	5.9	1.7	0.4
Haldimand-Norfolk	35.1	23.9	1.8	0.9	0.4
Haliburton, Kawartha, Pine Ridge	30.2	19.6	1.1	0.7	0.2
Halton Region	25.3	20.6	1.1	1.9	0.4
Hastings & Prince Edward Counties	16.9	17.7	1.5	1.1	0.2
Huron County	59.6	25.1	7.6	0.6	0.4
Kingston, Frontenac, Lennox and Addington	23.3	17.2	1.1	1.2	0.3
Lambton County	19.6	15.2	1.2	0.4	0.3
Leeds, Grenville and Lanark District	20.8	19.4	1.6	1.7	0.2
Middlesex-London	26.6	18.2	1.5	0.6	0.3
Niagara Region	30.1	19.8	0.6	1.2	0.3
North Bay Parry Sound District	13.6	22.2	0.8	2.1	0.3
Northwestern	16.8	20.5	0.6	1.1	0.2
Peel Region	23.7	22.4	0.9	1.4	0.5
Perth District	57.9	24.6	8.2	1.4	0.2
Peterborough County-City	23.1	19.7	1.5	1.0	1.0
Porcupine	8.7	19.6	0.7	0.9	0.4
Renfrew County and District	17.9	19.1	0.8	0.2	0.8
Simcoe Muskoka District	21.4	20.5	0.8	1.0	0.5
Southwestern	28.1	17.7	2.4	0.4	0.7
Sudbury and District	13.2	16.0	1.4	1.2	0.4
Thunder Bay District	20.4	20.9	0.4	1.1	0.4
Timiskaming	16.8	17.0	0.7	0.7	0.0

Toronto	31.3	22.1	1.0	2.1	0.6
Waterloo Region	27.9	21.8	2.1	1.5	0.3
Wellington-Dufferin-Guelph	39.8	23.9	3.5	1.8	0.5
Windsor-Essex County	23.6	18.5	0.9	1.1	0.4
York Region	31.5	24.2	1.0	3.3	0.4

[1]Mean incidence rate (total number of cases (N)/total population over 8 years
[2]Incidence rate (number of cases per 100,000 person-years)

Table A2: Significant high-rate spatial, space-time, and temporal clusters of infections caused by five major enteric pathogens, across the local public health units (PHUs) and regions, in Ontario, Canada (2010-2017), showing percent outbreak cases and percent travel-related cases in each significant cluster

Cluster type	Cluster #	# PHUs (n=35)	PHU	Regions	Cluster duration	p-value[1]	RR[2]	Observed # cases (O)	% Cases in cluster	% Cases linked to outbreak	% Travel-related cases
Campylobacter spp. N (IR) = 28,728 (26.5)											
Temporal	1	All	All	All	Jun 2013-Oct 2013	0.001	1.58	2297	8.0	0.0	14.5
Spatial	1	4	Grey Bruce	South West	N/A	<0.001	1.79	2150	7.5	0.4	10.2
			Wellington-Dufferin-Guelph	Central West							
			Huron County	South West							
			Perth District	South West							
	2	2	York region	Central East	N/A	<0.001	1.28	9715	33.8	0.2	14.2
			Toronto	Central East							
	3	1	Toronto	Central East	N/A	<0.001	1.24	6928	24.1	0.1	10.3
	4	1	York region	Central East	N/A	<0.001	1.21	2787	7.5	0.4	23.9
	5	1	Haldimand-Norfolk	Central West	N/A	<0.001	1.33	313	7.5	0.0	8.6
	6	1	Niagara region	Central West	N/A	0.003	1.14	1083	7.5	0.0	16.2
Space-time	1	4	Durham region	Central East	Jun 2011-Nov 2014	<0.001	1.40	5691	19.8	0.1	17.6
			York region	Central East							
			Toronto	Central East							

Cluster type	Cluster #	# PHUs (n=35)	PHU	Regions	Cluster duration	p-value[1]	RR[2]	Observed # cases (O)	% Cases in cluster	% Cases linked to outbreak	% Travel-related cases
	2	4	Haliburton, Kawartha, and Pine Ridge Grey Bruce Wellington-Dufferin-Guelph Huron County Perth District	Central East South West Central West South West South West	Jun 2010-Nov 2013	<0.001	1.97	1031	3.6	0.6	9.2
Salmonella spp. *N (IR)* = 22,640 (20.9)											
Temporal	1	All	All	All	Jul 2012-Sep 2012	0.001	1.50	1036	4.6	12.4	17.5
Spatial	1	4	York region Toronto Durham region Peel region	Central East Central East Central East Central East	N/A	<0.001	1.16	10696	47.2	8.1	25.6
	2	2	Durham region York region	Central East Central East	N/A	<0.001	1.16	3327	14.7	8.1	26.6
	3	6	Grey Bruce Wellington-Dufferin-Guelph Huron County Perth District Waterloo region	South West Central West South West South West Central West	N/A	<0.001	1.13	4620	20.4	6.8	27.9

Cluster type	Cluster #	# PHUs (n=35)	PHU	Regions	Cluster duration	p-value[1]	RR[2]	Observed # cases (O)	% Cases in cluster	% Cases linked to outbreak	% Travel-related cases
			Peel region	Central East							
	4	1	Toronto	Central East	N/A	0.001	1.07	4881	21.6	8.3	22.8
Space-time	Cluster 1	5	Peel region	Central East	Jul 2012-Sep 2012	<0.001	1.76	546	2.4	14.3	20.7
			Halton region	Central West							
			Toronto	Central East							
			Wellington-Dufferin-Guelph	Central West							
			York region	Central East							
	Cluster 2	1	City of Ottawa	Eastern	Mar-12	<0.001	4.24	69	0.3	82.6	17.4
Verotoxin-Producing *Escherichia coli* N (IR) = 1340 (1.2)											
Temporal	1	All	All	All	Jun 2011-Oct 2011	0.001	1.69	170	12.7	21.2	7.6
Spatial	1	4	Grey Bruce	South West	N/A	<0.001	4.96	245	18.3	14.3	4.5
			Wellington-Dufferin-Guelph	Central West							
			Huron County	South West							
			Perth District	South West							
	2	2	Huron County	South West	N/A	<0.001	6.81	88	6.6	3.4	3.4
			Perth District	South West							
	3	1	Grey Bruce	South West	N/A	<0.001	4.97	77	5.7	24.7	3.9

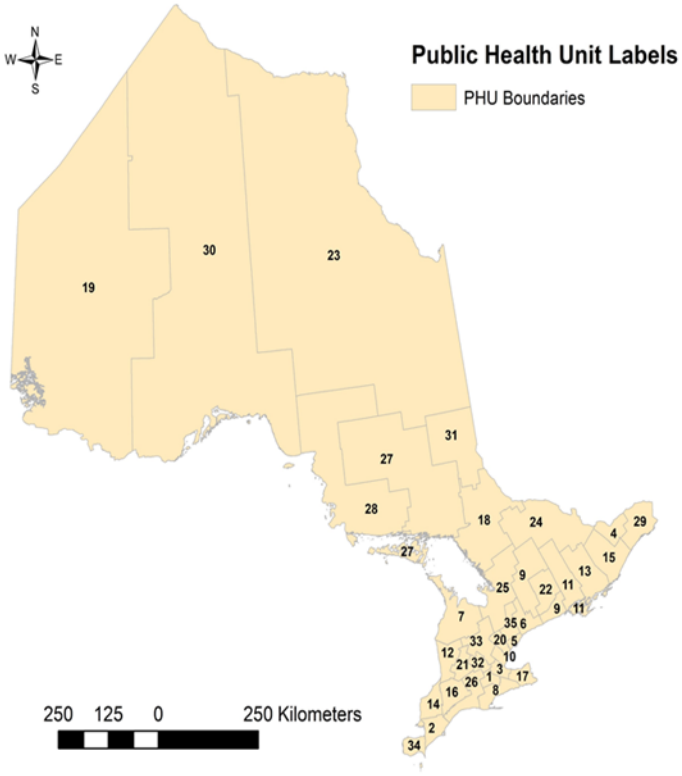
Cluster type	Cluster #	# PHUs (n=35)	PHU	Regions	Cluster duration	p-value[1]	RR[2]	Observed # cases (O)	% Cases in cluster	% Cases linked to outbreak	% Travel-related cases
	4	1	Wellington-Dufferin-Guelph	Central West	N/A	<0.001	2.98	80	6.0	16.3	6.3
	5	2	Haldimand-Norfolk	Central West	N/A	0.015	1.78	54	4.0	11.1	5.6
			Southwestern	South West							
Space-time	1	4	Grey Bruce	South West	Jun 2014-Sep 2017	<0.001	5.51	125	9.3	4.0	6.4
			Wellington-Dufferin-Guelph	Central West							
			Huron County	South West							
			Perth District	South West							
	2	9	Peterborough County-City	Central East	Jun 2011-Sep 2011	<0.001	2.63	60	4.5	8.3	10.0
			Haliburton, Kawartha, Pine Ridge	Central East							
			Hastings & Prince Edward Counties	Eastern							
			Durham Region	Central East							
			Kingston, Frontenac, Lennox & Addington*	Eastern							
			Simcoe Muskoka District	Central East							
			York Region	Central East							
			Toronto	Central East							
			Renfrew County and District	Eastern							
Yersinia spp. N (IR) = 1674 (1.5)											

Cluster type	Cluster #	# PHUs (n=35)	PHU	Regions	Cluster duration	p-value[1]	RR[2]	Observed # cases (O)	% Cases in cluster	% Cases linked to outbreak	% Travel-related cases
Temporal	1	All	All	All	Aug 2015-Sep 2017	0.001	1.52	618	36.9	1.6	22.8
Spatial	1	2	York Region	Central East	N/A	<0.001	2.11	765	45.7	0.0	13.3
			Toronto	Central East							
	2	1	York Region	Central East	N/A	<0.001	2.41	295	17.6	0.0	21.0
	3	1	Toronto	Central East	N/A	<0.001	1.52	470	28.1	0.0	8.5
Space-time	1	2	York Region	Central East	Apr 2014-Sep 2017	<0.001	1.93	368	22.0	0	14.7
			Toronto	Central East							
	2	13	Southwestern*	South West	Jul 2017-Jul 2017	0.006	4.28	21	1.3	0.0	19.0
			Haldimand-Norfolk*	Central West							
			Middlesex-London	South West							
			Brant County*	Central West							
			Waterloo Region	Central West							
			Perth District	South West							
			City of Hamilton	Central West							
			Huron County*	South West							
			Lambton County*	Eastern							
			Halton Region	Central West							
			Chatham-Kent	South West							
			Wellington-Dufferin-Guelph	Central West							

Cluster type	Cluster #	# PHUs (n=35)	PHU	Regions	Cluster duration	p-value[1]	RR[2]	Observed # cases (O)	% Cases in cluster	% Cases linked to outbreak	% Travel-related cases
			Niagara Region	Central West							
Listeria N (IR) = 471 (0.4)											
Temporal	1	All	All	All	Jul 2015-Aug 2016	0.001	2.06	125	26.5	30.4	6.4
Spatial	1	1	Toronto	Central East	N/A	<0.001	1.65	140	29.7	7.1	7.9
Space-time	1	7	Simcoe Muskoka District	Central East	Apr 2016-Aug 2016	<0.001	3.19	38	8.1	31.6	7.9
			Haliburton, Kawartha, Pine Ridge	Central East							
			York Region	Central East							
			Durham Region	Central East							
			Peterborough County-City	Central East							
			Peel Region	Central East							
			Toronto	Central East							

[1]Statistical significance at $p<0.05$
[2]Relative Risk
*PHU reported no cases during the study period

Figure A1: Ontario's public health unit labels



PHU #	Public Health Unit (PHU) Names
1	Brant County Health Unit
2	Chatham-Kent Health Unit
3	City of Hamilton Health Unit
4	City of Ottawa Health Unit
5	City of Toronto Health Unit
6	Durham Regional Health Unit
7	Grey Bruce Health Unit
8	Haldimand-Norfolk Health Unit
9	Haliburton, Kawartha, Pine Ridge District Health Unit
10	Halton Regional Health Unit
11	Hastings and Prince Edward Counties Health Unit
12	Huron County Health Unit
13	Kingston, Frontenac, and Lennox and Addington Health Unit
14	Lambton Health Unit
15	Leeds, Grenville and Lanark District Health Unit
16	Middlesex-London Health Unit
17	Niagara Regional Area Health Unit
18	North Bay Parry Sound District Health Unit
19	Northwestern Health Unit
20	Peel Regional Health Unit
21	Perth District Health Unit
22	Peterborough County-City Health Unit
23	Porcupine Health Unit
24	Renfrew County and District Health Unit
25	Simcoe Muskoka District Health Unit
26	Southwestern Public Health
27	Sudbury and District Health Unit
28	The District of Algoma Health Unit
29	The Eastern Ontario Health Unit
30	Thunder Bay District Health Unit
31	Timiskaming Health Unit
32	Waterloo Health Unit
33	Wellington-Dufferin-Guelph Health Unit
34	Windsor-Essex County Health Unit
35	York Regional Health Unit

Appendix B: Additional Tables – Chapter 4

Table B1: Current studies on the relationship between enteric diseases and community risk factors in Canada

Author	Study period	Study area	Pathogen	Key risk variable
Green et al, 2006b	1996-2004	Manitoba	*Campylobacter*	SES index Farm occupation Urban/rural status Farm animals density
Majowicz et al, 2007	2001-2003	Hamilton, and British Columbia, Ontario	Non-pathogen specific	Cultural group Education No. in household Annual household income Urban/rural status
Pearl et al, 2009	2000-2002	Alberta	Verotoxin-producing *Escherichia coli* O157	Cattle density SAC (statistical area classification) type Aboriginal population % movers % low income household
Varga et al, 2013a	2007-2009	Greater Toronto Area, Ontario	*Salmonella* Enteriditis	Ave. no. of children at home per family Ave. no. of persons per family Ave. no. of rooms per home Immigrant population Ave. median family income Proportion of university graduates btw 25 & 64 years of age Unemployment rate of persons 15 years of age or older Proportion of visible minority population
Pardhan-Ali et al, 2013	1991-2008	Northwest Territories	*Campylobacter* *Gardia* *Salmonella*	Households in core need No high school education Median income Single parent families Primary health facility Health expenditure per capita Physician billing per capita Drinking water source Water treatment type Waste disposal system Traditional foods Hunting/fishing Food price index

Author	Study period	Study area	Pathogen	Key risk variable
				Trapping Population density Internal mobility Rural
Varga et al, 2021	2015-2017	Ontario	Verotoxin-producing *Escherichia coli*	Average median family income Proportion of lone-parent families Proportion of visible minorities

Table B2: Distibution of incidence rates, per 100,000 persons, of reported cases of *Campylobacter spp*. and *Salmonella spp*, by Forward Sortation Area (FSA), Ontario, (2015-2017)

	***Campylobacter spp.*[1]**		***Salmonella spp.*[2]**	
Total # reported cases	Reporting FSAs N (%)[3]	IR	Reporting FSAs N (%)[3]	IR
0	13 (2.6)	0.0	13 (2.6)	0.0
1 to <4	58 (11.5)	1.5 – 56.0	67 (13.3)	1.5-31.7
5 to <9	88 (17.5)	5.1-59.9	96 (19.0)	3.6-68.6
10 to <50	322 (63.9)	7.1-95.0	313 (62.1)	7.0-49.5
51 to <100	21 (4.2)	18.9-88.9	15 (3.0)	15.6-34.2
≥100	2 (0.4)	43.2-71.2	0 (0.0)	0

[1]Total number of *Campylobacter* cases = 9691
[2]Total number of *Salmonella* cases = 8273
[3]Cases from 504 FSAs