Exploring Environmental Drivers and Potential Methods of Transmission of
Campylobacter in Ontario, Canada Using One Health Approaches

by

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EXPLORING ENVIRONMENTAL DRIVERS AND POTENTIAL METHODS OF TRANSMISSION OF CAMPYLOBACTERIOSIS IN ONTARIO, CANADA USING ONE HEALTH APPROACHES.

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Enteric illnesses from bacteria such as *Campylobacter* use the environment as a major reservoir during their transmission between humans and animals. Therefore, this thesis aimed to explore the environmental drivers and transmission pathways of *Campylobacter* in Ontario from a One Health perspective. The first study explored environmental factors and their effect on *Campylobacter* in the human and farm populations using Negative Binomial regression and case-crossover analyses. Results showed that campylobacteriosis incidence was affected by temperature, precipitation, and water level and flow. This lead to the second study in which a model of Ontario *Campylobacter* transmission was proposed to examine the hypothesis that house flies act as a mechanical vector. The model suggested that with the predicted changes to fly dynamics under climate change, we can expect increased campylobacteriosis incidence. The data from both studies provides insight into *Campylobacter* dynamics and how it may be affected as the global temperature rises.
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STATEMENT OF WORK

Chapter 2: In this chapter, Melanie Cousins identified environmental factors which were associated with increased risk of campylobacteriosis in humans in four regions of Ontario and Campylobacter positivity on farms in Waterloo, Ontario. The campylobacteriosis cases were provided by Public Health Ontario. The farm-level data were provided by the Animal Health Lab and the Public Health Agency of Canada’s FoodNet program. All data analysis was performed by Melanie Cousins with input from Drs. Amy Greer, Jan Sargeant, and David Fisman. The manuscript was written by Melanie Cousins, and reviewed and edited by Drs. Amy Greer, Jan Sargeant, and David Fisman. This paper has been submitted to *BMC Infectious Diseases* for review and has been formatted accordingly.

Chapter 3: Using results from the previous study as well as peer-reviewed literature, Melanie Cousins created a compartmental infectious disease model that incorporated a seasonally forced environmental compartment and flies as a mechanical vector to model transmission of campylobacteriosis in the Ontario human population. The model was parameterized and calibrated to the campylobacteriosis cases from Public Health Ontario. The model was built by Melanie Cousins with input from Drs. Amy Greer, Jan Sargeant, and David Fisman. All mathematical analyses were performed by Melanie Cousins. The manuscript was written by Melanie Cousins, and reviewed and edited by Drs. Amy Greer, Jan Sargeant, and David Fisman. This paper has been submitted to *Royal Society Open Science* for review and has been formatted accordingly.
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CHAPTER 1

INTRODUCTION, LITERATURE REVIEW, STUDY RATIONALE

1.0– INTRODUCTION

Since the late 19th century, it has been recognized that human and animal health share many commonalities, but it was not until after the severe acute respiratory syndrome (SARS) epidemic of 2003 that the concept of One Health in its current form, made its debut (van Helden, van Helden, & Hoal, 2013). The World Health Organization defines One Health as “an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes” (WHO, 2017). However, One Health is much more than just policies and legislation. The United States Centers for Disease Control and Prevention (CDC) adds that One Health “recognizes that the health of people is connected to the health of animals and the environment. The goal of One Health is to encourage the collaborative efforts of multiple disciplines-working locally, nationally, and globally-to achieve the best health for people, animals, and our environment” (CDC, 2017). Both definitions mention the coming together of multiple sectors. This open communication and ability to work together is crucial in the One Health framework. This could include human medicine and public health, veterinarians, ecologists, environmental chemists, health economists, and international organizations (Lerner & Berg, 2014). The CDC broadens the scope even further to include sharing of responsibility and resources to solve problems at a global scale (CDC, 2017). With the ability of humans to travel over long distances in a short period of time, diseases can also now travel much greater distances. Therefore, to truly control the spread of disease, one must think at a global scale.
Humans, animals, and the environment interact daily, yet these interactions have been left out of many epidemiological analyses. In order to maintain health across sectors, we must look at the system as a whole. In the context of infectious disease dynamics. One Health is an approach that aims to understand disease transmission by better understanding the entire system to identify causes, interventions, and outcomes of health. For example, many infectious diseases that transmit between humans and animals do so through the environment, and a relationship between all factors is necessary for the disease to occur. However, with the increases in greenhouse gas emissions and resulting climate change, the whole ecological system is changing. Therefore, we need to understand these base line interactions and dynamics in order to be able to be prepared for how things may change in the future.

2.0– CLIMATE CHANGE

Climate change is of growing concern in Canada and globally. Since the start of the 20\textsuperscript{th} century, global mean temperatures have risen 0.6°C (Rossati, 2017). Most scientists agree that the rising of carbon emissions and greenhouse gases into the atmosphere is caused by humans (Easterling et al., 2000; McMichael, Woodruff, & Hales, 2006). The associated elevation in temperature will have significant impacts on weather patterns and the global climate which will in turn affect the interactions that occur between ecosystems, microbes, insects, animals, and people. Climate change is expected to have a significant impact on environmental conditions and weather events, and carry over effects on infectious disease dynamics both in direct and indirect ways.
2.1 – CLIMATE CHANGE AND ITS EFFECT ON THE ENVIRONMENT

The Inter-Governmental Panel on Climate Change (IPCC) has estimated that the world temperature will increase 1.4-5.8°C by 2100 with greater increases in the winter than summer (McMichael et al., 2006; Oecol & Populations, 2000). Canada is expected to have longer, drier summers, and milder winters with increased winter precipitation in the form of rain, higher than average increases in temperatures (up to 4.5 °C by 2055), and a decrease in summer soil moisture (Charron et al., 2004). These increases in temperature are expected to change precipitation patterns and lead to an increase in extreme weather events such as extreme rain fall and flooding (Dore, 2005).

The warmer temperatures are likely to lead to less snowfall and an increase in winter rainfall (Dore, 2005). Also, warmer temperatures in the winter will lead to an earlier and more rapid snowmelt which could cause increased runoff, higher river water level and flow, and flooding events (Dore, 2005). In southern Canada, a 12% increase in annual precipitation has been noticed from 1900-1998 and it is expected that this increase in annual precipitation will continue to increase 0.5-1.0% per decade (Dore, 2005). This increase is most likely to be in the form of extreme precipitation events (Dore, 2005; Kunkel, 2003). As atmospheric temperatures increase, the saturation of water vapor pressure will also increase and the atmosphere will be able to hold more water vapor. Therefore, when precipitation events occur, the atmosphere will contain more water, leading to more rainfall per event (Dore, 2005).

These heavy precipitation events will in turn cause river levels to rise, faster water flows, and an increase in the likelihood of excess runoff and flooding events (Charron et al., 2004). Flooding is of significant concern as it will lead to increased erosion and severe runoff (Charron et al., 2004). In a study by Van Vilet et al (2013), northern latitude regions such as Canada will
experience an increase in river discharge and increased water temperatures (Van Vliet et al., 2013). For example, the river flow for the Mackenzie river is projected to increase by 22% and water temperatures are subject to a 1.1-1.4 °C increase in mean temperatures in 2071-2100 compared to 1971-2000 levels (Van Vliet et al., 2013). However, these changes will have much greater impacts than just affecting the environment alone. Humans, animals, and microorganisms have complex interactions with the environment. Therefore, changes to the abiotic environmental conditions will influence the ways in which humans, animals, and microorganisms interact.

2.2 – CLIMATE CHANGE AND ITS IMPACT ON INFECTIOUS DISEASES

Climate change will have a significant effect on the weather patterns observed in Canada and will have great impacts on the incidence of infectious diseases (Lafferty & Mordecai, 2016). This is especially true for pathogens that have complex relationships with the environment (Lafferty & Mordecai, 2016). Overall, the burden of human infectious diseases has been declining over the years. However, much of this reduction in disease burden is a result of public health prevention and control measures such as safe and effective vaccines, food safety regulations, and water and waste treatment infrastructure (Lafferty & Mordecai, 2016). These advances in technology and public health interventions as well as economic growth may be masking the potential effect of climate change on the incidence of infectious diseases (Lafferty & Mordecai, 2016).

Infectious diseases can be caused by many different types of pathogens. The term pathogen includes viruses, bacteria, and parasites (Alberts et al, 2002). These pathogens come in different sizes and shapes and all require specific conditions in which to survive (Alberts et al, 2002). This is especially critical for pathogens that have an environmental reservoir and that can successfully persist outside of the host, in the external environment for some period of time. Directly
transmitted pathogens can be transmitted by anthroponosis (between humans) or zoonosis (between animals and humans) both by physical contact or through environmental reservoirs (Patz et al., 2008). Pathogens transmitted by anthroponosis are typically best adapted for within host (humans) survival and therefore are less likely to be impacted by climate changes (Patz et al., 2008). However, zoonotic pathogens, some of which are adapted to persist in the environment, outside their hosts may be more vulnerable to climactic changes (Patz et al., 2008). For example, zoonotic enteric diseases such as campylobacteriosis and cholera exhibit seasonal fluctuations which suggests an association between disease occurrence and climactic factors (Patz et al., 2008). Environmental changes such as increases in temperature, winter rainfall, and heavy precipitation events, combined with the resulting increased river flow, water temperatures, and chance of flooding all interact to change pathogen survival, transmission, and dynamics in the environment. However, pathogens which require an arthropod vector are even more susceptible to environmental factors than directly transmitted pathogens as the host-pathogen system is more closely tied to the environment (Patz et al., 2008).

2.2a – Impacts of climate change on the pathogen

All pathogens have specific environmental conditions in which they are best suited to survive and multiply (Alberts et al, 2002). Increases in temperature directly affects pathogen enzyme function, membrane permeability, and respiration rate, as well as molecular stability (Lafferty & Mordecai, 2016). However, pathogens also have different abilities to adapt to changes in these factors. For example, pathogens from high latitudes can tolerate greater changes in temperature due to the variable climates in which they are best adapted. Comparatively, tropical pathogens have more limited thermoregulation abilities and heat tolerances and therefore, cannot tolerate large changes in temperature (Lafferty & Mordecai, 2016).
One specific example is *Salmonella spp.* bacteria. These bacteria can be transmitted to humans through food. Their ability to multiply in food is directly proportional to temperature when between 7.5-37°C. Therefore, as ambient temperatures increase, the ability of *Salmonella* to replicate also increases which can lead to higher bacterial loads along the food chain (Lake et al., 2009).

### 2.2b – Impacts of climate change on the host

On a larger scale, climate change will have an impact on where hosts are living or travelling within their environments. Many animal species are moving to higher elevations and higher latitudes putting them into new environments where new host-pathogen interactions may take place (Altizer, Ostfeld, Johnson, Kutz, & Harvell, 2013). Shifts to migratory patterns have also been noticed with changes to shorter migration routes or no migrations at all due to warmer temperatures over the winter (Altizer et al., 2013). For example, some monarch butterflies (*Danaus plexippus*) are over wintering in certain parts of the United States (Altizer et al., 2013). Compared to those that continue to migrate, these butterflies are experiencing an increase in infection with the parasite *Ophyrocystis elektroscirrha* (Altizer et al., 2013).

### 2.2c – Climate change and its impact on water and food-borne diseases

Water and food-borne illnesses are of major concern in developing and developed countries and according to models by Rossati (2017), are expected to increase by 10% by the year 2030 (Hunter, 2003; Rossati, 2017). Water and foodborne pathogens are primarily caused by viruses (hepatitis A), parasites (*Giardia duodenalis, Cryptosporidium parvum*), or bacteria (*Campylobacter* spp., *Salmonellae* spp., *Vibrio cholerae*) (Hunter, 2003). The main sources of waterborne diseases are drinking water (ground or surface) and recreational waters (Hunter, 2003). Water sources can become contaminated by the feces of livestock, pets, or wildlife near
the water systems or runoff from landfills, sewers, or agricultural lands (Government of Canada, 2013) which can lead to increased concentrations of virus, bacteria, and parasites. Foodborne illnesses are mainly contracted by eating contaminated meat and shellfish, vegetables that have been washed with contaminated water, raw milk, or eggs (Government of Canada, 2013). Both water and foodborne illnesses are usually categorized as enteric or diarrheal diseases meaning they cause gastrointestinal illness (Hunter, 2003). Symptoms usually include stomach cramps, nausea, vomiting, diarrhea, and low-grade fever (Hunter, 2003).

Enteric disease affected 88.7 per 100,000 population in the province of Ontario from 2007-2012 and made up 15% of all reportable diseases during this time, however there is significant under reporting when it comes to enteric diseases (Whitfield et al., 2017). The pathogens Salmonella, Campylobacter, and Giardia are consistently the leading causes of enteric disease (Whitfield et al., 2017). Most enteric diseases have low endemic levels in Canada with sporadic outbreaks (Naumova et al., 2007). Disease patterns in humans also exhibit consistent seasonal fluctuations, with the highest rates of disease in the warmer months (Naumova et al., 2007). These seasonal changes in disease incidence can be biological, suggesting a climactic link, as well as behavioral (Naumova et al., 2007). Since the pathogens use the environment as a major reservoir, seasonal changes to their environments may in turn affect how the pathogen survives and grows (Naumova et al., 2007). On the other hand, when temperatures start to warm humans change their patterns of behaviour. This includes spending more time outdoors potentially around surface and recreational waters as well as riskier food preparation habits such as barbequing (Naumova et al., 2007).

As mentioned in the previous section, all pathogens have an optimal temperature profile in which they can persist. Many enteric pathogens prefer warmer temperatures to grow and
multiply, for example Salmonellae’s ideal thermal range is 35-43°C and the pathogen does not survive well below 5°C (Hunter, 2003). Therefore, increases in ambient and water temperatures can directly influence these pathogens by altering their survival and population dynamics when outside of a host. Not only are the pathogens able to multiply at faster rates when temperatures are higher, they will be able to begin to replicate earlier in the spring and remain growing for longer into the autumn and winter (Hunter, 2003). For example, a higher incidence of cholera was observed in South America and Asia after El Niño events (Hunter, 2003). Also, in a study by Naumova et al. (2007), the authors found that disease incidence associated with Salmonellae and Campylobacter strongly followed the ambient temperature curve suggesting a strong relationship with ambient temperature (Naumova et al. 2007). Therefore, with the increasing temperatures expected under a climate warming scenario, these pathogens could be seen in greater numbers along the food chain which can lead to increased risk of pathogen exposure and ingestion of higher pathogen loads by humans (Lake et al., 2009).

However, there are also indirect effects of increased temperature that could influence the dynamics of water and foodborne illnesses by influencing the relationships between the main reservoir host and other organisms in the ecosystem. In this case, higher water temperatures not only impact the population growth of the pathogen but the growth of many other organisms within the broader ecological community. For example, the enteric pathogen V. cholerae uses shellfish as a main reservoir (Colwell, 1996). These shellfish mainly feed on phytoplankton in the water. After warm temperatures, such as after the long El Niño event of 1990-1995 in the tropical Pacific, there was a significant increase in phytoplankton blooms (Colwell, 1996). The abundance of food sources for the major shellfish reservoirs for V. cholera in turn led to a higher incidence of cholera disease among surrounding populations (Colwell, 1996). Secondly,
increases in global temperatures mean longer, warmer summers in temperate countries. This change in temperature profile may lead to more people engaging in summer activities for a longer period of the year. Such activities include barbequing, swimming, and the consumption of more fresh produce. All of these activities put the human population at greater risk of exposure to gastrointestinal pathogens (Lake et al., 2009).

Another indirect effect of climate change on water and foodborne diseases occurs due to changes in precipitation patterns. Heavy precipitation events, droughts, and flooding are all associated with waterborne outbreaks (Charron et al., 2004; Rossati, 2017; Hunter, 2003). This can be because heavy rain events (especially after a dry summer) and flooding may cause increased runoff which will flush animal, human, and wildlife manure into water reservoirs, groundwater, and/or recreational waters which may contaminate the water source and lead to outbreaks of waterborne pathogens (Charron et al., 2004). For example, in the Czech Republic and coastal areas of Maryland, increases in water contamination with leptospirosis and Campylobacter were documented after flooding and extreme precipitation events (Rossati, 2017). A study conducted in the United States looked at all of the reported waterborne outbreaks from 1948-1994 and found that 51% were preceded by heavy rain events (Hunter, 2003). This is important to note as it is theorized that climate change will result in both an increase in extreme precipitation events along with periods of drought. This combination is ideal for flooding and mass run-off as the water will not have the ability to soak into the soil.

2.2d - Climate Change and its impact on vector-borne diseases

Some pathogens require vectors for the transmission of infection between hosts (Hunter, 2003). Common vectors include mosquitos, ticks, and flies (Khasnis & Nettleman, 2005). These arthropod vectors are directly affected by temperature and other climactic factors in multiple
ways (Khasnis & Nettleman, 2005). For example, there is a direct relationship between El-Niño and increased malaria risk. This is partly due to increased temperature and partly due to increased rainfall leading to increased mosquito breeding sites (Hunter, 2003).

Increases in temperature influence the population density and distribution of the vector species as well as the ability and rate at which vectors can transmit the pathogens (Hunter, 2003; Khasnis & Nettleman, 2005). Vector populations will experience altered survival rates and population growth as a result of changes to climate. The rate of transmission to hosts will be altered due to changes in the feeding behaviour of the vectors, biting rate, vector susceptibility, the incubation period of the pathogen, and changes in seasonality of vector activity and pathogen transmission (Hunter, 2003; Khasnis & Nettleman, 2005).

Changes to precipitation are also expected to affect the vectors and their ability to transmit pathogens. Increased rainfall may lead to more surface water and increased vegetation which are breeding grounds for many vectors (Hunter, 2003). However, low rain fall may also lead to more breeding sites by creating more still water sources, for example slower moving rivers (Hunter, 2003). Heavy precipitation events may lead to flooding which could destroy vector habitats but may also lead to closer contact between vectors and their human and/or animal hosts (Hunter, 2003).

A vector of specific interest when thinking about bacteria which cause enteric illness is the house fly (Musca domestica). House flies are known to carry many pathogens which can infect humans such as Campylobacter and E. coli (Szalanski, Owens, McKay, & Steelman, 2004). Therefore, it is important to know how house fly population dynamics change at different temperatures in order to predict how fly populations may change in the future. Goulson et al. (2005) found that fly populations increase in warmer temperatures and predict that populations
may double by 2080 under the optimistic emissions scenario and triple under the worst-case scenario (Goulson et al., 2005). In a study by Shou et al. (2013), the authors studied how fly activity changes at different temperatures. These authors found that daytime activity increased as temperature increased until a maximum temperature of 30°C for males and 35°C for females (Shou et al., 2013). Therefore, it can be assumed that as global temperatures rise, so too will fly activity.

3.0 - CAMPYLOBACTER AND ITS ENVIRONMENT

*Campylobacter sp.* is a waterborne and food-borne pathogen as well as a vector-borne pathogen. Therefore, it is expected that there will be changes to the current disease patterns of campylobacteriosis (disease caused by *Campylobacter sp.*) as the climate changes (Epps et al., 2013). *Campylobacter sp.* is a bacterium that causes gastrointestinal illness in humans and can colonize many other animals but does not usually cause clinical illness (Epps et al., 2013). The bacteria is a gram-negative, motile, micro aerobic bacteria with respiratory-type metabolism in which some can grow aerobically and anaerobically (Epps et al., 2013). The two main strains that affect humans are *Campylobacter jejuni* and *Campylobacter coli* with *C. jejuni* accounting for the majority of human cases. These strains are of importance due to their ability to colonize and survive in multiple species of animals and in many different types of environments (Epps et al., 2013). These bacteria are found throughout most developing countries and many developed countries, such as Canada, the United States, and much of Europe (Epps et al., 2013). *Campylobacter sp.* is the leading cause of bacterial zoonotic disease in humans in the world infecting approximately 13 out of 100,000 population in the United States every year, typically as sporadic cases, within-family clusters, or outbreaks due to a common source such as
contaminated food eaten by a group of individuals. (Epps et al., 2013; Jacobs-Reitsma, Lyhs, & Wagennar, 2008).

3.1 - THE IMMUNE RESPONSE AND IMMUNITY:

Once the *Campylobacter sp.* organism is ingested by a human, it first encounters the mucus layer of the gastrointestinal epithelium. However, the bacteria have adopted strategies to overcome this barrier such as motility and the corkscrew morphology which reduces binding with mucin glycoproteins and allows easier passage through the mucus layer (Young, Davis, & Dirita, 2007). From here the bacteria invade the intestinal epithelial cells where the cells elicit a humoral response including the induction of cytokines, specifically IL-8 which is common in campylobacteriosis (Young et al., 2007). This leads to an inflammatory response at the site of infection which causes gastrointestinal symptoms. It is hypothesized that *Campylobacter sp.* elicits at least a short-term immune response that protects individuals from subsequent infection (Blaser, Checko, Bopp, Bruce, & Hughes, 1982). Antibodies have been seen in serum samples collected on the fifth day of illness, increase until 2-4 weeks, and then slowly decline over the next several months (Blaser et al., 1982). This assumed immunity is only to the same strain of the bacteria and the duration of immunity is not well documented (Blaser et al., 1982). In developing countries, children are exposed to *Campylobacter sp.* in contaminated water daily (Blaser et al., 1982). The young children develop campylobacteriosis, but as they age the infections become less severe and less often until they cease in older children and adults (Blaser et al., 1982). Similarly, children who are regularly exposed to raw milk or raised on farms appear to experience the same trend (Olson, Ethelberg, van Pelt, & Tauxe, 2008). Finally, older individuals tend to become infected only by less common serotypes suggesting a potential immunity as a result of repeated exposure to the more common serotypes (Olson et al., 2008).
3.2 - CAMPYLOBACTERIOSIS AND GUILLAIN BARRÉ SYNDROME:

Human illness due to the bacteria *Campylobacter sp.* results in clinical symptoms similar to many other food-borne illnesses. Individuals tend to experience fever, abdominal cramps, and diarrhea with or without blood in the stool (Epps et al., 2013; Young et al., 2007). Campylobacteriosis may occur after ingesting as few as 500-800 bacterial organisms (therefore the infectious dose necessary to cause disease is relatively low) and clinical symptoms usually take 2-5 days to appear and typically last from 3-7 days but can last up to 2 weeks in some individuals (Epps et al., 2013; Young et al., 2007). In developed countries, the disease is usually self-limiting with potential bloody diarrhea and mucous. In developing countries, watery diarrhea in children is predominant and these children get much more frequent infections. The more frequent exposure to the bacteria may contribute towards long term protection against re-infection in adulthood (Young et al., 2007). In severe cases, the infection can lead to Guillain Barré Syndrome (GBS) (van Doorn, Ruts & Jacobs, 2008; Epps et al., 2013). This is a rare, autoimmune disease that causes demyelination of neurons and/or deterioration of axonal nerves in the peripheral nervous system (van Doorn, Ruts & Jacobs, 2008; Epps et al., 2013). The annual incidence of GBS ranges from 1.3-2.3 per 100,000 people world-wide and approximately 20-50% of Guillain Barré Syndrome cases that have been documented in developed countries, including North America, Japan, and Australia, were preceded by *C. jejuni* infections (van Doorn, Ruts & Jacobs, 2008; Epps et al., 2013). After an infection, the body produces antibodies against *Campylobacter sp.* which may cross-react with self-gangliosides (Epps et al., 2013). The body will then attack the ganglion in the nervous system leading to many neurological and muscular effects (Epps et al., 2013). This syndrome is found in all age groups and both sexes but most commonly in adolescents to young adults and risk is 1.5 times higher in males compared to
females (Kuwabara, 2004; van Doorn, Ruts, & Jacobs, 2008). However, campylobacteriosis is more common in males and it is theorized that this is the reason for the higher rates of GBS among males (Kuwabara, 2004). GBS is also found in elderly people but it is thought that this demographic is more susceptible to autoimmune disease in general and that in this age group, the risk is not necessarily linked to Campylobacter sp. infection (Kuwabara, 2004).

3.3 - NATURAL RESERVOIRS:

In humans from developed countries, campylobacter is mainly a food-borne illness, meaning food animals are of great importance to the transmission process (Jacobs-Reitsma et al., 2008). However, there are many different transmission pathways and environmental and animal reservoirs of Campylobacter sp. which can result in human infection (Figure 1.1). Such pathways include the consumption of contaminated meats (up to 80% due to poultry), consumption of raw milk or contaminated water, and close contact with infected pets or other farm animals (Baker et al., 2012). For example, in a New Zealand study by Eberhart-Phillips et al. (1997) the top four risk factors for human Campylobacter sp. infection were: handling cow faeces in the last four days (OR=4.40, 95% CI 1.34 to 14.49), having sewage problems in the home in the last 10 days (OR=4.35, 95% CI 1.55 to 12.18), drinking unpasteurized milk in the last 10 days (OR=3.92, 95% CI 1.66 to 9.27), and eating raw or undercooked chicken in the last 10 days (OR=3.71, 95% CI 2.24 to 6.13).
3.3a – Transmission and animal reservoirs

*Campylobacter* sp. has a minimum growth temperature of 30°C (Olson et al., 2008) making warm-blooded mammals and birds the primary reservoirs. Due to poultry’s higher metabolic temperatures (41-45°C versus 37°C in humans), poultry are optimal reservoirs for *Campylobacter* sp. The bacteria also do not cause any negative health impacts to the poultry reservoir making poultry asymptomatic carriers of the bacteria. Cattle, sheep, and swine are also known reservoirs of *Campylobacter* sp. (Olson et al., 2008). In a study by Munroe *et al.* (1983), up to 58% of pig faeces were reported to contain *C. coli*, the more common *Campylobacter* species found in pigs. *Campylobacter* sp. has also been linked to diarrhea in cattle and abortions in cattle and sheep (Munroe *et al.*, 1983; Olson *et al.*, 2008). These animals are born free of the
bacteria but become exposed when born into environments contaminated with the bacteria. It was also found that cow and sheep faeces on the same farm contained the same strains of *C. jejuni* and *C. coli* (Baker et al., 2012). Wild birds, rodents, and pets are all other potential animal reservoirs of *Campylobacter*. However, these animals do not typically show clinical signs of disease (Wagenaar et al., 2014). As a result, many animal reservoir species can be shedding the bacteria into the environment for a long time which increases the pathogen load of the surrounding environment. If testing is not done on farm, it is possible to have a colonized poultry flock go undetected until slaughter (Wagenaar et al., 2014). This is a significant risk for the spread of the pathogen to other animals, humans which have close contact with animals or that may consume animal products that have not been cooked properly, and humans and animals that come into contact with the pathogen in the environmental reservoir.

Most pathogen transmission between animal species occurs via environmental pathways such as soil and water (Olson et al., 2008). When animals such as cattle, sheep, swine, poultry, wild birds, and humans are colonized they shed the bacteria in their faeces into the surrounding environment. This can then be ingested by grazing animals, or transferred through water and runoff to surrounding areas and potential water sources.

3.3b – Transmission and humans

*Campylobacter sp.*, in temperate climates, exhibits seasonality with human cases rising in March, peaking in June and July, and declining throughout the fall (Olson et al., 2008). This is likely due to a combination of factors. One hypothesis is that warmer temperatures are linked with more risky food habits (for example barbequing, suboptimal refrigeration and freezing temperatures, and/or increased contact with flies) as well as greater exposure to potentially contaminated water via recreational activities (Olson et al., 2008; Nichols, 2005). Another
hypothesis is that the seasonality coincides with increases in insect, rodent, and migratory bird populations, all of which may carry the pathogen with insects (specifically, flies), and migratory ducks and geese of particular interest (Olson et al., 2008). Flies are known to carry bacteria such as *Campylobacter sp.* on their bristles and may transfer the bacteria to human food which can infect humans upon consumption (Nichols, 2005).

### 3.3c – Transmission and survival in environmental reservoirs

*Campylobacter sp.* can survive very well in animal faeces. For example, they can live in cow and sheep faeces for up to 30 days at cooler temperatures (4°C) and up to 10 days in summer temperatures (Baker et al., 2012). However, they do not survive as long in poultry faeces, only 15 days in cooler temperatures and 2 days in warmer (Baker et al., 2012). This pattern is consistent with survival on many different foods (raw chicken for example), where survival was 1.5-15 times greater in 2°C temperatures versus 20°C. Although *Campylobacter sp.* do not multiply at these low temperatures, metabolic activity does not cease, these bacteria still produce ATP and display catalase activity. Also, bacterial levels in water are higher during the winter months compared to the summer months as *Campylobacter sp.* is sensitive to UV radiation. Water however is a main source of transmission between animals. Heavy rain events and flooding stir up sediments and release dormant *Campylobacter sp.* back into the water to be spread during run-off (Baker et al., 2012). Therefore, temperatures, sunlight, and rain events all potentially drive *Campylobacter sp.* transmission in the environment and may lead to increased cases in humans.

### 4.0 – EPIDEMIOLOGICAL MODELS

Traditional and more advanced epidemiological methods can be used to analyze *Campylobacter sp.* data to find trends, patterns, and associations. Previous studies have
examined the seasonality of *Campylobacter sp.*, as well as associations with many possible sources of the pathogen including weather effects (rainfall and humidity), environmental effects (water levels and turbidity), and contact or proximity to livestock (mainly poultry and ruminants) (White et al., 2009; Patrick et al., 2007).

### 4.1 - TRADITIONAL APPROACHES:

*Campylobacter sp.* show distinct summertime seasonality. Therefore, when analyzing data on human cases, it is necessary to take seasonality into account. This can be done by adding orthogonal sinusoidal oscillators with 52-week periods to the model to model the seasonal component (White et al., 2009). Incorporating seasonal smoothers allows for an examination of the discrepancies between the predicted seasonal pattern and the number of human cases observed which can give insight into specific influential factors (Naumova et al., 2007). When accounting for variations in weather or other environmental factors on case occurrence, time-lags must also be considered. For example, a heavy rainfall is unlikely to be associated with an increase in cases on the same day, therefore biologically plausible lags must be determined. *Campylobacter sp.* has an incubation period of 2-5 days (Blaser, 1997), therefore environmental conditions being considered must have occurred at least a few days prior to disease onset. When analyzing the data for these types of associations, there is added complexity in the analysis. For example, infectious disease count data typically have variances that are higher than expected in a typical Poisson distribution therefore using Poisson regression is not always appropriate to model for the epidemiological data (Imai et al., 2015; Dohoo et al., 2012). In this case, it is necessary to take the over dispersion of the data into consideration (Imai et al., 2015; Dohoo et al., 2012) Negative binomial regression analysis and quasi-Poisson regression analysis can account for the over-dispersion. Another challenge related to infectious disease count data, is that in many
instances, the dataset contains many zeros (which is common in *Campylobacter sp.* datasets as it is a sporadic disease in developed countries). In instances where there is an excess of zero-counts, a zero-inflated model may be required (Dohoo et al., 2012). Zero-inflated negative binomial regression models fit both a binary model, using a logistic regression model, and a negative binomial model (Dohoo et al., 2012). The logistic regression portion of the model explains the probability of a zero count given the predictor variables where the negative binomial portion explains how the predictor variable affect the mean of the non-zero cases (Imai et al., 2015; Dohoo et al., 2012).

These types of regression models have been used to examine associations between climactic and hydrological factors and cases of enteric illnesses such as campylobacteriosis. In a study by White *et al.* (2009), the authors used Poisson regression to explore the effect of environmental determinants on weekly campylobacteriosis cases in Philadelphia. Using the negative binomial regression methodology, they found that increasing relative humidity (IRR per % 1.017, 95% CI 1.008–1.025), increasing ambient temperatures (IRR per °C 1.041, 95% CI 1.011–1.072), and decreasing river temperatures (IRR per °C 0.922, 95% CI 0.883–0.962), were associated with increased rates of campylobacteriosis when occurring in the same week as case onset (White *et al.*, 2009). A Danish study, looked at climactic factors and their association with the incidence of campylobacteriosis in humans and prevalence of Campylobacter spp. in poultry using locally fitted linear models (Patrick *et al.*, 2007). The authors found that temperature and sunlight four weeks before infection were the best predictors for campylobacteriosis incidence and temperature three weeks before slaughter were the best predictors (Patrick *et al.*, 2007).
4.2 - CASE-CROSSOVER STUDY DESIGN:

The case-crossover study design is useful when trying to determine, “was this event triggered by something unusual that happened just before?” (Maclure & Mittleman, 2000). A case-crossover analysis is best suited for evaluating whether an exposure is associated with transient changes in the risk of a rare, acute-onset disease (Maclure, 1991). This design can be used to study environmental effects on Campylobacter occurrence. Since Campylobacter is a sporadic disease in Canada and most other developed countries and has an incubation period of only a few days, the pathogen is an ideal candidate for a case-crossover study. In this study design, each case serves as its own control at a different time-period. This self-matched design controls for constant characteristics that could potentially bias the associations. The exposure immediately preceding the event (hazard period) is compared to the expected exposure frequency at times when the event did not occur, the control period (Mittleman & Mostofsky, 2014).

Thomas et al. (2006) applied this method to environmental effects on waterborne outbreaks. In their study, the cases were outbreaks of waterborne disease and their exposures of interest were different environmental factors such as water turbidity and heavy rainfall. The hazard period was six weeks prior to an outbreak and the control period was matched by day in the other six-year time strata. This study found that warmer temperatures and heavy rainfall events were associated with waterborne outbreaks. The relative odds of an outbreak increased by a factor of 1.007 (95% CI = 1.002 – 1.012) for every degree-day above 0°C and by a factor of 2.283 (95% CI =1.216 – 4.285) for rainfall events greater than the 93rd percentile (Thomas et al., 2006). In another study by White et al. (2009), the lag period between environmental occurrence and the onset of cases followed a pattern that was consistent with the incubation period of Campylobacter which is 2-5 days. This study however did not find any acute associations using
case-crossover analysis. A case-crossover study design is analyzed using Mantel-Haenszel estimators or conditional logistic regression (Mittleman & Mostofsky, 2014).

Epidemiological models such as these can give insight into the specific, acute environmental drivers of case occurrence. These relationships can be used to inform other types of models including disease transmission models which allow researchers to explore other aspects of the disease dynamics.

5.0 – INFECTIOUS DISEASE MODELS

The mechanistic modelling of infectious diseases using mathematical frameworks has grown in popularity over the past decade (Höhle, 2015). These tools can be used to better understand the mechanisms of disease dynamics, and give insight into how to better control the spread of infections (Höhle, 2015). These models are used to describe the introduction and spread of a pathogen through a defined host population. The simplest structure is a compartmental model where individuals are classified based on their disease status: susceptible (S), infectious (I), or recovered (R) generally called SIR models (Höhle, 2015). The transitions between these states represent the disease dynamics. Changes in the population states over time are described by differential equations consisting of transition rates such as the transmission rate of the pathogen, or the rates of recovery from infection (Höhle, 2015).

The basic SIR models have been extended to consider more complex host-pathogen-environment interactions such as for the dynamics of waterborne diseases. For example, Tien & Earn (2010) proposed a simple SIR model with the addition of a water compartment (W) to describe the transmission routes of cholera. The addition of the W compartment accounts for the pathogen concentration in the water reservoir at any given point in time. The pathogen is shed into the water by the infected individuals. Once in the environment, the pathogen has a rate of
decay and a rate of infection for new susceptible hosts. By adding the water compartment the authors could model the person-person transmission route as well as the person-water-person transmission route of a waterborne disease like cholera (Tien & Earn, 2010). However, not only is *Campylobacter* spread via water, it is also a foodborne illness. In a model created by Singer *et al.* (2007) the authors added a colonized animal compartment (IA) which directly contributed to the infection rate of humans (IH). This model structure described the relationship between human cases and animal cases and how the consumption of food animals drives human infections (Singer *et al.*, 2007). These authors subsequently used this model to assess different intervention strategies at the food animal level to determine ways to avert human illness (Singer *et al.*, 2007).

Compartmental models can also incorporate different compartments for environmental factors that can influence disease transmission. In a model created by Baracchini *et al.* (2016) the authors wanted to add rainfall and temperature drivers into their model for cholera. They achieved this by creating an aquatic reservoir that fluctuated over time by volume, temperature, and environmental bacterial concentrations. The goal of their model was to determine if environmental reservoirs were of more importance to cholera transmission than person-person transmission. In their conclusions, they stated that the model could predict the full range of seasonal patterns of cholera in Bengal (Baracchini *et al.*, 2016).

Infectious disease models can capture the important components of host-pathogen-environment disease transmission dynamics. These models can become quite complex when trying to account for different reservoirs and routes of disease transmission. However, models do not need to perfectly represent all aspects of a host-pathogen system (Grassly & Fraser, 2008). Models are often simplified based on assumptions (biological or logical) to answer
specific questions or demonstrate specific dynamics of interest (Grassly & Fraser, 2008). For example, models are used as a communication tool to portray extremely complicated systems for decision making in health care (Caro et al., 2012). Therefore, these models are reduced to their simplest elements without losing the important message (Caro et al., 2012). Throughout the model building process, certain factors may appear to be of less importance or may not impact the model outcomes as much as anticipated and can therefore be removed from the model with little impact on the overall model projected outcomes (Grassly & Fraser, 2008).

Models can also be used to capture more complex systems such as vector-borne diseases. Incorporating vectors into a model creates an additional level of complexity to the basic SIR model as new compartments and interactions must be added. These models were first created by Ronald Ross and later modified by George MacDonald to model malaria transmission in Africa (MacDonald, 1955, 1956; Smith et al., 2012). Vectors become colonized when they contact (usually through biting) infectious humans (MacDonald, 1955, 1956; Smith et al., 2012). Once the pathogen is at a sufficient load within the vector, it can then become infectious to susceptible humans on a subsequent contact (MacDonald, 1955, 1956; Smith et al., 2012). In these models, humans can usually become infected from contact with both infectious humans and colonized vectors (MacDonald, 1955, 1956; Smith et al., 2012). These models can be adapted to capture the transmission of a pathogen to different reservoirs via a vector, whether through biting (mosquitos carrying malaria in Africa, [MacDonald, 1955, 1956]) or contact (contaminated hospital workers carrying bacteria through a hospital, [Doan et al., 2014]).

6.0 – THESIS OVERVIEW, PURPOSE AND RESEARCH

The transmission dynamics of *Campylobacter* within the human population are extremely complex (Wagenaar et al., 2013). The pathogen has many alternative, non-human reservoirs, the
survival and persistence of the pathogen within the environment is strongly influenced by climatic and hydrological conditions, and the pathogen can be transmitted from the animal and environmental reservoirs via insect vectors (e.g. flies). This makes *Campylobacter sp.* an excellent candidate for applying One Health approaches to better understand their dynamics.

The overall goals of this thesis were to 1) explore how the environment plays a role in the risk of campylobacteriosis and 2) explore how changes in the climate might affect campylobacteriosis incidence in the Ontario human population. These objectives were addressed using negative binomial regression and case-cross over methodologies as well as mathematical modelling. The first chapter provides a description of *Campylobacter sp.* and how climate change may affect the rate of disease in the human and pathogen presence in animal populations as well as the methodologies we used to explore the disease dynamics in more depth. Chapters 2 and 3 address the following specific research objectives:

1. Explore trends in the seasonality and determine the environmental drivers of *Campylobacter sp.* in the important food animals (poultry, sheep, cattle, and swine) and in humans in different regions of Ontario (Chapter 2).

2. Determine if there is a relationship between the environmental drivers, animal pathogen positivity, and human cases and how they interact. Specifically, whether environmental events precede animal cases which then lead to human cases, vice versa, or if the events lead to cases of animals and humans simultaneously (Chapter 2).

3. Create an infectious disease transmission model incorporating environmental factors, animal reservoirs, fly populations, and humans to model *Campylobacter* transmission in Ontario to test the hypothesis that house flies are drivers of disease transmission (Chapter 3).
4. Using this model, determine how predicted effects of climate change on fly population and activity will affect campylobacteriosis incidence in humans in Ontario in the future (Chapter 3).

7.0- REFERENCES


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CHAPTER 2
IDENTIFYING THE ENVIRONMENTAL DRIVERS OF CAMPYLOBACTER INFECTION RISK IN SOUTHERN ONTARIO, CANADA USING A ONE HEALTH APPROACH.

ABSTRACT

Background: Campylobacter bacteria infect both humans and animals. Sources of human exposure include contaminated food and water, contact with animals and/or their feces, and contact with infected individuals. The objectives of this study were to identify environmental conditions associated with Campylobacter cases in both humans and livestock reservoirs in Ontario.

Methods: Human Campylobacter cases from four health regions of Ontario, Canada were analyzed using logistic regression and case-crossover analysis to identify relationships between environmental factors (temperature, precipitation, and hydrology of the local watershed) and risk of infection. As a case study, we incorporated available animal data from the Waterloo health region to include environmental data and Campylobacter positive farms as potential exposures on human cases as a secondary analysis of a subset of our data.

Results: Human incidence exhibited strong seasonality peaking in the late spring and summer. There was a decreasing trend in three of the four health regions. In general, high temperatures, high precipitation, high water flow, and low water levels were associated with increased odds of Campylobacteriosis in humans at biologically plausible lag periods across all 4 health regions. When water levels were “low” in the Durham health region, the odds of campylobacteriosis were 2.17 (95% CI 1.39 to 3.39, p=0.001) times that of when water levels were “high” after a 17-day lag. In food animals, high temperatures and water level, and low water flow were associated with
an increase in the odds of a farm testing positive. Higher numbers of *C. jejuni* and *C. coli* positive farms were associated with increased odds of human cases after 10 days, and 23-25 days. After 23 days, increased *C. jejuni* positive cattle farms increased the odds of human campylobacteriosis by a factor of 1.26 (95% CI 1.08-1.47, p=0.003).

**Conclusion:** These results demonstrate an associations with climatic and hydrologic factors in both human and animal case occurrence after biologically plausible time periods. There is also evidence for zoonotic transmission however directionality was difficult to assess.

**BACKGROUND**

Campylobacteriosis is a bacterial enteric illness characterized by fever, abdominal pain, inflammation, and diarrhea with potential mucous or blood in the stool after a 2- to 5-day incubation period [1,2]. In more severe cases, disease complications have been associated with Guillain Barré syndrome, a neurological syndrome that can lead to respiratory paralysis [3]. Between 2007 and 2009 there were 10,916 reported cases of campylobacteriosis in Ontario resulting in a rate of 28.3 cases per 100,000 population [4]. In 2012, this number increased to 29.1 cases per 100,000, population making it the leading cause of bacterial gastrointestinal illness in Canada [5]. Campylobacter in humans can be contracted from many different sources. In Ontario, 20.4% of cases were due to international travel between 2007 and 2009 [4]. Of the domestic cases with a documented known exposure, 63.1% of cases were associated with food, 26.9% with contact with animals, 6% with contact with an infected individual and 2.8% with contact with contaminated water [4].

There are two main species of zoonotic *Campylobacter* that affect humans, *C. jejuni* and *C. coli*. The species *C. jejuni* is the most common zoonotic species with *C. coli* only accounting for 4% of the confirmed human cases [2]. In humans, campylobacteriosis demonstrates a
seasonal pattern with cases increasing over the spring, peaking in June and July, and falling slowly throughout the late summer and autumn [6].

These two species are also found in fecal matter shed by food animals. *C. jejuni* is found primarily in poultry, cattle, and sheep whereas, *C. coli* in most commonly found in swine and cattle [3]. In most animals, *Campylobacter* does not cause clinical disease; however, it has been linked to diarrhea in young cattle and sheep and abortions in adult cattle and sheep [6,7]. Livestock species typically acquire the pathogen during the post-partem period [3]. Whether these animals are clinical or not, they can begin to shed the pathogen into their environment via the faeces where it can persist for extended periods of time depending on climactic conditions [3]. It is suggested that factors that affect water dynamics such as precipitation events or water flow may influence how *Campylobacter* are distributed in the environment and the subsequent opportunities for humans and/or livestock to come in contact with the pathogen [3].

Many studies have explored associations between environmental factors and campylobacteriosis in humans or campylobacter levels in animals [9,10,11,12], but there has been little research into how all three interact. The objectives of this study were to: 1) identify environmental conditions associated with *Campylobacter* cases in humans in four regions of Ontario, and 2) as a case study, determine if there are temporal associations with environmental conditions, occurrence of *Campylobacter* in livestock reservoirs, and case occurrence in humans in the Waterloo health region of Ontario.

**METHODS**

**The Health Regions:**

The province of Ontario is divided into 36 different health regions. For this study, we selected four of these health regions based on data availability and comparability. These regions
include Waterloo, Wellington-Dufferin-Guelph, York, and Durham (Figure 2.1). These regions differ in terms of the major water reservoir, agricultural density, and population (Table 2.1). The Waterloo and Wellington-Dufferin-Guelph health regions share the Grand River as their major water reservoir which is a large and highly regulated water system [14]. The York health region is the most populous of the four regions and has the lowest agricultural density [15]. The Durham health region contains the smallest water reservoir (123 km²) but the second highest population [13,16].

The Waterloo health region is unique in that this region was the first surveillance site for the Public Health Agency of Canada, Food-Net enhanced surveillance for enteric pathogens. Therefore, this health region had additional on-farm sampling data available. This allowed for human-animal-environment interactions to be analyzed for both C. jejuni and C. coli. The three other health regions were chosen for further analysis to help explain associations in human-environment interactions of the C. jejuni species only and were chosen due to their different population and land-use characteristics (Table 2.1).

**Case data:**

Nine years (January 1, 2005 to January 31, 2014) of human case count data were obtained from Public Health Ontario (PHO). The data represent confirmed cases of *Campylobacter* from the integrated Public Health Information System (iPHIS). Individual patients were recorded as positive if the pathogen had been isolated from stool or body fluids or due to an epidemiological link to one or more laboratory confirmed cases. Cases that had travelled outside of Ontario within the incubation period of *Campylobacter* were excluded as it was assumed that these do not represent locally acquired cases. Cases were further separated by
pathogen species, *C. jejuni* or *C. coli* and all other species were excluded due to a lack of evidence of zoonotic transmission.

**Animal data:**

Two datasets describing *Campylobacter* positive livestock samples (including cattle, swine, sheep, and poultry) were obtained. The first dataset came from the Animal Health Laboratory (AHL) at the University of Guelph. The AHL is a reference laboratory and veterinarians from across the province submit samples from a variety of food animals to the AHL for diagnostic testing. The second dataset came from the Public Agency of Canada (PHAC). PHAC coordinates a targeted surveillance program called Food-Net Canada to identify risks to human health along the farm-to-fork continuum. This program conducted on-farm surveillance for *Campylobacter* from May 26, 2006 to December 10, 2012 within the Waterloo health region. This was done by taking a pooled fecal sample of random livestock farms within the Waterloo health region. For both the AHL and the Food-Net datasets, a confirmed case represented a positive farm (e.g. one or more samples submitted from a single farm location tested positive). *Campylobacter* positive farms were further characterized as being positive for *C. jejuni* or *C. coli*. All other species were excluded.

**Environmental data:**

Meteorological data including temperature (°C) and precipitation (mm) as well as hydrological data including river levels (m) and flow (m³/s) of the local watershed were obtained from Environment Canada for the period January 1, 2005 to December 31, 2014. In most cases, the weather station from the most populous area within the health region and the largest watershed within each health region were used to generate a daily environmental dataset for each health region. The Grand River at the town of Doon was used for hydrology in the Waterloo
health region, the Grand River at Shan Dam was used for the Wellington-Dufferin-Guelph health region, the Oshawa Creek in Oshawa was used for the Durham health region, and the Holland River at Holland Landing was used for the York health region.

**Statistical Methods:**

*Negative Binomial Regression Analysis:*

The specific objectives for our regression analyses were threefold: 1) to identify if associations exist between environmental factors and human campylobacteriosis (O1), 2) to identify if associations exist between environmental factors and *Campylobacter* positive farms (O2), and 3) to identify if associations exist between environmental factors, livestock reservoirs, and human campylobacteriosis (O3). This was done by creating three separate data sets that covered varying timespans and included different reservoirs depending on the specific research objective to be addressed. In order to address O1, the full data set from January 1, 2005 to January 31, 2014 was used for human cases of campylobacteriosis in the four health regions and included daily environmental data for the entire time period. For O2, a subset of the environmental data for Waterloo region were used as the on-farm data collection aspect of the Food-Net Canada surveillance program was only active from May 26, 2006 to December 10, 2012. In order to address O3, human case data from May 26, 2006 to December 10, 2012 were added to the dataset described for O2, resulting in a dataset that matched daily environmental data, with human cases, and positive farm data.

For objective 1 (O1), environmental and human case data were aggregated to weekly values (e.g. summing all reported human cases and averaging environmental and hydrological exposure data for each week). The environmental data were lagged zero- to four- weeks. Seasonality was assessed by adding oscillatory smoothers (sine and cosine terms). If the sine and cosine terms
were statistically significant (p<0.05) there was a seasonal trend. Therefore, the seasonal
smoother allowed for the detection of significant effects beyond the normal seasonal oscillations.
A yearly effect was assessed by adding a year term to the models. The yearly population of the
health region was added as a denominator to account for the changing baseline.

Univariate analyses for human cases and lagged environmental data (including sine, cosine,
and year terms when significant) were conducted using negative binomial regression if over
dispersion occurred [17]. The linearity assumption (exposure variables have a linear relationship
with the independent variable on the log-scale, but not on the observational scale) was tested
using the non-parametric regression method Lowess. Multivariable analyses were conducted
using manual backwards selection incorporating seasonality (sine and cosine terms) and yearly
effects when significant (α = 0.05) in the univariate analyses as well as all significant
associations from the univariate analyses based on a liberal p-value (α = 0.2). Interactions
between exposure variables were tested and remained in the model if significant (p<0.05) based
on the Wald test. Normality of the Anscombe residuals was used as the criterion for model fit.

Comparative tables were created to determine how the overall incidence of campylobacteriosis
varied at different levels of environmental variables. This was done by calculating the difference
between predicted incidences by inspecting contrasts for the environmental variables, holding all
variables steady and varying the variable of interest.

Case-crossover:

Case-crossover is a hybrid study design used to evaluate acute associations between exposure
variables and a case using self-matching [18,19,20]. This is conducted by comparing the time
before a case, the hazard period, to a time in which a case did not occur, the control period, to
identify unique, acute differences in exposure status. Case-crossover analysis was used to
evaluate associations between human case counts, positive farm counts, and daily environmental exposures as well as associations between humans and farms.

For dataset 1, human cases from the full data set (January 1, 2005 to January 31, 2014) were self-matched by day of week using a three-week hazard period. Three weeks was chosen to account for the time it takes for the bacteria to move into an area in which it can contact a susceptible host, the incubation period of the bacteria, and the time before a human case seeks medical attention. Four control periods were matched by day of week, with each hazard period. Control periods were chosen at random and could precede, straddle, or follow the hazard period. The environmental predictor variables were lagged from 0-28 days to assess temporal associations with both human and farm positives. Conditional logistic regression was conducted to obtain odds ratios. For further analysis, each exposure variable was converted into quantiles by stratum. Temperature, precipitation, and water flow were converted into tertiles (high, medium, low). Water level was divided at the median (high, low) due to the limited range in the data. The quantiles were also lagged from 0-28 days. Each quantile was compared to all other quantiles of each variable using conditional logistic regression.

The same analysis was conducted using a truncated version of the first dataset (ranging from May 26, 2006 to December 10, 2012). Dataset two used case-crossover methodology to assess associations between environmental exposure variables and *Campylobacter* positive farms. Dataset three, combined environmental predictor variables and positive farms as predictor variables for human case occurrence. As a comparison, the same dataset (3) was also used to examine positive farms as the dependent variable and environmental factors and human case counts were used as the predictor variables. All statistical analyses were performed using Stata version 14.0 (Stata corporation, College Station, TX, USA).
RESULTS

Descriptive Statistics:

There were a total of 5,675 human cases in the four health regions studied (table 2.2) from January 1, 2005-January 31, 2014. There were more cases in males (55.2%) than females (44.8%). Most of the cases occurred in the 20-29 age group (17.4%) and in those under 10 years of age (14.4%, Appendix Figure S1).

Due to the relatively small number of positive farms across the four health regions, Waterloo health region was selected for further analysis because of the enhanced surveillance data that were available from the Food-Net program. From the Animal Health Lab data, there were 13 positive farms in the Waterloo health region from January 10, 2008 to December 29, 2010. From the Food-Net surveillance program there were an additional 438 positive farms spanning May 26, 2006 to December 10, 2012. When combined, there were a total of 451 positive farms: 285 cattle (dairy and beef combined), 14 poultry, 1 goat, 5 sheep, and 146 swine farms (table 2.3).

Seasonality:

For human cases in the Waterloo, Wellington-Dufferin-Guelph, York, and Durham health regions there was a distinct seasonal trend, with most cases occurring from June to September (significant sine and cosine terms can be seen in Tables 4 to 8, average incidence per month can be seen in Appendix 1, Figure S2). A yearly trend was significant in two of the health regions, showing that cases were decreasing over time in Waterloo (coefficient = 0.940, 95% CI: 0.903-0.979, p=0.003) and York (coefficient = 0.934, 95% CI: 0.923-0.955, p<0.0001) health regions. There was no seasonality present in the animal data ($\chi^2 = 12.00$, p=0.213).

Traditional Regression Analysis:

Objective 1: Human-Environment Associations
After controlling for seasonality and yearly effects when significant, multivariable models were built to identify environmental factors that were associated with the risk of human campylobacteriosis using Negative Binomial regression. Multivariable models were built for the Waterloo, York, and Durham health regions but not for the Wellington-Dufferin-Guelph region. All models did not have any discrepancies with the model assumptions based on criteria outlined in the methods.

Within the Waterloo region, two similar but not equivalent multivariable models were fit to the data, one including water level as a significant predictor and one including water flow (see Table 2.4 and 2.5 for incidence rate ratios). For both models, maximum temperature significantly decreased the rate of campylobacteriosis in humans. There was a reduction in the rate of campylobacteriosis by 3.51 cases per 100,000 person-years (95% CI 2.95 to 3.54 cases per 100,000 person-years) when temperature was 25°C compared to 5°C in 2014. Since the yearly effect was significant, we investigated this effect in previous years. The reduction in rate of campylobacteriosis was 5.06 cases per 100,000 person-years (95% CI 4.09 to 5.10 cases per 100,000 person-years) in 2005. There was a reduction of 6.74 cases per 100,000 person-years (95% CI 0.85 to 38.54 cases per 100,000 person-years) at water levels of 4 m compared to 2 m. There was also reduction of 0.49 cases per 100,000 person-years (95% CI 0.23 to 1.03 cases per 100,000 person-years) when the flow of the grand river was 100 m/s versus 10 m/s.

In the York region, temperature and daily precipitation were both associated with a significant reduction in the rate of campylobacteriosis in humans (Table 2.6). There was a reduction of 1.92 cases per 100,000 person-years (95% CI 0.31 to 2.48 per 100,000 person-years) when temperature was at 25°C compared to 5°C. When precipitation was 10 mm
compared to 1 mm, there was also a reduction in the rate of campylobacteriosis by 0.86 cases per 100,000 person-years (95% CI 0.58 to 1.25 cases per 100,000 person-years).

The mean ambient temperature and the level of the Oshawa Creek were both significant predictors of campylobacteriosis in the Durham region (Table 2.7). There was a reduction in the rate by 3.02 cases per 100,000 person-years (95% CI 0.88 to 2.98 cases per 100,000 person-years) when the mean temperature was 25°C compared to 5°C. When comparing the incidence at water level 2.5 m versus 2 m, there was a reduction in the rate of campylobacter by 1.41 cases per 100,000 person-years (95% CI 0.58 to 3.43 cases per 100,000 person-years).

**Case-crossover Analysis:**

*Dataset 1: Human-Environment Associations*

In the Waterloo health region, both *C. jejuni* and *C. coli* species of *Campylobacter* were examined. Analysis of *C. jejuni* and *C. coli* data resulted in similar associations. There were greater *C. jejuni* case counts, therefore, results from the *C. jejuni* were reported. From the *C. jejuni* cases we found that ambient temperature had a positive association with human campylobacteriosis. When this variable was categorized into tertiles, the “high” tertile for maximum ambient temperature was associated with a 1.16 (95% CI 1.00 to 1.34, p=0.043) increase in the odds of campylobacteriosis after a 7-day lag compared to the lower two tertiles (Figure 2.2). The amount of precipitation also had a significant positive association with campylobacteriosis. The “highest” tertile of precipitation was associated with a 1.16 (95% CI 1.00 to 1.35, p=0.049) increase in odds of infection after a 17-day lag when compared to the other two tertiles for *C. jejuni* cases at a 24-day lag (Figure 2.2). The “highest” tertile of water flow was negatively associated with campylobacteriosis, with an odds ratio of 0.85 (95% CI 0.72 to 1.00, p=0.05) when compared to the lower two tertiles after an 18-day lag (Figure 2.3). When
modelled as a dichotomous variable, when the level of the Grand River was low, this was
associated with a 1.16 (95% CI 1.00 to 1.34, p=0.050) increase in odds compared to when the
levels were high after 18 days (Figure 2.2).

Appendix 1 contains complementary figures for results of the conditional logistic
regression from the case-crossover analyses for the remaining health units.

In the Wellington-Dufferin-Guelph health region, ambient temperature was positively
associated with C. jejuni cases in humans in both the continuous and quantile analyses. As a
continuous variable, for every 1°C increase in ambient temperature, the odds of
campylobacteriosis increased by 1.06 (95% CI 1.00 to 1.12, p=0.048) after a 23-day lag. In this
case, the “medium” tertile of maximum temperature was positively associated with a 1.71 (95%
CI 1.03 to 2.85, p=0.039) and 1.99 (1.20 to 3.30, p=0.008) increase in odds after 13- and 17-day
lags respectively when compared to the other two tertiles (Appendix, Figure A2.3). Total daily
precipitation was also positively associated with campylobacteriosis when run as a continuous
variable (OR=1.03, 95% CI 1.00-1.07, p=0.034) after an 8-day lag (Appendix, Figure A2.3).
However, the “low” tertile of precipitation was associated with increasing the odds of
campylobacteriosis in humans after a 24-day lag when compared to the higher two tertiles
(OR=1.75, 95% CI 1.02 to 3.02, p=0.043, Appendix, Figure A2.3). When examined as tertiles,
the flow of the Grand River was positively associated with C. jejuni infection in the “low” and
“medium” tertiles after 8- and 12- days respectively. When the water was flowing at “low”
speeds, the odds of campylobacteriosis was 1.72 (95% CI 1.04 to 2.86, p=0.035) when compared
to the other two tertiles (Appendix, Figure A2.3). The “low” tertile of water level was associated
with 1.85 (95% 1.08 to 3.17, p=0.025) increased odds of campylobacteriosis after a 5-day lag
(Appendix, Figure A2.3).
In the York health region, ambient temperature was negatively associated with campylobacteriosis when analyzed as a continuous variable but the “medium” tertile increased the odds of *C. jejuni* infection by 1.25 (95% CI 1.03 to 1.53, *p*=0.044) after a 27-day lag when compared to the other two terciles (Appendix, Figure A2.4). Daily precipitation was associated with an increase in the odds of campylobacteriosis after 20-days in both continuous analysis (OR=1.02, 95% CI 1.00 to 1.03, *p*=0.25) and through the “high” precipitation tertile (OR=1.24, 95% CI 1.01 to 1.51, *p*=0.038, Appendix 1, Figure S4). The “medium” and “high” terciles of river flow were associated with increased odds of campylobacteriosis after 15- and 19-days respectively (Appendix, Figure A2.4). High flows (OR=1.25, 95% CI 1.02 to 1.52, *p*=0.028) increased the odds more than medium flows (OR=1.24, 95% CI 1.02 to 1.51, *p*=0.031, Appendix 1, Figure S4). When the Holland River was at high levels, this was an associated with an increase in the odds of campylobacteriosis 1.21 (95% CI 1.00 to 1.46, *p*=0.050) times after 17 days (Appendix, Figure A2.4).

In the Durham region, ambient temperature was associated with increased odds of campylobacteriosis. As a continuous variable, the association was significant at 12-, 13- and 17-day lag periods. When categorized as terciles, the “medium” and “high” terciles were both associated with increased odds of campylobacteriosis with the “high” tertile being associated with a 1.69 (95% CI 1.10 to 2.60, *p*=0.017, Appendix, Figure A2.5). increase in odds after a 17-day lag and the “medium” tertile being associated with a 1.53 (95% CI 1.00 to 2.35, *p*=0.049) increase in odds after a 16-day lag. Daily precipitation had a significant positive association in every tertile ranging from 5- to 28-day lags. The “medium” tertile was associated with a 2.16 (95% CI 1.05 to 4.46, *p*=0.037) increase in the odds of campylobacteriosis after a 28- day lag (Appendix 1, Figure S5). The flow of the Oshawa Creek was negatively associated with
campylobacteriosis. This was seen when examined as a continuous variable after an 18-day lag period where for every 1 m/s increase in flow, the odds of campylobacteriosis were half (OR=0.51, 95% CI 0.29 to 0.88, p=0.016). Also, the “low” tertile for water flow was positively associated with campylobacteriosis at 6-, 7-, 17-, 18-, and 27-day lags when compared to the higher two tertiles (Appendix, Figure A2.5). Low water levels of the Oshawa Creek were also positively associated with campylobacteriosis. This was significant when analyzed as a continuous variable as well when categorized. When water levels were low, the odds of campylobacteriosis were twice as high as when the water levels are high after a 17-day lag (OR=2.17, 95% CI 1.39 to 3.39, p=0.001, Appendix, Figure A2.5).

Dataset 2: Animal-Environmental Associations

The same analysis as above was conducted for positive C. jejuni and C. coli farms. Farms were run as an entire group based on Campylobacter species, as well as separated based on the type of livestock farm.

An increase in ambient temperature was significantly associated with increased odds of C. jejuni and C. coli positive farms. When the variable was examined as tertiles, the “high” temperature tertile was most consistently associated with the highest increase in odds. This was seen in C. jejuni positive sheep and poultry farms as well as C. coli cattle and swine farms. The highest risk was seen on C. jejuni sheep farms where there was increased odds of 3.18 (95% CI 1.00-10.12, p=0.050) 10 days prior to a farm being identified as positive, when compared to the lower two tertiles (Figure 2.3).

Daily precipitation was also a significant predictor of odds in both C. jejuni and C. coli farms. When the analysis was conducted using a continuous variable for daily precipitation, every 1 mm increase in rainfall was associated with a 1.02 (95% CI 1.00-1.07, p=0.05) increase
in the odds of observing a *C. jejuni* positive farm after a 20-day lag period and a 1.03 (95% CI 1.01-1.05, p=0.011) increase in odds on *C. coli* farms after a 12-day lag period (Figure 2.3). However, when the data were aggregated into quantiles the patterns were less clear across species of *Campylobacter* and farm-type with different levels being significant in different species.

Finally, the flow and the amount of water in the Grand River were both significant variables of risk for *C. jejuni* and *C. coli* positive farms when the analysis was run using quantiles. When *C. jejuni* and *C. coli* positive farms were combined, low water flow was associated with a 1.49 (95% CI 1.09 to 2.04, p=0.012) increase in risk after 27 days and a 1.41 (95% CI 1.05 to 1.93, p=0.025) and 1.53 (95% CI 1.13 to 2.08, p=0.006) increase in risk after 15- and 16-day lags respectively (Figure 2.3). Also, when *C. jejuni* positive farms were combined, high water level was associated with increased odds of 1.40 (95% CI 1.02 to 1.92, p=0.037) after 17 days. Similarly, *C. coli* positive cattle farms, high water level was associated with increased odds 1.86 (95% CI 1.09 to 3.16, p=0.023) after 19 days (Figure 2.3).

**Dataset 3: Human-Animal-Environment Associations**

The same analysis was performed in only the Waterloo health region to explore if farm positivity was a potential predictor of increased risk of human campylobacteriosis or if human cases predicted an increase in *Campylobacter* positive farms. The analyses were conducted with *C. jejuni* and *C. coli* positive farms combined as well as separated by livestock species.

An increase in *C. jejuni* positive cattle farms was associated with an increased risk of human *C. jejuni* infection after 10, 17, 23, and 24 day lags (Figure 2.4) and an increase in *C. coli* swine farms was associated with increased odds of human *C. coli* infection after 20, 23, and 26 day lags. For example, after 23 days, for every increase in positive *C. jejuni* cattle farms, the
odds of campylobacteriosis increased by a factor of 1.26 (95% CI 1.08-1.47, p=0.003) and for every increase in positive C. coli swine farms, the odds increased by 5.67 (95% CI 1.46-22.08, p=0.012) times.

Human incidence was also a significant positive predictor for increased farm positivity of both C. jejuni and C. coli species of Campylobacter. For every new human C. jejuni infection, the odds of a positive cattle farm increased by 1.31 (95% CI 1.0-1.70, p=0.042) after 23 days (Figure 2.5). Similarly, for every new human C. coli infection, the odds of a positive C. coli farm (cattle and swine combined) increased by 2.90 (95% CI 1.00-8.42, p=0.50) after a 22-day lag period.

**DISCUSSION**

Although *Campylobacter* is the most common bacterial derived enteric disease worldwide, there remain significant unknowns. With the changing climate, it is important to understand baseline characteristics of pathogens such as these in order to be prepared for how their incidence may change in the future.

**Seasonality:**

*Campylobacter*, like most other enteric pathogens, infects males more often than females, and is most apparent in young children and young adults [6,9]. Our results are consistent with previous studies in this regard [6,9]. Our results also demonstrate the expected seasonal and yearly patterns of human campylobacteriosis in other parts of the country and the world [6,9]. In a study by Olson et. al (2008), *Campylobacter* rates were compiled from multiple regions around the United States [6]. In all states studied, the same seasonal pattern was apparent with cases increasing through the spring, peaking in June and July, and decreasing throughout the autumn [6]. These results were replicated in Wales [9]. However, the previous studies as well as a study
by Stanley & Jones (2003) in the UK, found seasonality in poultry, cattle, and sheep which was not found in our study [6,9,20]. Higher rates of pathogen shedding and higher carriage rates on poultry carcasses have also been found in the summer months [6,9]. This may not have been found in this study due to the limited number of farm samples submitted to the AHL as well as the nature of the on-farm surveillance program carried out by the PHAC’s Food-Net program.

The seasonal fluctuations observed in campylobacteriosis may be due to seasonal changes in environmental conditions (e.g. temperature). Using a case-crossover analysis, we found that maximum ambient temperature was positively associated with an increase in the odds of campylobacteriosis in all health regions when incorporated into the models as a continuous variable. Olsen et. al also found that human cases were positively associated with average temperature and sunlight 4 weeks prior to case onset [6]. There are many possible explanations for this seasonal fluctuation that exceed temperature alone. Many humans undergo behavioural changes in the warmer months that may put them at increased risk for exposure to Campylobacter. These include barbecuing and spending recreational time swimming in surface waters [6]. However, an alternative theory that we did not explicitly look at for the observed seasonal fluctuations is that flies may act as mechanical vectors, transporting Campylobacter spp. between reservoirs [4,6,12]. Fly populations fluctuate seasonally which is concurrent with observed incidence of campylobacteriosis which suggests a potential association [22].

Our results in the Waterloo, Wellington-Dufferin-Guelph, and York regions demonstrate a significant negative association with year, which was in line with a study by Olson et. al [6]. They found that the crude rates of campylobacteriosis decreased from 1996 to 2005 after adjusting for the increase in surveillance [6].

**Regression and case-crossover analyses:**
An important issue that arises is that the results of the regression analysis do not necessarily agree with the results obtained through case-crossover analysis. This may be for several different reasons. One plausible reason may be the aggregation of the data. The regression analyses had environmental variables aggregated into weekly averages which were then lagged and modelled against weekly aggregated human case counts. The case-crossover design allows for analyzing daily case counts with daily environmental exposures. This allows us to see more acute associations that may be missed or skewed when the data are aggregated [23]. Another explanation could be a bias called “ecological fallacy.” This refers to making inferences on the individual level based off aggregated group data [24]. When the case data were summed into weeks, we are no longer making inferences on a daily level but on a group of cases occurring over a one-week span.

Maximum ambient temperature was a significant variable in the regression analysis as well as the case-crossover for all health regions. This would suggest that *Campylobacter* bacteria are affected by the ambient temperature and this relationship parallels in human campylobacteriosis cases. The case-crossover design suggested that the rate of campylobacteriosis was at its highest when temperatures were at the medium and high temperature level. This finding is consistent with the biology of the pathogen. At low temperatures (0-4°C), *Campylobacter* survives longer in the environment, however it is in a dormant, non-pathogenic state [3]. In some regions, the medium temperature was associated with the highest increase in odds. This may be because *Campylobacter* can be sensitive to high temperatures and tend to die off more rapidly in the environment. There was a consistent lag period of approximately four weeks in both the regression and case-crossover analysis. This lag is consistent with findings by Olson *et al* (2008) the United States [6] as well as an international
study that found that increased temperature at a 4-week lag was a strong predictor of human cases in Denmark [11].

In the regression and case-crossover analysis, daily precipitation was also a significant variable in all health regions. The regression analyses suggested a decrease in risk after four weeks, whereas the case-crossover analysis suggesting an increase in risk after a 1- and 2-week lag. However, when examined as tertiles the medium and high levels were associated with the most risk in all health regions except Wellington-Dufferin-Guelph where low precipitation was significant. This could suggest that rain may be needed to move the *Campylobacter* to the watershed in which they can be spread. Heavy rain events may lead to flooding of local water reservoirs which can cause surrounding areas to come into contact with contaminated water.

Our results also suggest that the hydrology of the local water reservoirs is an important contributing factor to *Campylobacter* spread and campylobacteriosis in humans in Ontario. We found that increasing water flow was associated with an increase in risk in most health regions after a 2-week lag period in the case cross over analysis but a decrease in risk after a 4-week lag period in the regression analysis. When examined as tertiles, low flow was associated with increased odds of case occurrence in Waterloo, Wellington-Dufferin-Guelph, and Durham. In a similarly designed study of hydrology and campylobacteriosis in Philadelphia, results suggested higher water flow was associated with increased odds of campylobacteriosis in both continuous and quantile analysis [12]. Biologically, both could be plausible. High water flow may also be in accordance with high water level where the pathogen may be diluted. However, high water flow may also suggest flooding and run-off which could move the pathogen to new areas.

From both analyses, low water levels were associated with high risk of campylobacteriosis after 2-4 week lags in Waterloo, Wellington, and Durham. This contradicts
the findings of a study that examined hydrology of the Delaware river in Philadelphia, United States in which risk increased as water levels increased after a 1- to 2-week lag [12]. This could be due to factors such as the reservoir structure and the way in which the reservoirs are used. Low water levels could be indicative of higher concentrations of *Campylobacter* in the water.

Waterloo and Wellington-Dufferin-Guelph share the Grand River, which is a highly regulated water system and is surrounded by a high proportion of agriculture [14]. In Durham, the Oshawa creek is a very small watershed which is also primarily used for agricultural purposes [16]. The York health region however uses an unregulated watershed which is heavily surrounded by urban centers with high population density [15]. This is more similar to the Delaware river in Philadelphia which may suggest why the hydrological results of the York health region are more similar to those found in Philadelphia [12,15].

The results for *C. jejuni* and *C. coli* positive farms follow similar patterns to the human results. Since the animal data were not sufficient to build regression models, all results discussed are from the case-crossover models.

Ambient temperature was associated with an increase in risk in both *C. jejuni* and *C. coli* farms with the lag periods varying from 8-days on *C. jejuni* farms to 20-days in *C. coli* farms. Both lag periods are shorter than that found in humans (4-week lag). However, unlike in human cases, only the highest tertile for temperature were of most risk compared to low and medium temperatures. Little research has been done on how environmental factors affect *Campylobacter* risk in food animals. However, one study found that increased temperatures were associated with increased risk of *Campylobacter* in broiler chickens at slaughter at a 3-week lag [6].

Similar to human cases, increased daily precipitation was also associated with an increased risk of *Campylobacter* positive farms after a 2-week lag period. This suggests that if
there is a rain event, there may be an increase in *Campylobacter* positive farms two weeks later. Precipitation events may cause contaminated manure to wash over grazing grounds, allowing these animals to then become exposed.

Hydrological associations were seen when animals were separated by species of *Campylobacter* and species of animal. The flow rate of the Grand River was significantly associated with *Campylobacter* risk on all farms. It was found that low river flow rates were associated with an increased risk after a 2- to 3-week lag period. This is consistent with the theory mentioned earlier, that too high of water flow will cause the pathogen to be diluted. However, high water levels were positively associated with an increase in risk in *C. jejuni* farms run together and *C. coli* cattle farms. This could be because like high water flow, high water levels may suggest flooding in which contaminated water may spill over into areas of the farm in which they can then contact susceptible animals.

From the regression analysis, the results suggest that an increase in farms positive for *Campylobacter* was protective for humans. However, when case-crossover analysis was performed, the opposite was found. Again, this could be due to the issue of data aggregation.

When human cases were incorporated as a potential risk factor for positive farm occurrence, we found a positive association. An increase in human cases of both *C. jejuni* and *C. coli* was predictive of an increase in positive farms after 23- and 24-days. This could suggest that this is a cyclical pattern. Livestock reservoirs may shed the pathogen in their feces which then makes its way to the local water reservoirs. There, humans may come into contact with it and become infected. This would then cause infected humans to begin shedding the pathogen which then again travels to the local reservoirs where animals may come into contact with the pathogen again.
**Limitations**

As with many enteric pathogens, underreporting is a significant issue. This may then have biased the associations found. Also, due to the nature of the pathogen and how the surveillance was conducted, there were very few *C. jejuni* poultry and sheep farms as well as *C. coli* cattle farms. This may have caused important associations to be missed due to lack of power. For this reason, we also aggregated data for positive farms. However, this strategy may have biased associations as not all farms and all animals contact each other and the pathogen in the same way. Also, the pathogen does not affect all animals the same, for example many livestock do not exhibit symptoms and therefore are not isolated or treated when infected, and therefore the pathogen can move through the group. Also, some livestock are on pasture where they are exposed to more sources of *Campylobacter* such as wild life and water run-off and this may put these animals at higher risk than those kept inside.

By the nature of the case-crossover analysis, we were testing 28 different hypotheses (each lagged day) for each exposure variable each at 95% confidence. Therefore, it is likely that some of the significant associations found may have been due to chance alone. This limits the ability to be confident in interpreting significant results as being true associations.

There was no access to molecular data or geographical information. This would have enhanced the ability of our research to link cases by specific bacteria and by location. This could have helped strengthen our ability to detect the flow of the pathogen between humans and animals and further explain the zoonotic transmission potential.

**CONCLUSION**

In conclusion, *Campylobacter* are associated with environmental factors and these factors can influence how the bacteria interact with humans and animals alike. We found biologically
plausible timing for the environmental factors studied which complement the current knowledge of seasonality for this pathogen. It is still unclear the role that animals and humans play in regards to one another but they appear to be connected through their shared environments and these results suggest zoonotic transmission. With further research, we will be able to better understand Campylobacter transmission and dynamics in both humans and animals in Ontario, Canada and use these as baselines for the future.

REFERENCES


water and aquatic biofilm and their detection by immunofluorescent-antibody and rRNA staining. *Applied and Environmental Microbiology*, 49(1), 733–745.


TABLES

Table 2.1: Statistics for the four health regions under consideration. Data includes population and agricultural density from the 2011 Statistics Canada census and information about the regions’ main watershed.

<table>
<thead>
<tr>
<th>Health Region</th>
<th>Population†</th>
<th>Agricultural Density (farms/km²) †</th>
<th>Size of primary watershed (km²)</th>
<th>Top two land uses surrounding watershed</th>
<th>Regulated or natural</th>
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<tbody>
<tr>
<td>Waterloo (1)</td>
<td>507,095</td>
<td>1.015</td>
<td>6,800 †</td>
<td>agriculture pastures (44%) † agriculture crops (34%)</td>
<td>Regulated †</td>
</tr>
<tr>
<td>Wellington-Dufferin-Guelph (2)</td>
<td>261,965</td>
<td>0.606</td>
<td>6,800 †</td>
<td>agriculture pastures (44%) † agriculture crops (34%)</td>
<td>Regulated †</td>
</tr>
<tr>
<td>York (3)</td>
<td>1,032,525</td>
<td>0.470</td>
<td>600 §</td>
<td>agriculture (53%) § urban (23%) §</td>
<td>Natural §</td>
</tr>
<tr>
<td>Durham (4)</td>
<td>608,124</td>
<td>0.576</td>
<td>123 ¶</td>
<td>agriculture crops (51%) ¶ agricultural pastures (18%) ¶</td>
<td>Natural ¶</td>
</tr>
</tbody>
</table>

† (Statistics Canada, 2017) ‡ (Grand River Conservation Authority, 2014) § (The Lake Simcoe Region Conservation Authority, 2000) ¶ (Central Lake Ontario Conservation, 2002)

Table 2.2: Total *Campylobacter* cases by sex. The data spans January 1st 2005 to December 31st 2014 and is separated by health region.

<table>
<thead>
<tr>
<th>Health Region</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
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<tbody>
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<td></td>
<td>Cases</td>
<td>%</td>
<td>Cases</td>
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<tr>
<td>Waterloo (1)</td>
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</tbody>
</table>
Table 2.3: Total number of *Campylobacter* positive farms by species. The data spans May 26th 2006 to December 10th 2012 and is separated by species of bacteria and species of animal from the Animal Health Lab and Public Health Agency’s Food-Net program.

<table>
<thead>
<tr>
<th>Species</th>
<th>Number of Positive Farms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jejuni</strong></td>
<td></td>
</tr>
<tr>
<td>Cattle</td>
<td>225</td>
</tr>
<tr>
<td>Sheep</td>
<td>5</td>
</tr>
<tr>
<td>Poultry</td>
<td>14</td>
</tr>
<tr>
<td>Goat</td>
<td>1</td>
</tr>
<tr>
<td><strong>Coli</strong></td>
<td></td>
</tr>
<tr>
<td>Cattle</td>
<td>60</td>
</tr>
<tr>
<td>Swine</td>
<td>146</td>
</tr>
</tbody>
</table>

Table 2.4: Results of multivariable Negative Binomial regression analysis in the Waterloo health region.

<table>
<thead>
<tr>
<th>Incident Rate Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonal sine week</td>
<td>0.48</td>
<td>0.35, 0.65</td>
</tr>
<tr>
<td>Seasonal cosine week</td>
<td>0.40</td>
<td>0.31, 0.52</td>
</tr>
<tr>
<td>Year</td>
<td>0.95</td>
<td>0.91, 0.99</td>
</tr>
<tr>
<td>Water level, 4 week lag</td>
<td>0.43</td>
<td>0.21, 0.89</td>
</tr>
<tr>
<td>Maximum Temperature, 4 week lag</td>
<td>0.95</td>
<td>0.93, 0.98</td>
</tr>
<tr>
<td>Intercept</td>
<td>4.97E+42</td>
<td>5.40e+6, 4.58e+78</td>
</tr>
</tbody>
</table>

Table 2.5: Results of multivariable Negative Binomial regression analysis in the Waterloo health region.

<table>
<thead>
<tr>
<th>Incident Rate Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonal sine week</td>
<td>0.47</td>
<td>0.35, 0.64</td>
</tr>
<tr>
<td>Seasonal cosine week</td>
<td>0.40</td>
<td>0.31, 0.52</td>
</tr>
<tr>
<td>Year</td>
<td>0.95</td>
<td>0.91, 0.99</td>
</tr>
<tr>
<td>Water flow, 4 week lag</td>
<td>1.00</td>
<td>0.99, 1.00</td>
</tr>
<tr>
<td>Maximum Temperature, 4 week lag</td>
<td>0.97</td>
<td>0.93, 0.98</td>
</tr>
<tr>
<td>Intercept</td>
<td>1.33E+42</td>
<td>1.13e+6, 1.58e+78</td>
</tr>
</tbody>
</table>
Table 2.6: Results of multivariable Negative Binomial regression analysis in the York health region.

<table>
<thead>
<tr>
<th>Incident Rate Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonal sine week</td>
<td>0.59</td>
<td>0.51, 0.68</td>
</tr>
<tr>
<td>Seasonal cosine week</td>
<td>0.54</td>
<td>0.44, 0.65</td>
</tr>
<tr>
<td>Year</td>
<td>0.93</td>
<td>0.92, 0.96</td>
</tr>
<tr>
<td>Total Precipitation, 4 week lag</td>
<td>0.98</td>
<td>0.97, 1.00</td>
</tr>
<tr>
<td>Maximum Temperature, 2 week lag</td>
<td>0.99</td>
<td>0.96, 1.00</td>
</tr>
<tr>
<td>Intercept</td>
<td>8.13E+49</td>
<td>5.66E+34, 1.17E+65</td>
</tr>
</tbody>
</table>

Table 2.7: Results of multivariable Negative Binomial regression analysis in the Durham health region.

<table>
<thead>
<tr>
<th>Incident Rate Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonal sine week</td>
<td>0.52</td>
<td>0.40, 0.68</td>
</tr>
<tr>
<td>Seasonal cosine week</td>
<td>0.52</td>
<td>0.42, 0.64</td>
</tr>
<tr>
<td>Water Level, 1 week lag</td>
<td>0.45</td>
<td>0.26, 0.80</td>
</tr>
<tr>
<td>Mean Temperature, 4 week lag</td>
<td>0.97</td>
<td>0.95, 1.00</td>
</tr>
<tr>
<td>Intercept</td>
<td>3.00E-5</td>
<td>7.75E-06, 0.0001</td>
</tr>
</tbody>
</table>
Figure 2.1: Map of southern Ontario showing the study health regions including Waterloo, Wellington-Dufferin-Guelph, York, and Durham.
Figure 2.2: Conditional logistic regression results for human *C. jejuni* cases in the Waterloo health region. Panels show the “high” temperature tertile (A), the “high” precipitation tertile (B), the “high” water flow tertile (C), and the “low” water level quantile (D) from the case-crossover analysis over the 28-day lag period. The odds ratio (solid line) and 95% confidence interval (dashed line) are shown for the full 28-day period with the star indicating statistically significant associations.
Figure 2.3: Conditional logistic regression results for positive farms in the Waterloo health region. Panels show the “high” maximum temperature variable and *C. jejuni* positive sheep farms (A), total precipitation as a continuous variable on the occurrence of *C. coli* positive farms (B), the “low” water flow variable and *C. coli* positive farms (C), the “high” water level variable and *C. coli* positive cattle farms (D) from the case-crossover analysis over the 28-day lag. The odds ratio (solid line) and 95% confidence interval (dashed line) are shown for the full 28-day period with the star depicting significant associations.
Figure 2.4: Conditional logistic regression results of positive farms as a predictor variable and *C. jejuni* humans. The predictor variable was analyzed using a case-crossover study design over the 28-day lag period for *C. jejuni* humans in the Waterloo health region. The odds ratio (solid line) and 95% confidence interval (dashed line) are shown for the full 28-day period with the star depicting significant associations.
Figure 2.5: Conditional logistic regression results of human cases as a predictor variable and on *C. jejuni* positive cattle farms. The predictor variable was analyzed using a case-crossover study design over the 28-day lag period for *C. jejuni* positive cattle farms in the Waterloo health region. The odds ratio (solid line) and 95% confidence interval (dashed line) are shown for the full 28-day period with the star depicting significant associations.
CHAPTER 3

MODELLING THE TRANSMISSION DYNAMICS OF CAMPYLOBACTER IN ONTARIO, CANADA ASSUMING HOUSE FLIES, *MUSCA DOMESTICA*, ARE A MECHANICAL VECTOR OF DISEASE TRANSMISSION.

ABSTRACT

**Background:** Campylobacteriosis is the most common gastrointestinal illness in Canada, however its complex dynamics and multiple transmission routes have made it difficult to describe using a mathematical framework. Vector-borne disease transmission has been proposed as a potential transmission route of Campylobacter with houseflies acting as a mechanical vector. The objectives of this study were to 1) determine if a basic *SIR* compartment model that included flies as a mechanical vector and incorporated a seasonally forced environment compartment could be used to capture the observed disease dynamics in Ontario, Canada, and 2) use this model to determine potential changes to campylobacteriosis incidence using predicted changes to fly population size and fly activity under multiple climate change scenarios.

**Methods:** Using a framework that incorporated aspects of both compartmental models that include an environmental reservoir, and Ross MacDonald models for vector-borne diseases, we expanded a basic *SIR* compartmental model to include both a seasonally fluctuating environmental pathogen reservoir and seasonally fluctuating fly population dynamics. The model was fit to one year of data and validated against 8 and 12 years of data. The model was used to explore changes in human disease incidence using predicted increases in fly population size, activity level, and combination of population size and activity, under multiple climate change scenarios.
**Results:** The model adequately captured the observed incidence of campylobacteriosis in Ontario. Using predicted changes to fly populations under different climate scenarios in combination with a 25% increase to fly activity, our model predicted a 28.15% increase in incidence by 2050 using the medium-low emissions scenario and 30.20% increase using the high emissions scenario. Our model was more sensitive to changes in fly activity versus fly population.

**Discussion/Conclusion:** This model demonstrates that the dynamics of Campylobacter transmission can be captured by a model that assumes that the primary transmission of the pathogen occurs via fly vectors. This mechanism of disease transmission warrants further research because Canadian temperature profiles under a climate warming scenario will directly impact fly population dynamics. In the future, this model could be used to test interventions and prevention strategies, for example, reducing fly populations or fly contact with human food.

**BACKGROUND:**

Campylobacteriosis (the infection caused by the bacteria *Campylobacter*) affected 21 in 100,000 people in Ontario in 2017 and is the most common gastrointestinal illness in Canada [1]. Humans can contract these bacteria from a wide variety of sources including: contaminated food and water, contact with animals and animal feces, and contact with an infected individual or their fecal matter [2-4]. In a study in Ontario, of domestic cases of known exposure, 63% were food related, 27% from contact with animals, 6% from other individuals, and 3% from contaminated water [5]. Also, Ravel *et al.* (2016) researched campylobacteriosis source attribution through exposure assessment and comparative genomic fingerprinting (CGF) using isolates from clinical cases and potential sources in Canada [6]. They found that chicken meat was the most common source (65-69%) followed by contact with cattle or cattle faeces (14-19%), and lastly meat from
cattle was of minor importance [7]. This evidence suggests that contaminated food and contact with animals are of highest importance as the source of campylobacteriosis in Canada.

Human campylobacteriosis exhibits seasonal fluctuations in disease incidence with peaks in the summer months, June to August [7-11]. There are many hypotheses for the observed seasonality including: environmental/climactic changes, human behavioural changes, and more recently, flies as mechanical vectors and seasonal fluctuations in fly populations [8-10, 12]. There is evidence that campylobacteriosis is associated with certain environmental and climatic factors such as increased temperatures, increased humidity, and higher water flows [13-15].

Since *Campylobacter* use the environment to move between human and animal hosts, it is important to know how these bacteria are affected by environmental changes.

It has also been noticed that the seasonal fluctuations in campylobacteriosis coincide with times of highest fly population density and activity level [12]. It has been demonstrated that flies carry bacteria including *Campylobacter*, and these bacteria can be transferred to food and surfaces from which humans can then become infected [16]. Flies can also encounter these bacteria, carry them on their bodies, and transfer them amongst agricultural settings, such as between pens or barns, thus infecting food animals which can then be contacted or consumed by humans [12].

This theory requires attention as fly population size and activity are subject to increase along with the number of flies surviving the winter season under predictions of climate change [17, 18]. Climate change is predicted to cause an increase in temperature, humidity, and precipitation in Canada and places of similar latitude [19]. It is also expected that the winter season will be shorter and warmer with more precipitation falling as rain instead of snow [20]. In a study in the United Kingdom, temperature, humidity, and precipitation were all highly
correlated with fly population size [17]. Using a model, these authors projected the annual size of house fly populations under medium-low and high carbon emission scenarios [17]. Their results suggest up to a 244% increase in fly population size by 2080 under a high emissions scenario over the population in 2003 [17]. Fly activity is also predicted to increase as temperatures rise [18]. Shou et al., found that both sexes of house flies’ daytime activity increased with temperature until a threshold of 30-35°C respectively [18]. Therefore, as the ambient temperature rises, flies may become more active throughout the day. Since house flies are very sensitive to changes in the environment, it is important to know how flies may react to climate change and in turn change the dynamics of campylobacteriosis.

A mathematical modelling framework, can be used to simulate the spread of a pathogen through a population of individuals in order to quantify disease outcomes including the burden of disease, the number of secondary cases arising from a single case (R0), and/or the population attack rate [19]. Models can also be used to examine hypotheses related to data gaps, or disease prevention and intervention strategies [19].

Simple compartmental models have been expanded to capture the dynamics of waterborne diseases such as cholera [20-22]. In most cases this was done by adding a water compartment into which infected individuals shed the pathogen. Susceptible humans can then become infected by contact with this infected water reservoir or by contact with an infected individual. This allows the model to capture traditional person-person transmission (aka the “fast loop” [21]) as well as person-water-person transmission (or the “slow-loop” [21]). These types of models allow researchers to gain a more complete picture of the disease dynamics as well as test the impact of intervening on the different transmission routes.
Compartmental models have also been expanded to model vector-borne infectious
diseases, known as Ross-MacDonald models [23-25]. Ross and MacDonald developed a model
for mosquito-borne pathogen transmission that included latency due to the pathogen’s life cycle
[25, 26]. In the Ross-MacDonald model structure, a susceptible vector obtains the pathogen from
a host during blood feeding. Once the pathogen has multiplied to a sufficient level in the vector,
it can then be passed to a new susceptible host during a subsequent feeding [23, 24]. These
models have been adopted as the standard framework for many vector-borne diseases [25].

Due to Campylobacter’s zoonotic disease dynamics and multiple transmission routes, it is
a complex host-pathogen system to model. Skelly & Weinstein (2017) modelled human
campylobacteriosis that explicitly looked at infection from aquatic environments contaminated
by human and animal feces (treated and untreated water), and through food consumption,
preparation, and processing [26]. However, there are no models that attempt to capture the
observed seasonality either through the environment, through fly dynamics, or through these two
sources in combination. The objectives of this study were to: 1) determine if a basic SIR
compartment model that incorporates flies as a mechanical vector, and also incorporates a
seasonally forced environmental reservoir compartment could be used to capture the observed
disease dynamics in Ontario, Canada and, 2) use this model to explore possible changes to
campylobacteriosis incidence using projected changes to fly population dynamics and fly activity
level under different climate change scenarios.

METHODS:

Case Data:
We used two sets of data to parameterize and validate our model. Firstly, we had access to confirmed campylobacteriosis cases from Public Health Ontario (PHO) from January 1st 2005 to December 31st 2013. A positive individual had gastrointestinal illness symptoms and either the pathogen isolated from stool or body fluids, or had an epidemiological link to one or more laboratory confirmed cases. The positive cases were reported to the integrated Public Health Information System (iPHIS). Cases that had travelled outside of Ontario within the incubation period of *Campylobacter* were excluded as it was assumed that these do not represent locally acquired cases. Over the nine-year period, there were a total of 27,956 confirmed cases in Ontario. The campylobacteriosis cases showed seasonality with most cases occurring in the spring and summer months (June to September). The second form of data was publicly available “Monthly Infectious Disease Surveillance Reports” provided by PHO which is a summation of cases from iPHIS on a provincial level.

**Model Structure:**

A deterministic SEIR model was developed that included the addition of an environmental reservoir (*B*). This reservoir is a placeholder to include many of the potential transmission routes: contaminated water, contaminated food, contact with animals, and other environments contaminated by human and animal feces. The environmental reservoir is seasonally forced to account for the changing levels of bacteria in the reservoir depending on the season. *Campylobacter* are sensitive to changes in the environment which results in variability in the bacterial load in the environmental reservoir dependant on the season [7]. This dynamic occurs via direct changes to the biology of the bacteria in the environment as well as changes in the other aspects of the environmental reservoir. For example, high temperature and water levels are associated with increased odds of *Campylobacter*-positivity on farms [27]. This could lead to
increased shedding of the pathogen and therefore an increased environmental load [7]. High temperatures are also associated with increased carcass levels of *Campylobacter* on poultry which could lead to increased risk of food contamination [9, 28]. In order to mathematically allow for the seasonal oscillation of the environmental compartment (*B*), an “environmental parameter” was added to the model (*ζ*). This parameter is a scaling/augmenting factor (refer to equation 5).

This *SBEIR* model was then further expanded to include house flies, *Musca domestica*, as mechanical vectors (e.g. insects that carry the pathogen on the outside of the body and transmit through physical contact [29]). In this model (Figure 1), a susceptible human (*S*h) can become infected in three different ways: contact with an infectious human (*β*ᵢ), contact with the environmental reservoir (*β*b*), or consuming food that has been contaminated by a “contaminated” fly (*β*f*).

Susceptible flies enter the population at a seasonally fluctuating birth rate (*μ*b*) and leave the population at a seasonal rate dependant on the number of flies in each compartment (*μ*d*). The birth rate is seasonal because egg laying rates and larval development times fluctuate with temperature [30,12]. Female flies have more eggs in their lifetime at warmer temperatures (117.8 +/- 36.5 at 20°C versus 494.9 +/- 73.2 at 30°C) [32]. Also, warmer temperatures along with an increase in rainy days leads to larvae being able to develop into adult flies within days compared to months [12]. These two factors in combination, allow the fly population to increase exponentially as temperatures rise into the summer months. The fly birth rate includes both fly births from domestic flies that survived the winter as well as the influx of flies from warmer climates that occurs as temperatures rise [31]. Therefore, the birth rate is independent of the number of flies in the population. The death rate is seasonal because temperature also affects
adult fly survival [32]. Flies thrive at mean temperatures of 20–25°C. Survival decreases above and below this range [32].

In temperate climates, such as Ontario, most flies do not survive the cold winter temperatures [32]. In order to capture this, the model removes all flies above the initial fly population ($w = S_f 0$) at the end of each warm season. Therefore, the model restarts every year with the same number of susceptible flies and zero “contaminated” flies. Susceptible flies become “contaminated” when they contact the environmental reservoir ($\beta_b$). The flies pick up bacteria on their bristles. When they land on human food, they leave the bacteria behind. These bacteria can then infect a susceptible human when the food is consumed ($\beta_i$). It is assumed that the contaminated flies remain contaminated until they die. This dynamic disease transmission process is represented by the following equations:

1. $\frac{dS_h}{dt} = \mu_b (S_h + E_h + I_h + R_h) + \mu (S_h + E_h + I_h + R_h) - \beta_b S_h I_f - \beta_i S_h B - \beta_b S_h - \beta_i S_h - \mu_d S_h$

2. $\frac{dE_h}{dt} = \beta_i S_h I_h + \beta_b S_h B + \beta_i S_h + \beta_e S_h B - \gamma E_h - \mu_d E_h$

3. $\frac{dI_h}{dt} = \gamma E_h - \lambda I_h - \mu_d I_h$

4. $\frac{dR_h}{dt} = \lambda I_h - \mu_d R_h$

5. $\frac{dB}{dt} = \zeta \left( \sin \left( \frac{2\pi t}{365} \right) \right) B$

6. $\frac{dS_f}{dt} = \mu_b \left( -200 \sin \left( \frac{2\pi t}{365} \right) \right) - \beta_e S_h B - \mu_d \left( -200 \sin \left( \frac{2\pi t}{365} \right) \right) S_f$

7. $\frac{dI_f}{dt} = \beta_e S_h B - \mu_d \left( -200 \sin \left( \frac{2\pi t}{365} \right) \right) I_f$

Model Assumptions:

The model assumed homogenous mixing between the entire human population of Ontario, Canada. The model assumed that humans acquire life-long immunity to Campylobacter after they have recovered from an infection. Waning immunity was added to the model and had
minimal effect on the model outcomes and therefore was removed for simplicity. Due to the low case fatality rate [38], the model also assumed that there was no difference in death rates for those who had been infected and those who were uninfected.

Many of the assumptions revolve around flies and their contact. There is little empirical data on fly contact rates with both humans and the environment. Therefore, these parameters were estimated through model fitting.

**Model Fitting and Validation:**

Due to the number of unknown parameters, the model was fit to existing data in order to estimate these parameters. This was done by fitting the model’s unknown parameters to the first year of the PHO dataset (January 1st to December 31st, 2005) using the optimizing function in R [39]. This is an optimization technique based on Nelder–Mead, quasi-Newton and conjugate-gradient algorithms for general-purpose [39]. Initial parameter estimates were defined along with upper- and lower-bounds. Model fit was determined graphically by visually comparing the model output to the observed daily incidence data.

The model was validated using two techniques. First, the model was run for the remaining duration of the dataset (2006-2013). The predicted daily incidence was compared to the observed PHO incidence from January 1st 2006 until December 31st, 2013. This appeared to be a good fit graphically and therefore a second validation step was done to ensure the model outputs were accurate. Using the model predicted cumulative incidence from January 1st, 2005 to December 31st, 2017, the cumulative incidence was compared to incidence reported in the “Monthly Infectious Disease Surveillance Report” by PHO, with 15% of the cases removed to account for the proportion of cases that were assumed to have acquired the bacteria through international travel [1, 38].
Sensitivity Analysis:

A Latin Hypercube sensitivity analysis was performed on all parameters in the model with results depicted as partial rank correlation coefficients. A univariate sensitivity analysis was performed on the initial conditions that had uncertainty or that were estimated through model fitting.

Climate Change Conditions:

As the global temperature rises, the population dynamics of flies, as with many other vectors, are sure to change [17, 18]. In order to capture expected changes in fly population size, we used population predictions from Goulson et al. under moderate and high carbon emission scenarios [17]. Under a medium-low emission scenario, the authors predicted a 45.7% increase by 2020, an 84.3% increase by 2050, and a 156% increase by 2080 of annual fly population size compared to baseline population size estimates from 2003 [17]. Under a high emission scenario, the authors predicted a 45.7%, 128%, and 244% increase in annual fly population size [17]. This dynamic was captured in the model by changing the birth and death rate of the flies as well as increasing the number of flies that survive over the winter (table 3). The amount of fly activity also increases as temperatures increase and therefore are likely to increase under the warming temperatures associated with climate change [18]. This is of concern because as flies become more active, they may have more contact with the contaminated reservoir where they can pick up pathogens on their bodies. Therefore, this increased activity could also lead to more flies landing on our foods. Increase in fly activity was modelled by increasing the amount the flies contact the environment ($\beta_e$) and the amount the flies contact human food ($\beta_f$). We modelled this as a 25% to 100% increase in fly activity (table 3). These scenarios were also examined in combination (fly population X fly activity level) to determine the expected observed increase in human incidence.
of disease in these different scenarios. All scenarios were compared to the first year of the baseline scenario (January 1\textsuperscript{st} to December 31\textsuperscript{st}, 2005). This year was chosen for comparison as the predictions by Goulson \textit{et al.} (2005) were compared to 2003 fly populations and the surveillance data shows relatively stable incidence over the given time period.

**RESULTS:**

**Model fit:**

The optimization function in R finds unknown parameter values by finding parameters to minimize the difference between the observed data and the model output. After parameterization (parameters found in table 4), the model graphically appeared to have a good fit to the observed campylobacter incidence in Ontario from January 1\textsuperscript{st} to December 31\textsuperscript{st} 2005 (figure 2) meaning that it found the minimal difference and best fit statistically. Since parameters were estimated using the first year of the data and appeared to have a good fit, the model was run for the next eight years (the full duration of the dataset) using the best fit parameter values to validate the model. The daily incidence of the confirmed campylobacteriosis cases from PHO were graphically compared to the model and appeared to have a good fit (figure 3). For further validation, the cumulative incidence from 2005 to 2017 was compared to incidence reported in the “Monthly Infectious Disease Surveillance Report” by PHO. This also appeared to have a good fit (figure 4).

**Sensitivity Analysis:**

From the Latin hypercube sensitivity analysis, the model was most sensitive to the latent period ($\lambda$), the environmental parameter ($\zeta$) and the fly death rate ($\mu_d$) as seen by the high partial rank correlation coefficients in figure 5. The model was moderately sensitive to the transmission
parameters including flies and the environmental reservoir ($\beta_f$, $\beta_e$, $\beta_b$), but not to the person-to-person transmission rate ($\beta_i$).

From the univariate analysis, it was found that the model was least sensitive to the initial number of susceptible flies ($S_f$), and the upper bound of initial susceptible humans ($S_h \theta$) (Supplementary Materials, Table 1A). The model was highly sensitive to the initial environmental load ($B_0$) and the lower bound of the initial susceptible humans ($S_h \theta$) (Supplementary Materials, Table 1A). Therefore, it is necessary to have enough susceptible humans and enough bacterial load in the environment in order to initiate the spread of campylobacteriosis, until a certain threshold of susceptible humans is reached in which case it can no longer spread to a greater extent. However, if there are more bacteria in the environment, this can lead to much greater outbreaks.

**Climate Change Scenarios:**

Using the predictions of Goulson et al. (2005), under medium-low emission scenarios, which corresponds to a 156% increase in fly population size, the model showed that there could be a 6.67% increase in campylobacteriosis incidence by 2080 [17]. Under high emission scenarios which corresponds to a 244% increase in fly population size, the model showed a 10.35% increase in incidence (Figure 6, Supplementary Materials Table 2A).

When there was a 25% increase in fly activity, the model exhibited a 23.43% increase in human campylobacter incidence. When fly activity was doubled, the model predicted a 93.73% increase in incidence over the baseline of 25.04 cases per 100,000 population (Figure 7, Supplementary Materials Table 2A).

More realistically, both phenomenon will occur under climate change scenarios. Therefore, we examined combinations in which all predicted population increases were run
under the 25-100% activity increase scenarios. In this case, under medium-low carbon emissions, the model projected a 31.74% increase in incidence by 2080 if fly activity increased by 25% but up to a 107.02% increase if fly activity doubled. Under worst case scenarios (high carbon emissions causing 244% population increase and 100% activity increase), the model projected a 114.43% increase in campylobacter incidence in Ontario compared to the 2005 baseline (Figure 8, Supplementary Materials Table 2A).

**DISCUSSION:**

Using a novel model structure, we have identified the environmental conditions that appear to describe the observed incidence of campylobacteriosis in Ontario. In addition, we have identified how the incidence of campylobacteriosis in the Ontario human population could change under different climate change scenarios that act to change fly populations and activity levels. This is an important step towards identifying evidence in support of this hypothesis which may lead to more research in this area.

**Model Results:**

According to our model results, increased fly activity is more influential in increasing the human incidence of campylobacteriosis compared to increased overall fly population size. For example, a 50% increase in fly activity resulted in a 46.9% increase in the incidence of campylobacteriosis, however a 45.6% increase in fly population size resulted in a 1.9% increase in campylobacter incidence. In the worst-case scenario, our fly population model predicted a 10.3% increase in disease incidence. This pattern has been noticed in other mathematical models of vector-borne diseases. For example, in a model of mosquito transmission in Africa that included seasonality, the authors found that insecticide treated nets (ITN) were more effective at controlling the spread of disease when compared to indoor residual spraying (IRS) [40]. In this
case, the nets are controlling the ability for mosquitoes to enter the homes and therefore are limiting contact with humans whereas the spraying is controlling the size of the mosquito population. This has major implications for public health and therefore gives us insight into potential areas for intervention and control. For example, common practice for fly control includes spraying to reduce fly population size. However, according to our model, small populations that are highly active still contribute significantly to transmission. Controlling fly activity or decreasing the transmission rate between flies and human food may be more beneficial in this case. Intervention studies have been performed in which fly screens were used to prevent the entrance of flies into poultry barns [41]. For example, there was a reduction in *C. jejuni* prevalence in poultry barns in Denmark from 41% to 10% in those that had fly screens [41]. These interventions appear to be successful at the flock level and may provide insight into future intervention strategies.

**Limitations**

Modelling *Campylobacter* transmission is difficult because of its complex dynamics. As a result, this model makes a number of assumptions and simplifications. For example, the homogenous mixing assumption assumes that every individual has the same probability of contact with the environment, each other, and the flies [42]. In reality, this may not be the case. For example, with many enteric disease, there are high rates of transmission within households but little transmission between other infected individuals [43]. Certain individuals may also have more contact with the environment or certain components of the environmental reservoir or may be more at risk for contact with flies, such as those living in rural areas or on farms. This model may under- or overestimate the incidence depending on the importance of the heterogeneity of
the population. Therefore, other model structures may be required to overcome this assumption such as models stratified by age, living conditions, or level of risk.

Our model predicted incidence aligns well with the years of observed data but does diverge after 2013 and predicts higher incidence for the subsequent four years. This may be an indication that our model may overestimate the burden of campylobacteriosis when run further into the future.

This model was created to explore if flies as a mechanical vector for disease transmission to humans was a viable hypothesis. There were no data on fly population dynamics and contact rates with both humans and the environment in Ontario and therefore these parameters were estimated through model fitting. The model was also sensitive to the transmission rates involving flies ($\beta_f$ and $\beta_e$). These parameters are influential because they determine the rate at which susceptible humans are becoming infected and therefore are big drivers of the disease dynamics. These parameters were also found through parameterization. Therefore, this model would benefit from further research into collecting empirical data to obtain more informative upper and lower bounds on these parameters to create more accurate and informative models.

Our results showed that increasing the amount of fly activity leads to a greater increase in incidence and therefore, controlling fly contact may be a superior method of prevention that controlling fly population size. However, this may be a combination of the way in which we modelled increases to fly activity and the uncertainty around the amount fly activity will increase in the future. Increasing fly activity in our model involved increasing both the transmission parameter with humans ($\beta_f$) and the environment ($\beta_e$) by the intended percentage increase (ie. a 25% increase in activity resulted in a 25% increase in $\beta_f$ and a 25% increase in $\beta_e$). This could
have however been modelled as a synergistic effect by increasing each transmission parameter by 12.5% to create a total increase of 25%. Further research in this area is warranted.

An aspect of the biology that we did not address is that the retention of *Campylobacter* on flies may decline as temperatures increase [44]. This could be an important factor in how far flies can carry *Campylobacter* depending on the temperature. This could be tested in the future using our model in conjunction with projected fly population and activity changes under the different climate change scenarios.

Our model used predictions from Goulson *et al.* on climate change’s effect on fly population size based on the assumption from the UK Climate Impacts Programme that the global temperature will increase by 2.34°C by 2080 in an optimistic medium-low carbon emission scenario and by 3.88°C in a high emission scenario [17, 45]. Should the magnitude of climate change vary in North America, it would be expected that fly populations and activity would also vary accordingly.

**CONCLUSION:**

A mechanistic infectious disease model for the transmission of *Campylobacter* in the Ontario human population in which flies act as a mechanical vector between contaminated environments and human food consumption was created. The model was able to capture the observed daily and cumulative incidence data thus supporting the fly transmission hypothesis. Creating a model for *Campylobacter* which includes a seasonally fluctuating environmental compartment and fly populations will allow future researchers to test many different aspects of the transmission chain. This could include expanding the model to explicitly model specific transmission routes as well as test different prevention and control strategies.
REFERENCES


### TABLES

Table 3.1: Model parameters with values from literature (ranges used for sensitivity analysis) and assumptions.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value (range)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu_{bh} )</td>
<td>Human birth rate</td>
<td>0.000026 days(^{-1})</td>
<td>Statistics Canada, 2016</td>
</tr>
<tr>
<td>( \mu_{dh} )</td>
<td>Human death rate</td>
<td>0.000019 days(^{-1})</td>
<td>Statistics Canada, 2016</td>
</tr>
<tr>
<td>( \mu_i )</td>
<td>Human immigration rate</td>
<td>0.000016 days(^{-1})</td>
<td>Statistics Canada, 2016</td>
</tr>
</tbody>
</table>

**Human Demographic Parameters**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value (range)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta_i )</td>
<td>Person-person transmission rate</td>
<td>fitted</td>
<td></td>
</tr>
<tr>
<td>( \beta_b )</td>
<td>Environment-person transmission rate</td>
<td>fitted</td>
<td></td>
</tr>
<tr>
<td>( \beta_f )</td>
<td>Mechanical vector transmission rate</td>
<td>fitted</td>
<td></td>
</tr>
<tr>
<td>( \beta_e )</td>
<td>Environment-fly transmission rate</td>
<td>fitted</td>
<td></td>
</tr>
</tbody>
</table>

**Transmission Parameters**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value (range)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \gamma )</td>
<td>Latent period</td>
<td>0.65 (0.33-1) days(^{-1})</td>
<td>Skirrow, 1995; Blaser, 2008</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>Duration of infection</td>
<td>0.0476 (0.014-0.142) days(^{-1})</td>
<td>Karmali, 1979; Svedhem, 1979; Taylor, 1988; Blaser, 2008</td>
</tr>
<tr>
<td>( \zeta )</td>
<td>Environmental parameter</td>
<td>fitted</td>
<td></td>
</tr>
</tbody>
</table>

**Disease Parameters**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu_{bh} )</td>
<td>Fly birth rate</td>
<td>fitted</td>
<td></td>
</tr>
<tr>
<td>( \mu_{dh} )</td>
<td>Fly death rate</td>
<td>fitted</td>
<td></td>
</tr>
</tbody>
</table>

**Fly Demographic Parameters**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( S_0 )</td>
<td>Initial human susceptible population</td>
<td>fitted</td>
<td></td>
</tr>
<tr>
<td>( B_0 )</td>
<td>Initial environmental load</td>
<td>fitted</td>
<td></td>
</tr>
<tr>
<td>( E_{h0} )</td>
<td>Initial human exposed population</td>
<td>0</td>
<td>Assumption</td>
</tr>
<tr>
<td>( I_{h0} )</td>
<td>Initial human infectious population</td>
<td>9</td>
<td>PHO data</td>
</tr>
<tr>
<td>( R_{h0} )</td>
<td>Initial human recovered population</td>
<td>fitted</td>
<td></td>
</tr>
<tr>
<td>( S_{f0} )</td>
<td>Initial fly susceptible population</td>
<td>fitted</td>
<td></td>
</tr>
<tr>
<td>( I_{f0} )</td>
<td>Initial fly infectious population</td>
<td>0</td>
<td>Assumption</td>
</tr>
<tr>
<td>( w )</td>
<td>Number of flies survive winter</td>
<td>fitted (same as ( S_{f0} ))</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.2: Model initial conditions with values from literature and assumptions.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( S_0 )</td>
<td>Initial human susceptible population</td>
<td>fitted</td>
<td></td>
</tr>
<tr>
<td>( B_0 )</td>
<td>Initial environmental load</td>
<td>fitted</td>
<td></td>
</tr>
<tr>
<td>( E_{h0} )</td>
<td>Initial human exposed population</td>
<td>0</td>
<td>Assumption</td>
</tr>
<tr>
<td>( I_{h0} )</td>
<td>Initial human infectious population</td>
<td>9</td>
<td>PHO data</td>
</tr>
<tr>
<td>( R_{h0} )</td>
<td>Initial human recovered population</td>
<td>fitted</td>
<td></td>
</tr>
<tr>
<td>( S_{f0} )</td>
<td>Initial fly susceptible population</td>
<td>fitted</td>
<td></td>
</tr>
<tr>
<td>( I_{f0} )</td>
<td>Initial fly infectious population</td>
<td>0</td>
<td>Assumption</td>
</tr>
<tr>
<td>( w )</td>
<td>Number of flies survive winter</td>
<td>fitted (same as ( S_{f0} ))</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.3: Parameters used to calculate changes in fly population size and fly activity levels under climate change scenarios.

<table>
<thead>
<tr>
<th></th>
<th>$\mu_b$</th>
<th>$\mu_d$</th>
<th>$S_f/\omega$</th>
<th>$\beta_e$</th>
<th>$\beta_f$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>2.15 x 10^{-3}</td>
<td>1.67 x 10^{-3}</td>
<td>4910</td>
<td>5.10 x 10^{-11}</td>
<td>1.03 x 10^{-11}</td>
</tr>
<tr>
<td><strong>Increase in fly population size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium-Low Emissions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45.7%</td>
<td>2.196 x 10^{-3}</td>
<td>1.696 x 10^{-3}</td>
<td>5250</td>
<td>5.10 x 10^{-11}</td>
<td>1.03 x 10^{-11}</td>
</tr>
<tr>
<td>84.3%</td>
<td>2.175 x 10^{-3}</td>
<td>1.715 x 10^{-3}</td>
<td>5500</td>
<td>5.10 x 10^{-11}</td>
<td>1.03 x 10^{-11}</td>
</tr>
<tr>
<td>156%</td>
<td>2.204 x 10^{-3}</td>
<td>1.734 x 10^{-3}</td>
<td>6000</td>
<td>5.10 x 10^{-11}</td>
<td>1.03 x 10^{-11}</td>
</tr>
<tr>
<td>High Emissions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45.7%</td>
<td>2.196 x 10^{-3}</td>
<td>1.696 x 10^{-3}</td>
<td>5250</td>
<td>5.10 x 10^{-11}</td>
<td>1.03 x 10^{-11}</td>
</tr>
<tr>
<td>128%</td>
<td>2.197 x 10^{-3}</td>
<td>1.727 x 10^{-3}</td>
<td>5750</td>
<td>5.10 x 10^{-11}</td>
<td>1.03 x 10^{-11}</td>
</tr>
<tr>
<td>244%</td>
<td>2.186 x 10^{-3}</td>
<td>1.756 x 10^{-3}</td>
<td>6250</td>
<td>5.10 x 10^{-11}</td>
<td>1.03 x 10^{-11}</td>
</tr>
<tr>
<td><strong>Increase in fly activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25%</td>
<td>2.15 x 10^{-3}</td>
<td>1.67 x 10^{-3}</td>
<td>4910</td>
<td>6.37 x 10^{-11}</td>
<td>1.29 x 10^{-11}</td>
</tr>
<tr>
<td>50%</td>
<td>2.15 x 10^{-3}</td>
<td>1.67 x 10^{-3}</td>
<td>4910</td>
<td>7.64 x 10^{-11}</td>
<td>1.54 x 10^{-11}</td>
</tr>
<tr>
<td>75%</td>
<td>2.15 x 10^{-3}</td>
<td>1.67 x 10^{-3}</td>
<td>4910</td>
<td>8.92 x 10^{-11}</td>
<td>1.80 x 10^{-11}</td>
</tr>
<tr>
<td>100%</td>
<td>2.15 x 10^{-3}</td>
<td>1.67 x 10^{-3}</td>
<td>4910</td>
<td>1.02 x 10^{-10}</td>
<td>2.06 x 10^{-11}</td>
</tr>
</tbody>
</table>

Table 3.4: Model parameters and initial conditions found through model fitting.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_i$</td>
<td>Person-person transmission rate</td>
<td>1.034177e-13</td>
</tr>
<tr>
<td>$\beta_b$</td>
<td>Environmental-person transmission rate</td>
<td>3.380743e-07</td>
</tr>
<tr>
<td>$\beta_f$</td>
<td>Fly-person transmission rate</td>
<td>1.028844e-11</td>
</tr>
<tr>
<td>$\mu_b$</td>
<td>Fly birth rate</td>
<td>2.154924e-03</td>
</tr>
<tr>
<td>$\mu_d$</td>
<td>Fly death rate</td>
<td>1.67e-03</td>
</tr>
<tr>
<td>$\beta_e$</td>
<td>Environment-fly transmission rate</td>
<td>5.095899e-11</td>
</tr>
<tr>
<td>$\zeta$</td>
<td>Environmental parameter</td>
<td>2.237077e-02</td>
</tr>
<tr>
<td>$S_h\theta$</td>
<td>Initial human susceptible population</td>
<td>8e+06</td>
</tr>
<tr>
<td>B0</td>
<td>Initial environmental load</td>
<td>2.5e-02</td>
</tr>
<tr>
<td>R_h\theta</td>
<td>Initial human recovered population</td>
<td>4.57e+06</td>
</tr>
<tr>
<td>S_f\theta</td>
<td>Initial fly susceptible population</td>
<td>4.91e+03</td>
</tr>
<tr>
<td>w</td>
<td>Number of flies survive winter</td>
<td>4.91e+03</td>
</tr>
</tbody>
</table>
Figure 3.1: Compartmental diagram showing *Campylobacter* transmission in humans (top, h subscript) driven by flies (bottom, f subscript). Susceptible humans ($S_h$) are exposed ($E_h$) before becoming infectious to others ($I_h$) and then recover ($R_h$). Susceptible house flies ($S_f$) become contaminated ($I_f$) when they contact the environment ($B$). Person-person, environment-person, and mechanical vector transmission due to flies are denoted by the dotted lines. Rates of change are represented by Greek letters above the arrows.
Figure 3.2: Model fit to Public Health Ontario (PHO) confirmed campylobacteriosis daily incidence from January 1st to December 31st 2005.
Figure 3.3: Model validation (black line) to daily incidence from PHO confirmed cases (grey line) from January 1st 2006 to December 31st 2013. The first year (before the dotted line) was used for model fitting.
Figure 3.4: Model validation (black line) to cumulative incidence from Public Health Ontario Monthly Infectious Disease Surveillance Reports from 2005 to 2017 with 15% of cases removed due to international travel. The first year (before the dotted line) was used for model fitting.
Figure 3.5: Results of Latin Hypercube sensitivity analysis on all parameters in the model as partial rank correlation coefficients with the most sensitive parameters being the fly death rate ($\mu_d$) and the environmental parameter ($\zeta$).
Figure 3.6: Predicted incidence of campylobacteriosis at varying levels of increase to fly population size.
Figure 3.7: Predicted daily incidence of campylobacteriosis at varying levels of increase to fly activity.
Figure 3.8: Predicted incidence of campylobacteriosis at a combination of varying levels of increase to fly population size (lines) and activity (panels).
CHAPTER 4

SUMMARY, LIMITATIONS, AND CONCLUSIONS

The objectives of this thesis were to 1) determine to what extent *Campylobacter* is affected by environmental conditions and 2) to identify how campylobacteriosis incidence and farm-level positivity in Ontario might change in the future under climate change scenarios. Determining the baseline associations between *Campylobacter* and the environment is a necessary first step in understanding environmental drivers of *Campylobacter* transmission. Combining these associations with additional hypotheses regarding *Campylobacter* transmission routes, I then proposed a model to test hypotheses related to flies as mechanical vectors and their interaction with a seasonally fluctuating environmental compartment and humans, and explore future predictions of campylobacteriosis incidence.

SUMMARY OF MAJOR FINDINGS

In chapter 2, I identified environmental factors that were associated with increased odds of human campylobacteriosis and farm-level *Campylobacter* positivity in Ontario. These included increased temperature, water flow, and water level. Although humans, animals, and the environment are all a part of *Campylobacter*’s complicated dynamics, it is still unclear exactly how these three aspects work together to drive *Campylobacter* transmission.

One hypothesis that provides insight into a potential key link in connecting the three major reservoirs of *Campylobacter* are flies as a mechanical vector. In order to investigate the hypothesis, I created a mechanistic disease transmission model to capture *Campylobacter* dynamics in Ontario. This model was able to capture the observed incidence time series and therefore could be used to explore potential changes in incidence under multiple climate change scenarios. Using projected changes to fly population sizes and activity levels under climate
change scenarios, my model predicted significant increases to campylobacteriosis levels in Ontario in the years to come.

**LIMITATIONS**

More research is required to be able to identify underlying relationships between humans, animals, and the environment in terms of *Campylobacter* transmission. My research would have benefitted from genotyping data to be able to identify the flow of the bacteria through the reservoirs. Genotyping allows for better insight into whether the exact strain of *Campylobacter* found on a nearby farm matches that found in a human case. For example, *Campylobacter* shed from humans could make its way to the local water reservoir where it could then come in contact with the animal reservoirs. This allows more support into causality for zoonotic transmission, either human to animal or animal to human. Also, higher resolution geographical data would aid in more clearly identifying the relationship between farm-level *Campylobacter* and human campylobacteriosis. In our study, farms and cases were observed at a county level. If these factors were known at more exact geographical scales, I could have considered more accurate positive-farm density and case level associations. For example, I could have looked at whether cases were more likely in rural areas with higher agricultural density versus urban areas. These possible associations get lost when combined at a county level.

Also, farm-level data were at a minimum. There was very little surveillance data, and the data that we had were collected irregularly throughout the time period, and the sampling strategy was not outlined clearly, and when samples were taken, they were sparse. Therefore, it was hard to identify relationships between environmental factors and farm-level *Campylobacter* positivity. For example, it was hard to identify if the number of positive farms was simply a result of the number of farms sampled that day or if it was a result of the relationship with environmental
factors. This study would have benefitted from more consistent surveillance of on-farm levels of *Campylobacter* with clear protocol. This would aid in the ability for researchers to identify such environmental links.

Chapter 3 used as a theoretical approach to determine if considering house flies as a mechanical vector was a viable hypothesis for *Campylobacter* transmission. My model showed that this hypothesis did fit the data and therefore should be further explored. In order to create a more accurate model, empirical data on fly contact rates is necessary. As of now there is little information on fly contact rates with both humans and specific environmental reservoirs. These are important factors that affect disease transmission and require empirical data in order to be more confident in the model results. The model was especially sensitive to the fly death rate. These parameters are of specific interest for future research as they are very important to the overall model outputs. Therefore, more on temperature dependent fly birth and death rates and estimations of total fly populations in Ontario during each season would be essential information to inform the model. This could be done through observational studies or lab based studies. For example, seasonal or temperature dependant birth and death rates could be found through direct observation in the environment at multiple points in the year or through lab experimentation in which flies could be bred and observed for development time. A more difficult parameter to obtain would be an estimation of the overall number of flies in the province at the different times of the year.

The model was a simplified version of the very complex transmission pathways for *Campylobacter*. This was mainly because very few transmission models have been created for *Campylobacter* transmission within the human population and there are gaps in the necessary data for many of the transmission pathways. The environmental compartment encapsulated all
the potential transmission routes apart from person-person and environment-flies-person. This compartment could be broken down into foodborne, waterborne, contact with agricultural animals and their feces, or contact with wild animal and their feces, if there were data on the levels of *Campylobacter*, the seasonality and dynamics, and the amount each transmission route contributed to the overall disease dynamics. Also, the model was very sensitive to the level of *Campylobacter* in the environment. Therefore, this compartment is very influential and knowing more accurate values would create a much more biologically accurate model. Therefore, as more research is done, the more we can explicitly model these aspects of *Campylobacter* transmission and acquire more accurate values for the level of *Campylobacter* within each compartment.

**FUTURE RESEARCH OPPORTUNITIES**

The associations found in chapter 2, along with the more in depth research mentioned above, could be used as part of a syndromic surveillance system as “red flags” to inform public health of potential increased risk of outbreaks. For example, if Ontario is experiencing a warmer than usual spring or is having extensive precipitation leading to high water levels, this may be picked up by the system as a potential high risk outbreak situation. This could then allow public health and the agricultural sector to be on alert for outbreaks or high prevalence of *Campylobacter*, as well as enhance surveillance along the farm-to-fork continuum.

My model in chapter 3 provides great promise to the theory that flies act as a mechanical vector for *Campylobacter* transmission between animal reservoirs, the environment, and humans. Therefore, this model could be used to test different intervention and control strategies for controlling fly populations and fly contact with either the reservoirs (agricultural settings, livestock and their feces, contaminated environments) or human food. This model could also be adapted to explicitly model other aspects of the transmission routes for example human contact
with animals and animal feces directly. This could be done by the addition of an animal reservoir compartment and could account for seasonal fluctuations in animal positivity and amount of animal shedding into the environment explicitly. This could only be done if the necessary data were to become available. This model would also be useful for exploring the direct effects of climate change on levels of *Campylobacter* in the environment under different climate change scenarios. For example, the model could be used to predict changes to campylobacteriosis incidence after large rain events or extremely hot summers. This would allow public health to be more prepared if a spike in incidence is to be expected.

**CONCLUDING REMARKS**

This research has demonstrated that *Campylobacter* is affected by changes to the climate and environment and has provided some insight into how *Campylobacter* and campylobacteriosis incidence may change in the future under climate change. Using the baseline associations found in chapter 2 along with disease modelling approaches such as those in chapter 3, we can explore how campylobacteriosis will be affected by our ever-changing climate. The results of this work suggest that we may expect to see a potentially greater burden of campylobacteriosis and potentially other enteric illnesses. Therefore, we need to start preparing. This could include increasing surveillance and identifying early warning signs, researching potential intervention and prevention strategies, and reallocating public health resources for quick detection and treatment of enteric illnesses. This is a One Health problem and we need to be looking for One Health solutions.
APPENDICES

ADDITIONAL TABLES

Table A2.1: Comparing incidence of campylobacteriosis in the Waterloo health region in the year 2014 at varying temperatures.

<table>
<thead>
<tr>
<th>Year</th>
<th>Water Level (m)</th>
<th>Maximum Temperature (°C)</th>
<th>Predicted Incidence (95% CI) (cases per 100,000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>4</td>
<td>5</td>
<td>6.08 (4.07 to 9.10)</td>
</tr>
<tr>
<td>2014</td>
<td>4</td>
<td>25</td>
<td>2.57 (1.12 to 5.56)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
<td>3.51 (2.95 to 3.54)</td>
</tr>
</tbody>
</table>

Table A2.2: Comparing incidence of campylobacteriosis in the Waterloo health region in the year 2005 at varying temperatures.

<table>
<thead>
<tr>
<th>Year</th>
<th>Water Level (m)</th>
<th>Maximum Temperature (°C)</th>
<th>Predicted Incidence (95% CI) (cases per 100,000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>4</td>
<td>5</td>
<td>8.74 (5.77 to 13.16)</td>
</tr>
<tr>
<td>2005</td>
<td>2</td>
<td>25</td>
<td>3.68 (1.68 to 8.06)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
<td>5.06 (4.09 to 5.10)</td>
</tr>
</tbody>
</table>

Table A2.3: Comparing incidence of campylobacteriosis in the Waterloo health region in the year 2014 at varying water levels.

<table>
<thead>
<tr>
<th>Year</th>
<th>Water Level (m)</th>
<th>Maximum Temperature (°C)</th>
<th>Predicted Incidence (95% CI) (cases per 100,000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>2</td>
<td>25</td>
<td>9.31 (1.97 to 44.10)</td>
</tr>
<tr>
<td>2014</td>
<td>4</td>
<td>25</td>
<td>2.57 (1.12 to 5.56)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
<td>6.74 (0.85 to 38.54)</td>
</tr>
</tbody>
</table>

Table A2.4: Comparing incidence of campylobacteriosis in the Waterloo health region in the year 2014 at water flows.

<table>
<thead>
<tr>
<th>Year</th>
<th>Water Flow (m/s)</th>
<th>Maximum Temperature (°C)</th>
<th>Predicted Incidence (95% CI) (cases per 100,000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>10</td>
<td>25</td>
<td>2.46 (1.15 to 5.25)</td>
</tr>
<tr>
<td>2014</td>
<td>100</td>
<td>25</td>
<td>1.97 (0.92 to 4.22)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
<td>0.49 (0.23 to 1.03)</td>
</tr>
</tbody>
</table>

Table A2.5: Comparing incidence of campylobacteriosis in the York health region in the year 2014 at varying temperatures.

<table>
<thead>
<tr>
<th>Year</th>
<th>Precipitation (mm)</th>
<th>Maximum Temperature (°C)</th>
<th>Predicted Incidence (95% CI) (cases per 100,000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>1</td>
<td>5</td>
<td>7.28 (5.72 to 9.15)</td>
</tr>
<tr>
<td>2014</td>
<td>1</td>
<td>25</td>
<td>5.36 (3.24 to 8.84)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
<td>1.92 (0.31 to 2.48)</td>
</tr>
</tbody>
</table>
Table A2.6: Comparing incidence of campylobacteriosis in the York health region in the year 2014 at varying amounts of precipitation.

<table>
<thead>
<tr>
<th>Year</th>
<th>Precipitation (mm)</th>
<th>Maximum Temperature (°C)</th>
<th>Predicted Incidence (95% CI) (cases per 100,000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>1</td>
<td>25</td>
<td>5.36 (3.24 to 8.84)</td>
</tr>
<tr>
<td>2014</td>
<td>10</td>
<td>25</td>
<td>4.49 (2.66 to 7.59)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table A2.7: Comparing incidence of campylobacteriosis in the Durham health region in the year 2014 at varying temperatures.

<table>
<thead>
<tr>
<th>Year</th>
<th>Water Level (m)</th>
<th>Mean Temperature (°C)</th>
<th>Predicted Incidence (95% CI) (cases per 100,000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>2</td>
<td>5</td>
<td>7.38 (4.78 to 11.44)</td>
</tr>
<tr>
<td>2014</td>
<td>2</td>
<td>25</td>
<td>4.36 (1.80 to 10.56)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table A2.8: Comparing incidence of campylobacteriosis in the Durham health region in the year 2014 at varying water levels.

<table>
<thead>
<tr>
<th>Year</th>
<th>Water Level (m)</th>
<th>Mean Temperature (°C)</th>
<th>Predicted Incidence (95% CI) (cases per 100,000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>2</td>
<td>25</td>
<td>4.36 (1.80 to 10.56)</td>
</tr>
<tr>
<td>2014</td>
<td>2.5</td>
<td>25</td>
<td>2.94 (1.21 to 7.12)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table A2.9: Comparing incidence of campylobacteriosis in the Waterloo health region in the year 2014 at varying number of positive farms.

<table>
<thead>
<tr>
<th>Water Level (m)</th>
<th>Mean Temperature (°C)</th>
<th>Number of Positive Farms</th>
<th>Predicted Incidence (95% CI) (cases per 100,000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>25</td>
<td>1</td>
<td>2.85 (1.26 to 6.5)</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>5</td>
<td>2.04 (0.88 to 4.77)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table A2.10: Results of case-crossover analysis of environmental exposures continuous variables on *C. jejuni* human cases in the Waterloo health region.

<table>
<thead>
<tr>
<th>Maximum Temperature</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>lagged 19 days</td>
<td>1.015702</td>
<td>1.000156, 1.03149</td>
<td>0.048</td>
</tr>
<tr>
<td>Total Precipitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 24 days</td>
<td>1.010442</td>
<td>1.001309, 1.019659</td>
<td>0.025</td>
</tr>
<tr>
<td>Water Flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 3 days</td>
<td>1.00211</td>
<td>0.9999608, 1.004265</td>
<td>0.054</td>
</tr>
</tbody>
</table>
Table A2.11: Results of case-crossover analysis of environmental exposure variables as quantiles on *C. jejuni* human cases in the Waterloo health region.

<table>
<thead>
<tr>
<th>Environmental Exposure</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.16022</td>
<td>1.004487, 1.33964</td>
<td>0.043</td>
</tr>
<tr>
<td>lagged 7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Precipitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.8509707</td>
<td>0.7384958, 0.9805758</td>
<td>0.026</td>
</tr>
<tr>
<td>lagged 18 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>1.242867</td>
<td>1.009305, 1.530476</td>
<td>0.041</td>
</tr>
<tr>
<td>lagged 4 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.16247</td>
<td>1.000943, 1.350062</td>
<td>0.049</td>
</tr>
<tr>
<td>lagged 17 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Water Flow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0.850735</td>
<td>0.7238716, 0.99983</td>
<td>0.050</td>
</tr>
<tr>
<td>lagged 10 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Water Level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.158057</td>
<td>1.00023, 1.340788</td>
<td>0.050</td>
</tr>
<tr>
<td>lagged 18 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0.8574318</td>
<td>0.7403765, 0.9929937</td>
<td>0.040</td>
</tr>
<tr>
<td>lagged 18 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table A2.12: Results of case-crossover analysis of environmental exposures as continuous variables on *C. jejuni* human cases in the Wellington-Dufferin-Guelph health region.

<table>
<thead>
<tr>
<th>Environmental Exposure</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 23 days</td>
<td>1.059442</td>
<td>1.000443, 1.12192</td>
<td>0.048</td>
</tr>
<tr>
<td><strong>Total Precipitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 1 days</td>
<td>1.034938</td>
<td>1.004098, 1.066725</td>
<td>0.026</td>
</tr>
<tr>
<td>lagged 8 days</td>
<td>1.033647</td>
<td>1.002576, 1.06568</td>
<td>0.034</td>
</tr>
</tbody>
</table>
Table A2.13: Results of case-crossover analysis of environmental exposure variables as quantiles on *C. jejuni* human cases in the Wellington-Dufferin-Guelph health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 1 days</td>
<td>0.5280902</td>
<td>0.2899649, 0.9617688</td>
<td>0.037</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 13 days</td>
<td>1.712211</td>
<td>1.028851, 2.849456</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>1.988179</td>
<td>1.197187, 3.301786</td>
<td>0.008</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 17 days</td>
<td>0.4360808</td>
<td>0.220705, 0.861632</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>Total Precipitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 4 days</td>
<td>0.573652</td>
<td>0.3371623, 0.9760185</td>
<td>0.040</td>
</tr>
<tr>
<td>lagged 24 days</td>
<td>1.751596</td>
<td>1.017318, 3.051859</td>
<td>0.043</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 18 days</td>
<td>0.3557778</td>
<td>0.1262984, 1.002213</td>
<td>0.050</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 23 days</td>
<td>0.5163276</td>
<td>0.2675357, 0.9964809</td>
<td>0.049</td>
</tr>
<tr>
<td>lagged 24 days</td>
<td>0.4093441</td>
<td>0.2008327, 0.8343391</td>
<td>0.014</td>
</tr>
<tr>
<td>lagged 26 days</td>
<td>0.4676895</td>
<td>0.2361857, 0.9261082</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>Water Flow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 8 days</td>
<td>1.722175</td>
<td>1.037966, 2.857402</td>
<td>0.035</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 12 days</td>
<td>1.79915</td>
<td>1.079653, 2.99813</td>
<td>0.024</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 8 days</td>
<td>0.4784416</td>
<td>0.2484101, 0.9241854</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Water Level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 5 days</td>
<td>1.851995</td>
<td>1.080906, 3.173156</td>
<td>0.025</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 5 days</td>
<td>0.545155</td>
<td>0.318131, 0.9341873</td>
<td>0.027</td>
</tr>
</tbody>
</table>
Table A2.14: Results of case-crossover analysis of environmental exposures as continuous variables on *C. jejuni* human cases in the York health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 14 days</td>
<td>0.9776588</td>
<td>0.957055, 0.9987062</td>
<td>0.038</td>
</tr>
<tr>
<td>Total Precipitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 20 days</td>
<td>1.014883</td>
<td>1.001833, 1.028103</td>
<td>0.025</td>
</tr>
<tr>
<td>Water Level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 19 days</td>
<td>2.253948</td>
<td>1.028046, 4.941686</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Table A2.15: Results of case-crossover analysis of environmental exposure variables as quantiles on *C. jejuni* human cases in the York health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 25 days</td>
<td>0.8136083</td>
<td>0.6647009, 0.9958741</td>
<td>0.045</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 19 days</td>
<td>0.7676551</td>
<td>0.6201554, 0.9502366</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.254043</td>
<td>1.029735, 1.527211 0.024</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 20 days</td>
<td>0.7094141</td>
<td>0.5079206, 0.9908407</td>
<td>0.044</td>
</tr>
<tr>
<td>Total Precipitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 20 days</td>
<td>1.235712</td>
<td>1.011811, 1.509159</td>
<td>0.038</td>
</tr>
<tr>
<td>Water Flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 15 days</td>
<td>1.239677</td>
<td>1.019545, 1.507339</td>
<td>0.031</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 19 days</td>
<td>1.245319</td>
<td>1.023893, 1.51463</td>
<td>0.028</td>
</tr>
<tr>
<td>Water Level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 17 days</td>
<td>1.207936</td>
<td>0.9998258, 1.459363</td>
<td>0.050</td>
</tr>
</tbody>
</table>
Table A2.16: Results of case-crossover analysis of environmental exposures as continuous variables on *C. jejuni* human cases in the Durham health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 7 days</td>
<td>0.9304372</td>
<td>0.8755673, 0.9887456</td>
<td>0.020</td>
</tr>
<tr>
<td>lagged 8 days</td>
<td>0.9260761</td>
<td>0.8713921, 0.9841917</td>
<td>0.013</td>
</tr>
<tr>
<td>lagged 12 days</td>
<td>1.066505</td>
<td>1.000888, 1.136425</td>
<td>0.047</td>
</tr>
<tr>
<td>lagged 13 days</td>
<td>1.07919</td>
<td>1.011267, 1.151689</td>
<td>0.022</td>
</tr>
<tr>
<td>lagged 17 days</td>
<td>1.0854</td>
<td>1.021625, 1.153157</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Total Precipitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 16 days</td>
<td>1.031579</td>
<td>1.008729, 1.054946</td>
<td>0.007</td>
</tr>
<tr>
<td>lagged 21 days</td>
<td>0.9252075</td>
<td>0.8591405, 0.9963551</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>Water Level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 17 days</td>
<td>0.0027432</td>
<td>0.000012, 0.6200261</td>
<td>0.033</td>
</tr>
<tr>
<td>lagged 18 days</td>
<td>0.0001856</td>
<td>4.05e-07, 0.08511</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Water Flow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 18 days</td>
<td>0.5069934</td>
<td>0.2919015, 0.880579</td>
<td>0.016</td>
</tr>
</tbody>
</table>
Table A2.17: Results of case-crossover analysis of environmental exposure variables as quantiles on *C. jejuni* human cases in the Durham health region.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 4 days</td>
<td>0.6003297</td>
<td>0.3693297, 0.9758102</td>
<td>0.040</td>
</tr>
<tr>
<td>lagged 8 days</td>
<td>1.606469</td>
<td>1.057778, 2.439777</td>
<td>0.026</td>
</tr>
<tr>
<td>lagged 17 days</td>
<td>0.5940183</td>
<td>0.36576, .9647246</td>
<td>0.035</td>
</tr>
<tr>
<td>lagged 21 days</td>
<td>0.5639829</td>
<td>0.3443011, 0.9238327</td>
<td>0.023</td>
</tr>
<tr>
<td>Medium</td>
<td>1.534554</td>
<td>1.001096, 2.352276</td>
<td>0.049</td>
</tr>
<tr>
<td>High</td>
<td>1.690543</td>
<td>1.097999, 2.602858</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>Total Precipitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 7 days</td>
<td>1.803566</td>
<td>1.132855, 2.871374</td>
<td>0.013</td>
</tr>
<tr>
<td>lagged 20 days</td>
<td>1.661787</td>
<td>1.052335, 2.624199</td>
<td>0.029</td>
</tr>
<tr>
<td>Medium</td>
<td>2.161452</td>
<td>1.048381, 4.456276</td>
<td>0.037</td>
</tr>
<tr>
<td>High</td>
<td>1.598756</td>
<td>1.036222, 2.46667</td>
<td>0.034</td>
</tr>
<tr>
<td>lagged 5 days</td>
<td>1.570981</td>
<td>1.012568, 2.437348</td>
<td>0.044</td>
</tr>
<tr>
<td>lagged 16 days</td>
<td>0.5530366</td>
<td>0.3158157, 0.968443</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>Water Flow</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 6 days</td>
<td>1.564953</td>
<td>1.036143, 2.363648</td>
<td>0.033</td>
</tr>
<tr>
<td>lagged 7 days</td>
<td>1.780383</td>
<td>1.179824, 2.686639</td>
<td>0.006</td>
</tr>
<tr>
<td>lagged 17 days</td>
<td>1.657865</td>
<td>1.098273, 2.502581</td>
<td>0.016</td>
</tr>
<tr>
<td>lagged 18 days</td>
<td>1.575541</td>
<td>1.043189, 2.379561</td>
<td>0.031</td>
</tr>
<tr>
<td>lagged 27 days</td>
<td>1.575541</td>
<td>1.043189, 2.379561</td>
<td>0.031</td>
</tr>
<tr>
<td>High</td>
<td>0.5903751</td>
<td>0.3588705, 0.9712216</td>
<td>0.038</td>
</tr>
<tr>
<td>lagged 6 days</td>
<td>0.5498472</td>
<td>0.3311307, 0.9130292</td>
<td>0.021</td>
</tr>
<tr>
<td>lagged 17 days</td>
<td>0.48168</td>
<td>0.283871, 0.8173277</td>
<td>0.007</td>
</tr>
<tr>
<td>lagged 19 days</td>
<td>0.5871879</td>
<td>0.3569338, 0.9659763</td>
<td>0.036</td>
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</table>
Table A2.18: Results of case-crossover analysis of environmental exposures as continuous variables on *C. coli* human cases in the Waterloo health region.

<table>
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<tr>
<th>Water Level</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low lagged 17 days</td>
<td>2.166714</td>
<td>1.386183, 3.386745</td>
<td>0.001</td>
</tr>
<tr>
<td>lagged 18 days</td>
<td>2.156474</td>
<td>1.379625, 3.370758</td>
<td>0.001</td>
</tr>
<tr>
<td>High lagged 17 days</td>
<td>0.4593422</td>
<td>0.2935747, 0.7187108</td>
<td>0.001</td>
</tr>
<tr>
<td>lagged 18 days</td>
<td>0.4615293</td>
<td>0.2949723, 0.7221332</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Environmental Exposure</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Temperature lagged 7 days</td>
<td>1.104526</td>
<td>1.018884, 1.197366</td>
<td>0.016</td>
</tr>
<tr>
<td>lagged 8 days</td>
<td>1.1061</td>
<td>1.021925, 1.197208</td>
<td>0.013</td>
</tr>
<tr>
<td>Total Precipitation lagged 21 days</td>
<td>1.06843</td>
<td>1.02527, 1.113407</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Table A2.19: Results of case-crossover analysis of environmental exposure variables as quantiles on *C. coli* human cases in the Waterloo health region.

<table>
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<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Temperature</strong></td>
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<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 0 days</td>
<td>0.3694452</td>
<td>0.1407441, 0.9697724</td>
<td>0.043</td>
</tr>
<tr>
<td>lagged 7 days</td>
<td>0.3756302</td>
<td>0.1431254, 0.9858353</td>
<td>0.047</td>
</tr>
<tr>
<td>lagged 16 days</td>
<td>0.2979788</td>
<td>0.1035903, 0.8571397</td>
<td>0.025</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 16 days</td>
<td>2.24478</td>
<td>1.081673, 4.658593</td>
<td>0.030</td>
</tr>
<tr>
<td><strong>Total Precipitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 11 days</td>
<td>2.746424</td>
<td>1.099905, 6.857723</td>
<td>0.030</td>
</tr>
<tr>
<td>lagged 20 days</td>
<td>0.4074636</td>
<td>0.1887207, 0.8797477</td>
<td>0.022</td>
</tr>
<tr>
<td>lagged 21 days</td>
<td>0.2896362</td>
<td>0.1292796, 0.648897</td>
<td>0.003</td>
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<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 11 days</td>
<td>0.2944569</td>
<td>0.0887103, 0.9773931</td>
<td>0.046</td>
</tr>
<tr>
<td>lagged 21 days</td>
<td>3.065904</td>
<td>1.466353, 6.410302</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Water Flow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 9 days</td>
<td>0.2915724</td>
<td>0.087375, 0.9729842</td>
<td>0.045</td>
</tr>
<tr>
<td>lagged 10 days</td>
<td>0.2828348</td>
<td>0.084626, 0.9452833</td>
<td>0.040</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 20 days</td>
<td>2.17185</td>
<td>1.00524, 4.692344</td>
<td>0.048</td>
</tr>
<tr>
<td>lagged 21 days</td>
<td>2.535442</td>
<td>1.170857, 5.490394</td>
<td>0.018</td>
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</table>
Table A2.20: Results of case-crossover analysis of positive farms as a continuous exposure variable on *C. jejuni* human cases in the Waterloo health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Positive Farms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 2 days</td>
<td>0.7361399</td>
<td>0.5927407, 0.9142311</td>
<td>0.006</td>
</tr>
<tr>
<td>lagged 5 days</td>
<td>0.7090186</td>
<td>0.5672845, 0.8861644</td>
<td>0.003</td>
</tr>
<tr>
<td>lagged 6 days</td>
<td>0.7891098</td>
<td>0.6425845, 0.9690465</td>
<td>0.024</td>
</tr>
<tr>
<td>lagged 10 days</td>
<td>1.433427</td>
<td>1.25304, 1.639782</td>
<td>0.000</td>
</tr>
<tr>
<td>lagged 17 days</td>
<td>1.346684</td>
<td>1.169216, 1.551089</td>
<td>0.000</td>
</tr>
<tr>
<td>lagged 19 days</td>
<td>0.7122824</td>
<td>0.568208, 0.8928881</td>
<td>0.003</td>
</tr>
<tr>
<td>lagged 23 days</td>
<td>1.267627</td>
<td>1.094672, 1.467909</td>
<td>0.002</td>
</tr>
<tr>
<td>lagged 24 days</td>
<td>1.255096</td>
<td>1.082656, 1.455003</td>
<td>0.003</td>
</tr>
<tr>
<td>Positive Cattle Farms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 2 days</td>
<td>0.73713</td>
<td>0.5881359, 0.923869</td>
<td>0.008</td>
</tr>
<tr>
<td>lagged 5 days</td>
<td>0.6770975</td>
<td>0.5318089, 0.8620785</td>
<td>0.002</td>
</tr>
<tr>
<td>lagged 6 days</td>
<td>0.7074043</td>
<td>0.5602048, 0.8932818</td>
<td>0.004</td>
</tr>
<tr>
<td>lagged 10 days</td>
<td>1.475991</td>
<td>1.288291, 1.691038</td>
<td>0.000</td>
</tr>
<tr>
<td>lagged 17 days</td>
<td>1.305412</td>
<td>1.124617, 1.515273</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>lagged 19 days</td>
<td>0.7205689</td>
<td>0.569805, 0.9112233</td>
<td>0.006</td>
</tr>
<tr>
<td>lagged 23 days</td>
<td>1.257993</td>
<td>1.07999, 1.465335</td>
<td>0.003</td>
</tr>
<tr>
<td>lagged 24 days</td>
<td>1.312698</td>
<td>1.132097, 1.52211</td>
<td>&lt;0.001</td>
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Table A2.21: Results of case-crossover analysis of positive farms as a continuous exposure variable on *C. coli* human cases in the Waterloo health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Positive Farms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 20 days</td>
<td>2.850055</td>
<td>1.027361, 7.906484</td>
<td>0.044</td>
</tr>
<tr>
<td>lagged 23 days</td>
<td>2.934788</td>
<td>1.103612, 7.804356</td>
<td>0.031</td>
</tr>
<tr>
<td>lagged 26 days</td>
<td>2.998965</td>
<td>1.126867, 7.981235</td>
<td>0.028</td>
</tr>
<tr>
<td>Positive Swine Farms</td>
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<td></td>
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</tr>
<tr>
<td>lagged 20 days</td>
<td>4.963655</td>
<td>1.259033, 19.56889</td>
<td>0.022</td>
</tr>
<tr>
<td>lagged 23 days</td>
<td>5.666141</td>
<td>1.453958, 22.08121</td>
<td>0.012</td>
</tr>
<tr>
<td>lagged 26 days</td>
<td>6.040218</td>
<td>1.542362, 23.65478</td>
<td>0.010</td>
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</table>
### Table A2.22: Results of case-crossover analysis of environmental exposures and human cases as continuous variables on *C. jejuni* positive farms in the Waterloo health region.

<table>
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<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Temperature</strong></td>
<td></td>
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</tr>
<tr>
<td>lagged 10 days</td>
<td>1.032251</td>
<td>1.000067, 1.065471</td>
<td>0.050</td>
</tr>
<tr>
<td><strong>Total Precipitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 20 days</td>
<td>1.023454</td>
<td>1.000584, 1.046846</td>
<td>0.044</td>
</tr>
<tr>
<td><strong>Water Level</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>lagged 28 days</td>
<td>0.2443231</td>
<td>0.0601392, 0.9925932</td>
<td>0.049</td>
</tr>
<tr>
<td><strong>Water Flow</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>lagged 28 days</td>
<td>0.9938102</td>
<td>0.9877746, 0.9998827</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Human Cases</strong></td>
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<td></td>
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</tr>
<tr>
<td>lagged 11 days</td>
<td>0.7290108</td>
<td>0.53848, 0.9869574</td>
<td>0.041</td>
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### Table A2.23: Results of case-crossover analysis of environmental exposure variables as quantiles on *C. jejuni* positive farms in the Waterloo health region.

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<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Intervals</th>
<th>P-value</th>
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</thead>
<tbody>
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<td><strong>Total Precipitation</strong></td>
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</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 7 days</td>
<td>0.5705393</td>
<td>0.3291556, 0.9889399</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Water Flow</strong></td>
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<tr>
<td>Low</td>
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<td></td>
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</tr>
<tr>
<td>lagged 27 days</td>
<td>1.490936</td>
<td>1.090134, 2.039098</td>
<td>0.012</td>
</tr>
<tr>
<td>High</td>
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</tr>
<tr>
<td>lagged 27 days</td>
<td>0.6522928</td>
<td>0.4519487, 0.9414474</td>
<td>0.022</td>
</tr>
<tr>
<td><strong>Water Level</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>lagged 17 days</td>
<td>0.6958603</td>
<td>0.507409, 0.9543022</td>
<td>0.024</td>
</tr>
<tr>
<td>High</td>
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<td></td>
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<tr>
<td>lagged 17 days</td>
<td>1.397871</td>
<td>1.020194, 1.915363</td>
<td>0.037</td>
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Table A2.24: Results of case-crossover analysis of environmental exposures and human cases continuous variables on *C. jejuni* positive cattle farms in the Waterloo health region.

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<th>Odds Ratio</th>
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<th>P-value</th>
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</thead>
<tbody>
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<td>Mean Temperature</td>
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</tr>
<tr>
<td>lagged 27 days</td>
<td>0.958895</td>
<td>0.9924086, 0.9968246</td>
<td>0.034</td>
</tr>
<tr>
<td>Human Cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 11 days</td>
<td>0.7048494</td>
<td>0.5054224, 0.9829651</td>
<td>0.039</td>
</tr>
<tr>
<td>lagged 23 days</td>
<td>1.308354</td>
<td>1.009567, 1.69557</td>
<td>0.042</td>
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</table>

Table A2.25: Results of case-crossover analysis of environmental exposure variables as quantiles on *C. jejuni* positive cattle farms in the Waterloo health region.

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<th>Odds Ratio</th>
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<th>P-value</th>
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</thead>
<tbody>
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<td>Total Precipitation</td>
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<td></td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 7 days</td>
<td>0.5469173</td>
<td>0.3032568, 0.9863542</td>
<td>0.045</td>
</tr>
<tr>
<td>Water Flow</td>
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<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 27 days</td>
<td>1.517691</td>
<td>1.088133, 2.116823</td>
<td>0.014</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>lagged 14 days</td>
<td>0.6581938</td>
<td>0.4462586, 0.9707802</td>
<td>0.035</td>
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</table>
Table A2.26: Results of case-crossover analysis of environmental exposures as continuous variables on *C. jejuni* positive sheep farms in the Waterloo health region.

<table>
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<th>Environmental Exposure</th>
<th>Odds Ratio</th>
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<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Precipitation</td>
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<td></td>
</tr>
<tr>
<td>lagged 9 days</td>
<td>1.095299</td>
<td>1.00397, 1.194935</td>
<td>0.04</td>
</tr>
<tr>
<td>lagged 15 days</td>
<td>1.1108</td>
<td>1.013368, 1.2176</td>
<td>0.025</td>
</tr>
<tr>
<td>Water Level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 28 days</td>
<td>14.40688</td>
<td>1.386025, 149.7508</td>
<td>0.026</td>
</tr>
<tr>
<td>lagged 9 days</td>
<td>14.01702</td>
<td>1.243369, 158.0198</td>
<td>0.033</td>
</tr>
<tr>
<td>lagged 24 days</td>
<td>2963.84</td>
<td>2.813164, 3122586</td>
<td>0.024</td>
</tr>
<tr>
<td>lagged 25 days</td>
<td>5897.26</td>
<td>10.96601, 3171406</td>
<td>0.007</td>
</tr>
<tr>
<td>lagged 26 days</td>
<td>393.2627</td>
<td>2.401991, 64386.4</td>
<td>0.022</td>
</tr>
<tr>
<td>Water Flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 8 days</td>
<td>1.008587</td>
<td>1.000389, 1.016853</td>
<td>0.04</td>
</tr>
<tr>
<td>lagged 9 days</td>
<td>1.009124</td>
<td>1.000706, 1.017612</td>
<td>0.034</td>
</tr>
<tr>
<td>lagged 25 days</td>
<td>1.034665</td>
<td>1.005403, 1.06478</td>
<td>0.02</td>
</tr>
<tr>
<td>lagged 26 days</td>
<td>1.01991</td>
<td>1.001171, 1.039002</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Table A2.27: Results of case-crossover analysis of environmental exposure variables as quantiles on *C. jejuni* positive sheep farms in the Waterloo health region.

<table>
<thead>
<tr>
<th>Environmental Exposure</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 1 days</td>
<td>3.186306</td>
<td>1.00124, 10.13998</td>
<td>0.050</td>
</tr>
<tr>
<td>lagged 5 days</td>
<td>4.505125</td>
<td>1.344871, 15.09153</td>
<td>0.015</td>
</tr>
<tr>
<td>lagged 10 days</td>
<td>3.182662</td>
<td>1.000435, 10.12494</td>
<td>0.050</td>
</tr>
<tr>
<td>lagged 16 days</td>
<td>3.272295</td>
<td>1.028599, 10.41019</td>
<td>0.045</td>
</tr>
<tr>
<td>Total Precipitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 11 days</td>
<td>3.319286</td>
<td>1.043507, 10.5583</td>
<td>0.042</td>
</tr>
</tbody>
</table>
Table A2.28: Results of case-crossover analysis of environmental exposures as continuous variables on *C. jejuni* positive poultry farms in the Waterloo health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 28 days</td>
<td>0.8744701</td>
<td>0.7726743, 0.9896771</td>
<td>0.034</td>
</tr>
<tr>
<td>Total Precipitation</td>
<td>1.081111</td>
<td>1.010922, 1.156173</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Table A2.29: Results of case-crossover analysis of environmental exposure variables as quantiles on *C. jejuni* positive poultry farms in the Waterloo health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>3.412266</td>
<td>1.140158, 10.21223</td>
<td>0.028</td>
</tr>
<tr>
<td>lagged 17 days</td>
<td>2.942059</td>
<td>1.016015, 8.519275</td>
<td>0.047</td>
</tr>
<tr>
<td>Medium</td>
<td>3.037482</td>
<td>1.051417, 8.775111</td>
<td>0.040</td>
</tr>
<tr>
<td>High</td>
<td>3.619035</td>
<td>0.9993606, 72.70393</td>
<td>0.050</td>
</tr>
<tr>
<td>Total Precipitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3.088015</td>
<td>1.031613, 9.24361</td>
<td>0.044</td>
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</tbody>
</table>
Table A2.30: Results of case-crossover analysis of environmental exposures and human cases as continuous variables on *C. coli* positive farms in the Waterloo health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 7 days</td>
<td>1.050575</td>
<td>1.019535, 1.082561</td>
<td>0.001</td>
</tr>
<tr>
<td>lagged 14 days</td>
<td>1.039785</td>
<td>1.008786, 1.071735</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Total Precipitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 12 days</td>
<td>1.029944</td>
<td>1.006824, 1.053595</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>Human Cases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 22 days</td>
<td>2.903684</td>
<td>1.00056, 8.42659</td>
<td>0.050</td>
</tr>
</tbody>
</table>
Table A2.31: Results of case-crossover analysis of environmental exposure variables as quantiles on *C. coli* positive farms in the Waterloo health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
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<td><strong>Maximum Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 0 days</td>
<td>1.347431</td>
<td>0.5117026, 0.9618541</td>
<td>0.028</td>
</tr>
<tr>
<td>lagged 19 days</td>
<td>0.6781957</td>
<td>0.4921244, 0.9346202</td>
<td>0.018</td>
</tr>
<tr>
<td>lagged 27 days</td>
<td>0.714078</td>
<td>0.5209404, 0.9788209</td>
<td>0.036</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 0 days</td>
<td>1.347431</td>
<td>1.003716, 1.808848</td>
<td>0.047</td>
</tr>
<tr>
<td>lagged 2 days</td>
<td>1.342087</td>
<td>0.9994999, 1.8021</td>
<td>0.050</td>
</tr>
<tr>
<td>lagged 6 days</td>
<td>0.6929903</td>
<td>0.497051, 0.9661696</td>
<td>0.031</td>
</tr>
<tr>
<td>lagged 22 days</td>
<td>1.342692</td>
<td>1.002348, 1.798599</td>
<td>0.048</td>
</tr>
<tr>
<td>lagged 27 days</td>
<td>1.419897</td>
<td>1.061236, 1.899773</td>
<td>0.018</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 7 days</td>
<td>1.52209</td>
<td>1.139228, 2.03362</td>
<td>0.004</td>
</tr>
<tr>
<td>lagged 14 days</td>
<td>1.554519</td>
<td>1.164079, 2.075914</td>
<td>0.003</td>
</tr>
<tr>
<td>lagged 15 days</td>
<td>1.485185</td>
<td>1.110969, 1.985452</td>
<td>0.008</td>
</tr>
<tr>
<td>lagged 24 days</td>
<td>1.34738</td>
<td>1.005232, 1.805983</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Total Precipitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 24 days</td>
<td>1.428558</td>
<td>1.049451, 1.944617</td>
<td>0.023</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 1 days</td>
<td>0.3280931</td>
<td>0.1711652, 0.6288961</td>
<td>0.001</td>
</tr>
<tr>
<td>lagged 5 days</td>
<td>1.55664</td>
<td>1.04093, 2.32785</td>
<td>0.031</td>
</tr>
<tr>
<td>lagged 9 days</td>
<td>1.632538</td>
<td>1.089814, 2.445535</td>
<td>0.017</td>
</tr>
<tr>
<td>lagged 11 days</td>
<td>1.607246</td>
<td>1.074162, 2.404888</td>
<td>0.021</td>
</tr>
<tr>
<td>lagged 13 days</td>
<td>0.5626942</td>
<td>0.3194699, 0.991094</td>
<td>0.046</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 8 days</td>
<td>0.7046687</td>
<td>0.4967845, 0.9995442</td>
<td>0.050</td>
</tr>
<tr>
<td>lagged 21 days</td>
<td>1.360075</td>
<td>1.005399, 1.83987</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Water Flow</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 15 days</td>
<td>1.418462</td>
<td>1.045075, 1.925254</td>
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</tr>
<tr>
<td>lagged 16 days</td>
<td>1.531283</td>
<td>1.129213, 2.076515</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% Confidence Interval</td>
<td>P-value</td>
</tr>
<tr>
<td>----------------</td>
<td>------------</td>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 16 days</td>
<td>0.6005615</td>
<td>0.4173184, 0.8642659</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 12 days</td>
<td>0.6724862</td>
<td>0.4717928, 0.9585515</td>
<td>0.028</td>
</tr>
<tr>
<td>lagged 13 days</td>
<td>0.6582981</td>
<td>0.4604336, 0.9411921</td>
<td>0.022</td>
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</table>

Table A2.32: Results of case-crossover analysis of environmental exposures as continuous variables on *C. coli* positive cattle farms in the Waterloo health region.
Table A2.33: Results of case-crossover analysis of environmental exposure variables as quantiles on *C. coli* positive cattle farms in the Waterloo health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 0 days</td>
<td>0.4072514</td>
<td>0.2111367, 0.7855275</td>
<td>0.007</td>
</tr>
<tr>
<td>lagged 19 days</td>
<td>0.3259438</td>
<td>0.1600844, 0.6636457</td>
<td>0.002</td>
</tr>
<tr>
<td>lagged 23 days</td>
<td>2.280509</td>
<td>1.365733, 3.80801</td>
<td>0.002</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 7 days</td>
<td>0.4162481</td>
<td>0.2105444, 0.8229261</td>
<td>0.012</td>
</tr>
<tr>
<td>lagged 19 days</td>
<td>1.864035</td>
<td>1.118043, 3.107775</td>
<td>0.017</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 7 days</td>
<td>1.839853</td>
<td>1.102396, 3.070637</td>
<td>0.020</td>
</tr>
<tr>
<td>lagged 8 days</td>
<td>1.952113</td>
<td>1.1715, 3.252877</td>
<td>0.010</td>
</tr>
<tr>
<td>lagged 14 days</td>
<td>1.713259</td>
<td>1.024409, 2.865316</td>
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</tr>
<tr>
<td>lagged 24 days</td>
<td>1.71495</td>
<td>1.024885, 2.869642</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>Total Precipitation</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 2 days</td>
<td>2.081682</td>
<td>1.134513, 3.819612</td>
<td>0.018</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>lagged 2 days</td>
<td>0.2810896</td>
<td>0.100178, 0.7887092</td>
<td>0.016</td>
</tr>
<tr>
<td>lagged 21 days</td>
<td>1.95203</td>
<td>1.104697, 3.449291</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Water Flow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 21 days</td>
<td>2.181344</td>
<td>1.30671, 3.641406</td>
<td>0.003</td>
</tr>
<tr>
<td>lagged 26 days</td>
<td>0.4298642</td>
<td>0.217216, 0.850689</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Water Level</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 19 days</td>
<td>0.5724246</td>
<td>0.3369729, 0.9723925</td>
<td>0.039</td>
</tr>
<tr>
<td>High</td>
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<td></td>
</tr>
<tr>
<td>lagged 19 days</td>
<td>1.856039</td>
<td>1.090308, 3.159549</td>
<td>0.023</td>
</tr>
</tbody>
</table>
Table A2.34: Results of case-crossover analysis of environmental exposures as continuous variables on *C. coli* positive swine farms in the Waterloo health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 7 days</td>
<td>1.061798</td>
<td>1.024173, 1.100805</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Total Precipitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 6 days</td>
<td>1.037122</td>
<td>1.009857, 1.065122</td>
<td>0.007</td>
</tr>
<tr>
<td>lagged 26 days</td>
<td>1.027797</td>
<td>1.004723, 1.051402</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Table A2.35: Results of case-crossover analysis of environmental exposure variables as quantiles on *C. coli* positive swine farms in the Waterloo health region.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 11 days</td>
<td>0.6511308</td>
<td>0.4419943, 0.9592235</td>
<td>0.030</td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>lagged 7 days</td>
<td>1.646133</td>
<td>1.180592, 2.29525</td>
<td>0.003</td>
</tr>
<tr>
<td>lagged 8 days</td>
<td>1.517971</td>
<td>1.086126, 2.121517</td>
<td>0.015</td>
</tr>
<tr>
<td>lagged 15 days</td>
<td>1.494879</td>
<td>1.068093, 2.0922</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>Total Precipitation</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>lagged 6 days</td>
<td>0.6800553</td>
<td>0.4832089, 0.9570917</td>
<td>0.027</td>
</tr>
<tr>
<td>lagged 8 days</td>
<td>1.42937</td>
<td>1.002052, 2.038913</td>
<td>0.049</td>
</tr>
<tr>
<td>lagged 28 days</td>
<td>1.503229</td>
<td>1.046204, 2.159902</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 1 days</td>
<td>0.5071255</td>
<td>0.2681857, 0.9589484</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 6 days</td>
<td>1.561461</td>
<td>1.106194, 2.204099</td>
<td>0.011</td>
</tr>
<tr>
<td>lagged 20 days</td>
<td>0.5901137</td>
<td>0.3862734, 0.9015225</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Water Flow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lagged 27 days</td>
<td>1.574933</td>
<td>1.076101, 2.305001</td>
<td>0.019</td>
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</table>
Table A3.1: Univariate sensitivity analysis on initial conditions estimated through parameterization to campylobacteriosis incidence reported to Public Health Ontario in 2005.

<table>
<thead>
<tr>
<th>Initial Condition</th>
<th>Value</th>
<th>Minimum Test Value</th>
<th>Maximum Test Value</th>
<th>Percent Change from Minimum (%)</th>
<th>Percent Change from Maximum (%)</th>
</tr>
</thead>
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<tr>
<td>S₀</td>
<td>8 x10⁶</td>
<td>1x10⁶</td>
<td>1.3 x10⁷</td>
<td>-57.57</td>
<td>6.29</td>
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<tr>
<td>B₀</td>
<td>2.5 x10⁻²</td>
<td>1 x10⁻³</td>
<td>1 x10⁻¹</td>
<td>-55.88</td>
<td>55.88</td>
</tr>
<tr>
<td>S₀/ w</td>
<td>4910</td>
<td>100</td>
<td>10000</td>
<td>-3.45</td>
<td>3.65</td>
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</table>
Table A3.2: Percentage increase of *Campylobacter* incidence under climate change scenarios that affect the fly population size and amount of fly activity.

<table>
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<tr>
<th>Scenario</th>
<th>Percent Increase in annual incidence (%)</th>
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<td><strong>Baseline</strong></td>
<td>25.04 cases / 100,000 population</td>
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<tr>
<td><strong>Fly Population Size Increase</strong></td>
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<td>2050: 84.3%</td>
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<td>2050: 128%</td>
<td>5.41</td>
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<tr>
<td>2080: 244%</td>
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ADDITIONAL FIGURES

Figure A2.1: Average incidence of *Campylobacter* per 100,000 population by age group. The data spans January 1st 2005 to December 31st 2013 and is separated by health region. The bars represent the minimum and maximum incidence.
Figure A2.2: Average incidence of *Campylobacter* per 100,000 population by month. The data spans January 1st 2005 to December 31st 2013 and is separated by health region. The bars represent the minimum and maximum incidence.
Figure A2.3: Conditional logistic regression results for the human *C. jejuni* cases in the Wellington-Dufferin-Guelph health region. Panels show the “medium” temperature tertile (A), the “low” precipitation tertile (B), the “low” water flow tertile (C), and the “low” water level quantile (D) from the case-crossover analysis over the 28-day lag. The odds ratio (solid line) and 95% confidence interval (dashed line) are shown for the full 28-day period with the star depicting significant associations.
Figure A2.4: Conditional logistic regression results for the human \textit{C. jejuni} cases in the York health region. Panels show the “medium” temperature tertile (A), the “high” precipitation tertile (B), the “high” water flow tertile (C), and the “high” water level quantile (D) from the case-crossover analysis over the 28-day lag. The odds ratio (solid line) and 95\% confidence interval (dashed line) are shown for the full 28-day period with the star depicting significant associations.
Figure A2.5: Conditional logistic regression results for the human *C. jejuni* cases in the Durham health region. Panels show the “high” temperature tertile (A), the “medium” precipitation tertile (B), the “low” water flow tertile (C), and the “low” water level quantile (D) from the case-crossover analysis over the 28-day lag. The odds ratio (solid line) and 95% confidence interval (dashed line) are shown for the full 28-day period with the star depicting significant associations.