Evaluating the Environmental and Social Determinants of Enteric Disease in New Zealand

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“Man maketh a death which Nature never made”.

-Edward Young

ABSTRACT

Globally, enteric disease is a leading cause of illness and death. Projected climate change and agricultural intensification is expected to substantially influence zoonoses emergence and resurgence. New Zealand has high rates of enteric zoonoses, intensified livestock production and a considerable impact of regional climate on local weather. This thesis investigates the influence of climate variability, livestock density and social and demographic factors on four important enteric diseases in New Zealand: campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis.

Section I presents a conceptual framework that describes how linkages between environmental and social factors drive zoonotic disease transmission. In New Zealand, a review of the published literature emphasises the significance of environmental change for enteric zoonoses. A description of reported and hospitalised cases show marked demographic and social variations in disease burden.

Section II focuses on identifying potential risk factors through a detailed evaluation of temporal patterns in these diseases. The Gini-coefficient is used to establish temporal variation in disease incidence patterns globally. A novel seasonality index shows regionally consistent, summer peaks for campylobacteriosis and salmonellosis. Cryptosporidiosis displays spring peaks in in predominantly agricultural countries and in summer elsewhere, whereas giardiasis shows little seasonality. In New Zealand, salmonellosis incidence is positively associated with La Niña linked warmer wetter conditions, while cryptosporidiosis is positively related to El Niño linked cooler, drier conditions. A nonlinear and temporally lagged model describes the positive, but complex association between runoff rate and disease risk.

Cryptosporidiosis and giardiasis are recognised by the WHO as ‘Neglected Diseases’. Section III examines the importance of environmental and social factors in influencing spatial and temporal patterns in these two diseases. Cryptosporidiosis incidence rates and spatial relative risk patterns indicate higher risk in rural areas, with areas dominated by livestock showing recurrent disease clusters in spring. Multivariate space-time analyses show that while dairy cattle density, rural living and being less than four years old are significant risk factors, high population density and temperature appear protective. Giardiasis patterns demonstrate minimal seasonality and negligible associations with climatic variables, with disease clusters detected in urban areas. Multivariate analyses identify rural living and being less than four years old as significant risk factors while dairy cattle density appears protective, although the inter-relationships between rurality and livestock densities makes the interpretation of these findings complex.

Overall, in New Zealand, the influence of climate variability and livestock intensification on enteric zoonotic disease patterns is strongly modulated by human population characteristics. This relationship suggests that projected climate change and agricultural intensification are likely to have a disproportionate impact on vulnerable populations. Cross disciplinary research will be crucial to improve public health responses to projected environmental change. This work may be applied to understand the implications of environmental change for other diseases in New Zealand, and elsewhere.

PREFACE

Ecology *noun* (from Greek: Oikos, "house"; Logia, "study of") is defined as the branch of biology that deals with the relations of organisms to one another and the study of their interactions with the environment.

I come to this thesis trained as a Wildlife Ecologist. What brought me here was an interest in combining my knowledge of the natural environment with human health; a curiosity sparked with the innocuous drinking of unpasteurised goat's milk offered to me while interviewing villagers living on the fringes of Protected Tiger Reserves in India. Were these nomadic pastoralists at risk from animal diseases? Could we achieve improved human and animal health by reducing some forms of human-animal contact?

Growing up in India is also a huge motivator for this Public Health thesis. As part of our regular school curriculum, we had to visit villages and clean and disinfect homes, while introducing the occupants to basic public health concepts such as hand washing and having separate areas for washing soiled clothes and cooking utensils. Working on this thesis has given me a greater appreciation for how people can reduce their risk of infection and has provided me with an opportunity to be involved in improving human health.

I bring to this thesis the understanding that humans are but one part of a complex system, and that the traditional human centred approach to health may not fully capture the cascading impacts of global environmental influences such as climate change. My background has allowed me to explore my main interest, which is, to better understand the dynamics of infectious disease transmission among humans in the context of their physical and natural environment. While such an approach undoubtedly has its challenges, I am encouraged by the increasing acknowledgement of the role of the ecological environment in driving the dynamics of infectious disease spread.

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This thesis is dedicated to my parents whose unwavering support and motivation gave me the courage to venture into the scary world of infectious disease modelling. While geographically far away in India, you will always be my “go to” people.

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To my two greatest cheerleaders, Mathias and Zaira, thank you for giving me the incentive to work extra hard on the rainy days so I could take the sunny days off, saying “yummy” to toast and baked beans on a particularly hard day and above all for asking the question “But what does a PhD do?”. Your insatiable zest for life and laughter has made this PhD a wonderful journey.

A heartfelt thank you to my supervisors; Simon Hales, Nigel French and Michael Baker. Over the past three years, you have supported my digressions from the PhD path, and allowed me the freedom to explore my research interests. Your complementing research strengths have introduced me to a wide range of concepts and ideas. It has been a privilege being your student.

To all the people in the Department of Public Health, and the wider University of Otago, Wellington campus, I am grateful for your support and encouragement. Thank you to the statisticians, Nevil, Tak and James who always willingly answered my questions. Also, special thanks to the people up at the Hopkirk Research Institute at Massey University, Palmerston North, especially Jonathan Marshall who somehow made the mathematics sound, and look, doable.

I couldn’t possibly end without acknowledging the Otago PhD coffee group and my corridor mates on level G. You were my one stop shop for everything non - PhD related and a fantastic stress busting team.

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PUBLICATIONS FROM THESIS

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Lal A, Baker MG, French NP, Hales S. 2013. Potential effects of global environmental changes on cryptosporidiosis and giardiasis transmission Trends in Parasitology 29 (2):83-90.

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GLOSSARY

This glossary defines the terms below based on their usage in the current study.

Anthropogenic	According to the Merriam-Webster Dictionary it is defined as relating to, or resulting from, the influence of human beings on nature
Environmental Change	According to the World Health Organisation, it is defined as large-scale and global environmental hazards to human health. In the present study, this is restricted to referring to climate variability and change, and livestock intensification resulting in changes in land use patterns.
Zoonoses	According to the World Health Organisation, a zoonosis is any disease or infection that is naturally transmissible from vertebrate animals to humans.
Enteric Zoonoses	We expand the definition of zoonoses to include the definition of Eisenberg et al. (2007) which identifies pathogen transmission cycles being classified as ‘environmentally mediated, including non-human hosts’ (Group IIIb).

ABBREVIATIONS

CAU	Census Area Unit
DALY	Disability Adjusted Life Years
DHB	District Health Board
DLNM	Distributed Lag Non Linear Model
ENSO	El Niño Southern Oscillation
ESR	Institute of Environmental Science and Research Limited
GHG	Green House Gases
IPCC	Intergovernmental Panel on Climate Change
MB	Meshblock
MLST	Multi-locus sequence typing
NIWA	National Institute of Water and Atmospheric Research
NZDep	New Zealand Index of Socio-Economic Deprivation
SARIMA	Seasonal Auto Regressive Moving Average Model
SOI	Southern Oscillation Index
TA	Territorial Authority
UK	United Kingdom
US	United States
YLD	Years Lost to Disabilitie

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SECTION I: CHAPTER 1 GENERAL INTRODUCTION

1.1 Global change and zoonotic diseases

Globalisation and population growth, in conjunction with intensified agricultural production has, and will, result in unprecedented human modification of ecosystems (Jackson, Kirby et al. 2001, Ellis, Klein Goldewijk et al. 2010). The impacts of such large scale biophysical changes will test the resilience of humans and the natural systems we rely on (IPCC 2007). Of concern is the rise of infectious diseases in humans, and the role of animals in their transmission (Wilcox and Gubler 2005). Over 60 % of known infectious agents pathogenic to humans are zoonotic (Taylor, Latham et al. 2001), with over three quarters of recorded emerging infectious disease events originating in a non-human animal source (Jones, Patel et al. 2008). One of the best known illustrations of this threat is the H1N1 influenza virus, introduced from domestic swine. Within months of being detected in 2009, this strain caused the first human influenza pandemic of the twenty-first century (Smith, Vijaykrishna et al. 2009).

Changes in climate and land use patterns have been implicated in the rising incidence of zoonotic diseases in humans (Lambin, Tran et al. 2010, Mills, Gage et al. 2010). In Australia, 24 % of the reviewed emerging infectious diseases in humans were associated with native vegetation loss and land cover change (McFarlane, Sleigh et al. 2013). These environmental changes can facilitate pathogen evolution and adaptation (Gandon, Hochberg et al. 2013), can introduce previously unexposed populations to pathogens, thereby expanding host range (Jones, Patel et al. 2008), and provide better ecological conditions for pathogen transmission (Murray and Daszak 2013).

In an examination of the global burden of zoonoses as estimated using Disability Adjusted Life Years (DALYs), zoonoses accounts for an estimated 26 % of the total infectious disease burden in low income countries and 0.7 % in high income countries (Grace, Gilbert et al. 2012). A recent report that highlights the overlap between zoonoses and poverty hotspots suggests that relatively few countries are excessively burdened with both poor livestock farmers and zoonoses (Grace, Mutua et al. 2012). These populations will also experience increasing climate

variability and intensified livestock production (Thornton, van de Steeg et al. 2009, Thornton 2010). Thus, in regions with inadequate resources for disease control and prevention, environmental changes could become a dominant driver of human zoonotic diseases. A constraint to management is our rudimentary understanding of how ecological processes interact with social factors to drive infectious disease emergence and spread (Weiss and McMichael 2004, Plowright, Sokolow et al. 2008).

The policy relevant “One Health” approach recognises the interdependency between ecosystems, human and animal health (United Nations 2008). In reality, there is little integration across these disciplines, with policy responses continuing to be sector specific. The absence of a common framework linking the animal and human interface is commonly cited as an important reason for this disciplinary segregation (Coker, Rushton et al. 2011). Clarifying the role of large scale environmental processes will develop our understanding of how wider socio-environmental interactions can mediate zoonotic disease risk. Modelling historical relationships of environmental and social factors with disease incidence will improve models that predict health responses under scenarios of environmental change. The aim is to reflect in policy the important role of large scale environmental processes in influencing human health (Parkes, Bienen et al. 2005, Parkes and Horwitz 2009).

1.2 Chapter aim

To provide a broad overview of the importance of enteric zoonotic diseases and the factors that historically determined disease patterns. Here, I introduce and provide the conceptual framework to underpin this thesis; and explore how large scale climatic variability and agricultural land use can independently, and together with social and demographic factors, influence the patterns of human enteric zoonoses.

1.3 Enteric zoonotic infections

Enteric infection is a global health concern as it is a leading cause of illness and death (Eisenberg, Trostle et al. 2012). The total annual number of diarrheal

illnesses is estimated at 2.8 billion (Kosek, Bern et al. 2003). In 2011, an estimated 700,000 diarrhoeal episodes resulted in death (Walker, Rudan et al. 2013). As diarrhoea is an indicator of enteric infection (Norman, Pedley et al. 2010), the total burden of enteric infections including asymptomatic patients is likely to be higher. In the United States (US) from 1989-1996, the average, annual percentage increase in the number of deaths related to enteric infection in the elderly was 116 % (Peterson and Calderon 2003). While enteric infections tend to be self-limiting, they can be fatal in susceptible populations such as children, the elderly and the immune compromised (Stark, Barratt et al. 2009, Lund and O'Brien 2011).

The enteric zoonotic pathogens *Giardia*, *Cryptosporidium*, *Campylobacter* and *Salmonella* were chosen as the focus for this thesis. The choice of enteric pathogens for this study is based on their contribution to enteric disease burden worldwide, and their transmission cycles being classified as 'environmentally mediated, including non-human hosts- Group IIIb' (Eisenberg, Desai et al. 2007). These characteristics make them particularly sensitive to environmental changes, and especially relevant to this thesis.

It has been estimated that 93.8 million cases of gastroenteritis due to non-typhoidal *Salmonella* occur annually (Majowicz, Musto et al. 2010). In Europe, projection of the economic costs of additional cases of salmonellosis that result from climate change effects in 2071-2100 are €140 million to €280 million per annum (Watkiss and Hunt 2012). In Australia, compared with the Years Lost due to Disabilities (YLDs) in 2000, "increasing temperature and demographic changes may lead to a 9 %–48 % increase in the YLDs for *Salmonella* infection by 2030 and a 31 %–87 % increase by 2050 in the temperate region, and a 51 %–100 % increase by 2030 and an 87 %–143 % increase by 2050 in the subtropical region, if other factors remain constant" (Zhang, Bi et al. 2012).

Similarly, campylobacteriosis is estimated to affect 13 million people annually in the US (Altekruse and Swerdlow 2002), with the 2002 costs of campylobacteriosis in the Netherlands estimated at €21 million per annum (Mangen, Havelaar et al. 2005). In New Zealand, an increase in

campylobacteriosis risk is predicted with projected increases in average weekly rainfall and absolute humidity (Brock 2011).

Giardia and *Cryptosporidium* are the most frequently isolated enteric parasites of both humans and domestic animals (Hunter and Thompson 2005), which is indicative of considerable zoonotic transmission. *Cryptosporidium* has been identified as one of the enteric pathogens associated with increased case fatality in children between 1-2 years of age in developing countries (Kotloff, Nataro et al. 2013). This is in contrast to *Campylobacter* and *Salmonella*, which did not appear to contribute significantly to enteric infections in children (Kotloff, Nataro et al. 2013).

In several studies, these diseases are associated with cattle density (Jagai, Griffiths et al. 2010, Kabore, Levallois et al. 2010) and climatic variables (Kovats, Edwards et al. 2004, Kovats, Edwards et al. 2005, Britton, Hales et al. 2010), suggesting that climate and land use change may be important determinants of future distribution. The selected pathogens are also thought to have different dominant routes of transmission, which suggest different implications of future environmental change for disease occurrence.

1.4 Environmental and social determinants of enteric zoonotic diseases

I review the environmental and social determinants of human campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis adapting a framework developed to examine the environmental determinants of infectious disease (Eisenberg, Desai et al. 2007) and similar to that developed for public health surveillance (Baker, Easther et al. 2010).

Disease determinants are separated into distal and proximal components (Figure 1.1). First, I consider distal determinants, which influence disease transmission through a number of intermediate steps. Associations between distal climatic and agricultural factors and reported disease incidence are used to explore the role of climate variability and agricultural practices on pathogen survival and transmission. Proximal exposures directly determine disease transmission. Here, I

consider population and individual-level characteristics that can influence exposure and subsequent spread. I also suggest global to individual level environmental, social, public health and clinical interventions to help reduce future disease burden.

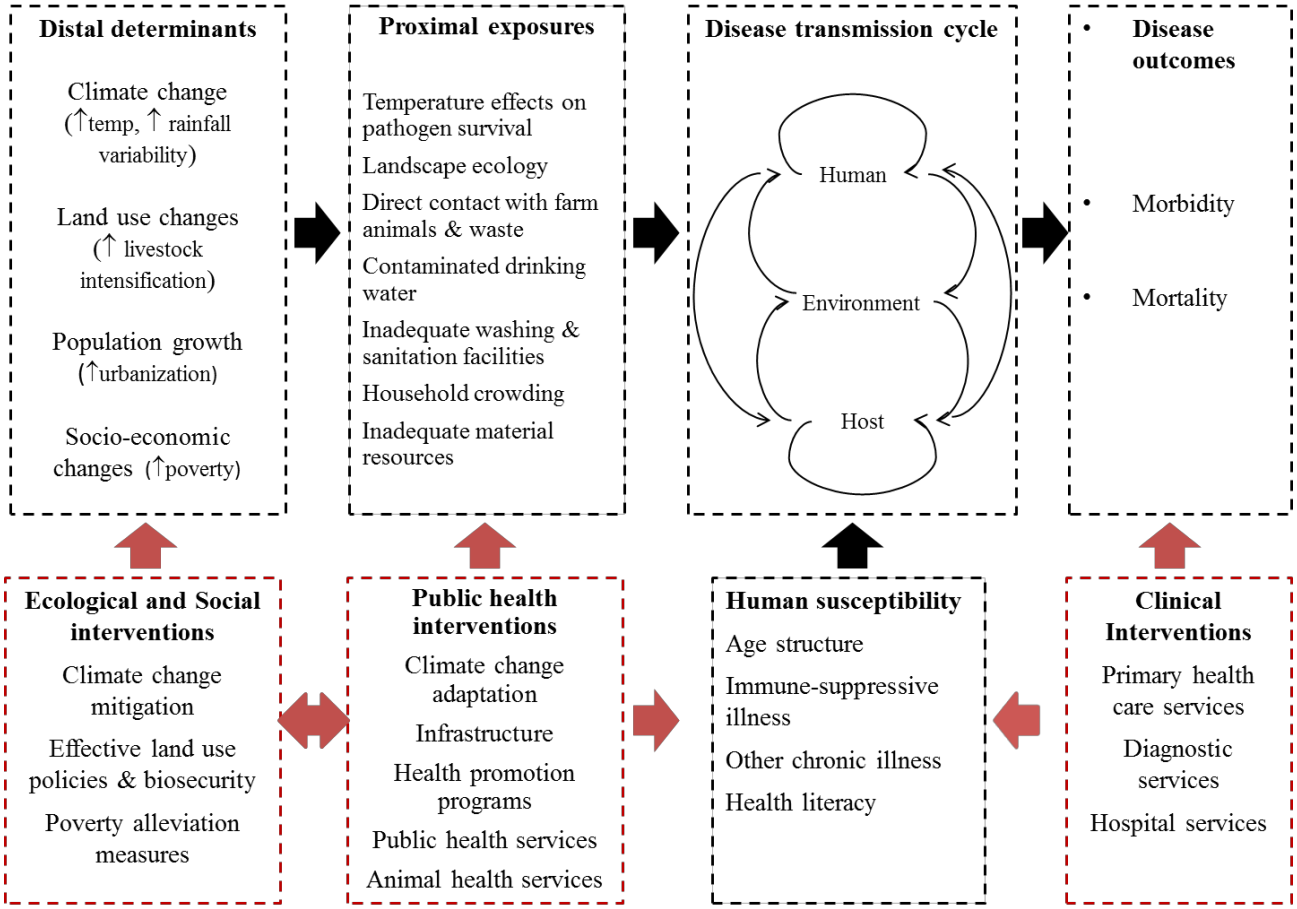


Figure 1.1 Environmental and social factors that influence enteric zoonotic disease incidence. Distal determinants influence proximal determinants which in turn modify the disease transmission cycle to influence disease risk. The transmission cycle includes animal hosts and environmental reservoirs. Interventions operate at multiple levels, including: (1) Global ecological and social interventions to reduce environmental pathogen load); (2) Public health interventions to reduce population exposure to pathogens and (3) Individual level, clinical interventions to improve disease outcomes (adapted from Lal et al. 2013)

1.4.1 Climate variability, land use change and enteric zoonotic diseases

The Fourth Assessment Report of the Intergovernmental Panel on Climate Change (IPCC) documents a global temperature rise of almost 1°C over the last century with further increases projected, depending on the extent of future greenhouse gas (GHG) emissions into the atmosphere (IPCC 2007). Along with increased temperatures, global sea level rise, changes in precipitation patterns and an increase in frequency of extreme weather events are forecast (IPCC 2007). Concurrently, conversion of land for agricultural production has been cited as the most dominant driver of land cover change globally (Hansen, Stehman et al. 2008), with significant forest cover loss (Hansen, Stehman et al. 2010). If current trends of agricultural intensification in industrialised countries and sustained land clearing (extensification) in emerging economies continue, ~1 billion hectares of land would be cleared globally by 2050 (Tilman, Balzer et al. 2011). Over the same period, the global livestock population is projected to increase from 1.5 billion to 2.6 billion (Rosegrant, Fernandez et al. 2009). Taken together, climate change and intensification of livestock production will be two of the biggest environmental influences on society.

1.4.1.1 Climate change

The bacterial diseases, campylobacteriosis and salmonellosis tend to peak in summer and decrease in winter (Kovats, Edwards et al. 2004, Kovats, Edwards et al. 2005, Keegan, Majowicz et al. 2009). Bacterial pathogens are sensitive to changes in heat, moisture, oxygen, light and nutrients (Griffiths and Park 1990). Increased temperatures could provide optimal conditions to enhance pathogen survival and proliferation (D'Souza, Becker et al. 2004, Kovats, Edwards et al. 2004), and therefore increase pathogen load in animal reservoirs (Ravel, Smolina et al. 2010) and prolong transmission seasons (Semenza and Menne 2009). Warmer temperatures may also influence human host behaviour such as barbequing, providing opportunities for pathogen transmission through consumption of undercooked food (Eberhart-Phillips, Walker et al. 1997).

Historical time- series modelling of cryptosporidiosis incidence with rainfall have reported positive associations in a global meta-analysis of cryptosporidiosis seasonality (Jagai, Castronovo et al. 2009). High rainfall may increase runoff,

contaminating water sources (Tryland, Robertson et al. 2011) and cause resuspension of infectious oocysts from river beds and storm drain sediments (Atherholt, LeChevallier et al. 1998). *Giardia* spp. and *Cryptosporidium* spp. are also resistant to conventional water treatment techniques (Coffey, Bergin et al. 2010). Therefore, the increased pathogen load resulting from heavy rainfall may overwhelm drinking water and sewage infrastructure, leading to outbreaks. The influence of extreme precipitation and flooding may be more direct, severe and long lasting for populations that are socially, economically and/or geographically marginalised (Ahern, Kovats et al. 2005). Deliberate migration and forced displacement resulting from the loss of food and freshwater sources, homes and livelihoods are expected with such extremes (McMichael and Lindgren 2011). In the absence of adequate infrastructure, follow on effects such as insufficient shelter and sanitation, poor nutrition and limited healthcare access may increase disease incidence in these populations.

Conversely, a global cross sectional study of diarrhoeal incidence in children under 5 years found a negative association between rainfall and diarrhoea rates (Lloyd, Kovats et al. 2007). In Australia, a negative relationship between weekly rainfall, relative humidity and cryptosporidiosis incidence and a positive association with temperature suggests that extended dry periods may also affect transmission (Hu, Tong et al. 2007, Hu, Mengersen et al. 2010). Droughts can lead to greater effluent pathogen concentration in surface and groundwater sources (Ajeagah, Njine et al. 2010) and increased run off from unsaturated land (Boxall, Hardy et al. 2009). Subsequent periods of intense rainfall can result in the flushing out of this high pathogen load, resulting in increased disease occurrence. Prolonged dry conditions can decrease the permeability of the soil thereby increasing flooding risk (Stanke, Kerac et al. 2013). In poorer countries, water scarcity may result in substandard sanitation (Singh, Hales et al. 2001), while unreliable water supply may necessitate water storage (Ayalew, Boelee et al. 2008). Extreme rainfall could contaminate stored water leading to outbreaks.

Effective climate change adaptation will play a vital role in determining the ability of future populations to cope with climate change related health impacts (Figure 1.1) (Ebi and Burton 2008). Potential adaptation options, which are not specific to

climate change, include stricter regulation of food production practices, improved water and sanitation infrastructure and increased protection of water sources.

1.4.1.2 Land use changes

Positive associations of disease incidence with livestock density in New Zealand (Snel, Baker et al. 2009), the US (Jagai, Griffiths et al. 2010) and Scotland (Pollock, Ternent et al. 2009), and higher infection rates in rural areas in Canada (Odoi, Martin et al. 2004, Odoi, Martin et al. 2004), suggest that livestock are a major source and reservoir for human enteric disease. In Scotland, human *Cryptosporidium* hominis (human strain) cases were associated with higher population density, while high ruminant density and rural living were associated with increased risk for *C*. parvum (livestock strain) cases (Pollock, Ternent et al. 2009). In the Netherlands, while chicken was the leading *Campylobacter* reservoir in urban children, cattle was the major risk factor for rural children (Mughini Gras, Smid et al. 2012). In New Zealand, campylobacteriosis source attribution studies have found that ruminant strains pose a greater risk to rural children (Mullner, Shadbolt et al. 2010). In the South Island, peak infection rates of a predominantly livestock strain of *Salmonella* in humans have been reported to coincide with a seasonal epidemic in sheep (Clarke and Tomlinson 2004). Thus, agricultural land use, in particular livestock production, may enhance zoonotic infection risk to humans.

Agricultural land use can modify landscape structure and aquatic ecosystem functioning (Wilkes, Edge et al. 2009), with consequences for pathogen infectivity and transport (Johnson, Townsend et al. 2010). Transport networks constructed in support of agriculture can affect pathogen spread (Myers and Patz 2009) and constrain (Bates, Trostle et al. 2007) or promote population connectivity (Trostle, Hubbard et al. 2008). Thus, landscape structure may also play an important role in disease transmission by determining the degree to which ecological systems are physically connected and human populations are socially interconnected.

Determining the effect of interactions between climate change and livestock production on disease occurrence in humans is particularly challenging (Boxall, Hardy et al. 2009). Climatic changes will affect livestock forage quality and

quantity, water availability and stock susceptibility to infection, all of which will eventually influence zoonotic transmission potential to humans (Thornton, van de Steeg et al. 2009). Given the potential for future climatic changes and intensive livestock production, interventions aimed at known pathways could help reduce human disease burden (Figure 1.1). For example, waterborne transmission of pathogens from livestock during periods of heavy rainfall can be limited by good management. A recent study found that vegetated strips when placed near dairy calf areas significantly reduced the concentration of *Giardia* cysts in runoff during storm events (Miller, Lewis et al. 2007). As young livestock have the highest pathogen load, targeted control measures aimed at young cattle could reduce the size of the infection reservoir. Farm level responses to expected changes in climate are likely to be a major determinant of future zoonotic disease incidence in humans (Morgan and Wall 2009). At the regional level, land use policies should consider pathogen transmission among and across animal populations (Figure 1.1) (Quine, Barnett et al. 2011). Ultimately, this could benefit public health, by reducing the risk of zoonotic transmission.

Based on this review, Table 1.1 summarises the ways in which a changing climate and livestock intensification can influence environmental pathogen load and subsequent transmission.

Table 1.1 Influence of environmental changes on enteric zoonotic pathogens

Expected environmental change	Effect on pathogen survival/transmission[a]	Change in risk[b]
Increasing temperature	↑ Oocyst die off rate	-
	↑ Desiccation	-
	↑ Mechanical transmission by alternate vectors	+
	↑ Lengthening of transmission season	+
	↑ Introduction into areas previously too cold	+
Increasing rainfall	↑ Runoff	+
	↑ Re-suspension of oocysts in water courses	+
	↑ Flooding	+
	↑ Contamination of water courses by sewage effluent	+
Decreasing rainfall	↑ Concentration in water courses	+
	↑ Water storage	+
	↓ Runoff	-
	↑ Runoff from unsaturated land	+
	↑ Contamination of groundwater sources	+
Livestock intensification	↑ Pathogen sources/reservoirs	+
	↑ Contamination of water courses	+
	↑ Contamination of food sources	+
	↑ Population Connectivity	+
	↓ Population Connectivity	-
	↑ Ecological Connectivity	+
	↓ Ecological Connectivity	-

[a](↑) Increase, (↓) Decrease
[b] (+) Increase in disease risk, (-) Decrease in disease risk

1.4.2 Socio-economic changes

Campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis are common enteric infections in poor countries (Guerrant, Hughes et al. 1990). Although the Global Burden of Disease estimates show that there has been a recent decline in the communicable diseases (Lozano, Naghavi et al. 2012), the burden of diarrhoeal diseases is poor countries continues to be substantial (Murray, Vos et al. 2012). Here, I concentrate on distal determinants such as socio-economic

changes that most likely to explain health disparities between high and low income nations. I also highlight the role of proximal exposures such as population behaviour and individual age and immune status in determining exposure and susceptibility to infection.

1.4.2.1 Socio-economic factors and infrastructure

Reducing socio-economic inequalities can lessen population vulnerability to global environmental change (McMichael, Friel et al. 2008). For example, in the US, being elderly, socio-economically disadvantaged and having inadequate access to health care was associated with cryptosporidiosis and giardiasis risk following a flood (Collins, Jimenez et al. 2012). Another study showed that unemployment rate and lower educational status were significant risk factors for campylobacteriosis (Weisent, Rohrbach et al. 2012). These findings suggest suggests that populations with adequate economic resources will be more resilient to the effects of environmental change.

For rich countries, steps to increase adaptation capability may involve strengthening and extending the population coverage of existing infrastructure such as water supplies (Figure 1.1). In England and Wales, it was estimated that targeted strategies aimed at improving drinking water supplies would lead to a reduction of ~6770 cryptosporidiosis cases in the community every year (Lake, Nichols et al. 2007). Similarly, the >50% drop in campylobacteriosis cases in New Zealand following poultry industry interventions (Sears, Baker et al. 2011) suggests that for developed economies, enhanced food regulation and enforcement could minimise food-borne transmission of these pathogens (Lake, Gillespie et al. 2009). In contrast, for developing nations, there is an urgent need to provide basic improvements such as microbiologically safe drinking water (Souter, Cruickshank et al. 2003) and sanitation facilities which could help protect against enteric infections in these low income settings (Figure 1.1).

1.4.2.2 Population behaviour

Frequency of exposure to pathogens is, to a large extent, driven by human behaviour. In Zambia, the peak in *Cryptosporidium* infections at the start of the rainy season (Nchito, Kelly et al. 1998) has been attributed to renewed watering holes serving as a playing area for children and water source for animals, with

increased opportunities for zoonotic transmission (Morse, Nichols et al. 2007). Foreign travel plays an important role in explaining summer peaks in campylobacteriosis and salmonellosis in the UK and Europe, with differences in seasonality due to the countries visited and dominant strains prevalent in these destinations (Ekdahl and Andersson 2004, Ekdahl, de Jong et al. 2005).

Historically, increasing affluence has resulted in a shift towards increased livestock production (Thornton 2010). In China, the diversification of diets and increasing income – coupled with comparatively poor food safety mean that food-borne parasitic zoonoses have become a considerable public health concern (Zhou, Chen et al. 2008). This aspect of changing human consumption patterns is of special significance in this thesis. From 2008 to 2012, dairy exports from New Zealand to China showed a five-fold increase, while sheep meat exports more than tripled (Statistics New Zealand 2012). According to the Ministry of Primary Industries, "New Zealand dairy production has risen 77 % over the past 20 years - from three million dairy cattle in 1989 to six million dairy cattle in 2009". Importantly, this growth is forecast to continue. This rising demand has important implications for livestock production and subsequently, the potential for zoonotic transmission from livestock in New Zealand.

1.4.2.3 Individual characteristics

Individual factors such as age and immune status may be important in conferring effective protection, or increasing vulnerability to disease. Individual factors can influence the pathogen load in humans and their ability to spread. In Germany, researchers found that compromised immunity was a risk factor for symptomatic *Giardia* infections (Espelage, an der Heiden et al. 2010). A retrospective study of a cryptosporidiosis outbreak in New Zealand found a risk reduction in males associated with farming activities (Grinberg, Pomroy et al. 2011), suggesting possible immunity due to sustained exposure. Interestingly, in a comparison of *Campylobacter* infection in developing and developing countries, it was reported that infections in developed countries tended to be at an older age and generally of a single strain as compared to infections in developing countries. Authors attributed this to the frequent and multiple exposures at infancy to a wide range of *Campylobacter* strains present endemically in developing countries, resulting in

host immunity which prevents subsequent infection at a later age (Havelaar, van Pelt et al. 2009). Thus, while population socio-economic factors, infrastructure and culture affect exposure to pathogens, intrinsic host characteristics influence susceptibility to infection and transmission potential.

Decreasing susceptibility to infection may be achieved by targeting interventions at the individual level. These include increasing social protection measures, health care education, disease surveillance as well as developing clinical tools to aid early diagnosis of conditions that may increase vulnerability to these diseases (e.g. HIV) (Figure 1.1).

In summary, this review emphasises the significant influence of climatic factors and agricultural land use patterns on enteric pathogen load and transmission. It also indicates that population characteristics will serve either as an amplifier or a buffer for the extent of exposure to this environmentally sensitive pathogen load. The framework presented here offers a preliminary template to understand the complex interactions between environmental and social factors in driving enteric disease risk. It supports the view that incorporating the dynamic nature of these relationships is necessary to provide a more realistic picture of possible health responses to future environmental change (McMichael 2013). In addition, it shows that ecological, social and public health interventions may be integrated to enhance ecosystem and human health.

Of key relevance to this thesis, the framework shows that our currently limited understanding of these interactions is likely to worsen the uncertainties associated with predictions of health impacts due to future environmental change. My thesis will address this issue by examining how environmental and social factors influence the spatial and temporal patterns in enteric zoonoses in New Zealand.

1.5 New Zealand: A microcosm for assessing the role of environmental and social factors on enteric zoonotic disease

New Zealand has recently experienced rapid agricultural intensification (Bouwman, Goldewijk et al. 2011). Increased livestock stocking rates (MacLeod and Moller 2006) is considered one of the keystones to achieving this greater agricultural production (Statistics New Zealand 2012). Sustained international

demand and economic incentives has resulted in an increase in dairy cattle numbers by 23 % from 5.2 million cattle in 2007 to 6.4 million in 2012 (Statistics New Zealand 2012). Such intensification of livestock production may increase the public health risk from zoonotic pathogens (Crump, Murdoch et al. 2001, Derraik and Slaney 2007). Although wildlife is acknowledged as a source of enteric pathogens, recent work on *Campylobacter* has shown that a small proportion of human cases may be attributed to wildlife genotypes found in environmental water (Mullner, Jones et al. 2009) and that these genotypes show the lowest similarity with human isolates (French N and Molecular Epidemiology and Veterinary Public Health Group Hopkirk Institute 2008).

While local weather variations are influenced by New Zealand's topography, historical evidence from marine and sediment cores are indicative of a substantial effect of regional climate. The most notable regional influence on New Zealand's climate are the El Niño Southern Oscillation (ENSO) (Gomez, Carter et al. 2004) and the Interdecadal Pacific Oscillation (IPO) (Salinger, Renwick et al. 2001). Through its effect on regional circulation patterns, global climate change may have a substantial impact in New Zealand (Plummer, Salinger et al. 1999), with potentially considerable health risks (McMichael, Woodruff et al. 2003).

This evidence raises the question – do the historical relationships between climate variability, livestock land use and enteric zoonotic diseases indicate that projected environmental change may influence the burden of enteric zoonotic diseases in New Zealand? What are the social and demographic factors that may worsen, or enhance, human health in the face of such environmental change?

1.6 How this thesis contributes to our understanding of the environmental and social factors influencing enteric zoonotic disease incidence

The overall aim of this thesis is to gain an advanced understanding of how global environmental changes, specifically climatic variability and agricultural intensification, interact with social and demographic factors to influence human health.

1.6.1 Thesis Objectives

This thesis has three main objectives.

Fundamental to this research was establishing the importance of environmental and social factors in determining enteric disease incidence, and assessing the implications of future environmental change for disease risk.

Objective 1: To develop a framework to understand how environmental and social factors interact to influence enteric zoonotic diseases (Chapter 1) and describe the potential for these factors to influence enteric disease patterns in New Zealand (Chapter 2 and 3).

While seasonality in these diseases is widely acknowledged; the likely drivers of such patterns are less well understood. Understanding seasonal patterns could provide important insights into seasonal determinants of enteric disease risk.

Objective 2: To assess commonalities and differences in seasonal patterns across geographical regions (Chapter 4), followed by a detailed evaluation of temporal variations in disease incidence in New Zealand (Chapter 5 and 6).

To understand how projected environmental change will impact human health we require a comprehensive understanding of how the environmental and social determinants identified in Section 1.4 interact across space and time to influence enteric disease patterns in New Zealand.

Objective 3: To identify the likely dominant environmental and social drivers and transmission pathways in different regions and seasons by assessing space-time interactions in disease patterns (Chapter 7, 8 and 9).

1.6.2 Thesis methodology

Traditional methods in the health sector to evaluate disease risk from specific exposures have been to define direct cause-effect associations relating to individual diseases, rather than long term, large scale processes having widespread health effects acting through multiple pathways (Campbell-Lendrum, Corvalán et al. 2007). Disease causation and risk factors are attributed to individual characteristics with the underlying assumption that populations are groups of individuals (Diez-Roux 1998). The narrow view may act as a barrier to

creating public health policies focussed on climate change effects. The wider socio-ecological environment sets the context for disease transmission and maintenance in a population (McMichael 1999) and is key to determine exposure and susceptibility to infection (Pearce 1996), particularly to environmental changes. When assessing the health impact of large scale processes such as environmental change, there is an increasing need to "focus on methodologies that that address the ''real-world'' complexities such as multi-factorial causal webs and non-linear dose response relationships" (Xun, Khan et al. 2010). This methodology presents the challenge of integrating complex often competing objectives of environmental sustainability, social equity and human health. Nonetheless, this eco-epidemiological approach is crucial to understand infectious disease dynamics and underpins the work in this thesis.

In this thesis I present a combination of novel applications of existing methods as well as development of new statistical approaches to understand how environmental and social factors can interact to influence disease patterns. For example, although the Gini co-efficient was developed for economic analysis in 1912 (Gini 1912), it has been innovatively applied in Chapter 4 to understand seasonality in enteric diseases. Although preliminary, I present the first analysis of the association between runoff and disease incidence using Distributed Lag Non-Linear Models (DLNM) in Chapter 6. Using recently developed computer intensive methods, I am able to simultaneously examine the fine spatial and temporal associations between environmental and social factors and disease incidence in Chapter 9. Through the eco-epidemiological research presented in this thesis, I build on existing approaches that integrate spatial and statistical methods and contribute to the development of new analytical tools. These methods may be modified and applied by public health authorities to describe and identify the environmental and social determinants of other infectious diseases.

1.6.3 Thesis structure

This thesis is composed of three sections (Figure 1.2). Due to the different approaches used, detailed methods are addressed individually in each chapter.

Section I (Chapters 1-3) address Objective 1. These chapters are descriptive, and review the influence of environmental and social factors on enteric disease

incidence, synthesise the previous relevant research in New Zealand and present a description of campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis cases in New Zealand from 1997-2008. This section provides an overview of the likely environmental and social determinants of enteric zoonoses, globally, and in New Zealand.

In Chapter 2, I synthesise previous research in New Zealand to assess the potential for climatic change and agricultural intensification to influence enteric zoonotic disease risk. This chapter provided a rationale for why this thesis was important in a New Zealand context. Chapter 3 is a description of the epidemiological characteristics of campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis cases from 1997-2008 in New Zealand. Notification and hospitalisation trends in season, age, sex, rurality, ethnicity and socio-economic deprivation are compared across the four diseases. I used this chapter to determine which demographic factors were likely to affect the spatial and temporal variability in incidence patterns and needed to be considered for subsequent analyses.

Section II (Chapters 4-6) address Objective 2. I establish the evidence for seasonality in campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis and assess temporal associations of enteric disease incidence with climatic variables in New Zealand. In this section I provide a snapshot of global seasonality in these diseases and provide a detailed analysis of the role of climatic factors in influencing seasonal patterns in enteric diseases in New Zealand. To better understand temporal variability in these diseases, I begin this section with a global review of seasonality across the four diseases (Chapter 4). The next two chapters quantify the temporal association between climate variation and disease incidence in New Zealand using time-series methods. In Chapter 5, I use Seasonal Autoregressive Integrated Moving Average (SARIMA) models to investigate the association between monthly disease incidence and regional climate variability. In an effort to understand how rainfall may influence disease incidence through agricultural runoff, in Chapter 6 I use Distributed Lag Non-Linear (DLNM) models to investigate the relationship of weekly runoff rate and enteric disease incidence.

Sections III (Chapters 7-9) address Objective 3. In this section, I consider both space and time dimensions. *Cryptosporidium* spp. and *Giardia* spp. infections have been identified as 'Neglected Diseases' by the World Health Organisation (Savioli, Smith et al. 2006).These pathogens have a high probability of infection at low doses with a high excretion rate, and are resistant to a range of chemical treatments (Dumètre, Aubert et al. 2012). This section is committed to understanding the epidemiology of cryptosporidiosis and giardiasis in New Zealand.

To detect regions in New Zealand with recurrent disease clusters, I use SaTScan in Chapter 7 to identify space-time clusters for cryptosporidiosis and giardiasis. In Chapter 8 using a Bayesian approach, I illustrate spatial patterns in the relative risk of cryptosporidiosis and giardiasis across the country. Through an analysis of temporal patterns in outbreak probability I identify plausible outbreaks. In Chapter 9 I use a multivariate, retrospective, spatio-temporal model to evaluate the influence of climatic (average weekly temperature and rainfall), land use (urban-rural status and livestock densities), population demography (population density, ethnicity, age, socio-economic deprivation, quality of public drinking water supplies) on cryptosporidiosis and giardiasis risk.

In Chapter 10, I summarise thesis findings to consider the implications of a changing climate, increasing agricultural intensification and changing demography for population health. I conclude with research challenges in the future.

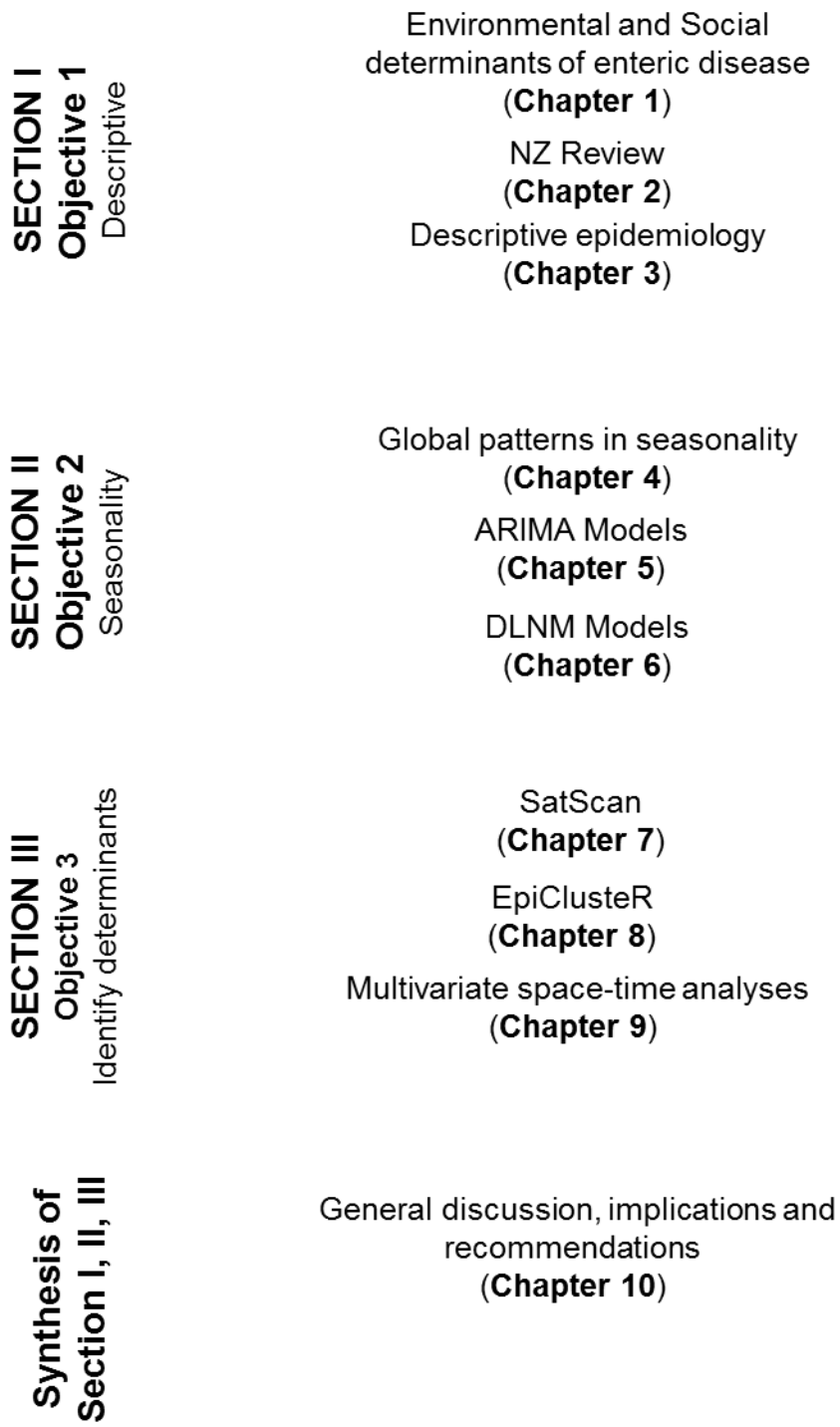


Figure 1.2 Diagrammatic representation of thesis structure

CHAPTER 2 WEATHER VARIABILITY, AGRICULTURAL LAND USE AND ENTERIC ZOONOTIC DISEASES IN NEW ZEALAND

2.1 Introduction

Recent trajectories of land use and climate change (IPCC 2007, Tilman, Balzer et al. 2011) suggest that human pressures on ecosystems will increase in the future, with important implications for infectious disease risk (Cutler, Fooks et al. 2010, Murray and Daszak 2013) (Chapter 1).

In New Zealand, rates of zoonotic enteric disease in humans are among the highest reported for any developed country (Baker, Sneyd et al. 2007, Snel, Baker et al. 2009) and are a major public health concern (Lake, Cressey et al. 2010). A pastoral focused economy is frequently cited as a significant reason for this pattern (Crump, Murdoch et al. 2001, Derraik and Slaney 2007), since livestock are an important pathogen reservoir (Davies-Colley, Nagels et al. 2004, Grinberg, Pomroy et al. 2005). Furthermore, in other countries, climate variability has been linked with increased enteric disease (Fleury, Charron et al. 2006). New Zealand also has recent trends of increased surface temperatures and increased frequency of extreme weather events (Plummer, Salinger et al. 1999, Gehrels, Hayward et al. 2008). Reviewing the role of weather and agricultural land use variables on enteric disease risk in New Zealand would clarify the ways in which these environmental factors may influence zoonotic disease incidence. Ultimately, this knowledge may help anticipate and manage infection risks.

2.2 Chapter aim

This chapter presents a critical appraisal of previous research that assess the influence of weather and agricultural land use variables on the incidence of enteric zoonotic diseases in New Zealand. By highlighting important gaps in the research, this chapter provides a rationale for the current study. For the purposes of this thesis, agricultural land use variables are used as indicators of ecological change that may influence pathogen load, transmission and opportunities for pathogen-host contact.

2.3 Methods

2.3.1 Systematic search strategy

PubMed, Web of Science and Embase, were searched for publications that quantified the association between climatic factors and/or agricultural factors and campylobacteriosis, salmonellosis, giardiasis and cryptosporidiosis incidence in humans. The keywords used were: ("New Zealand", "climate" "weather", "land use" "agriculture", "zoonotic", "enteric"), AND ("campylobacteriosis" "campylobacter", "salmonellosis" "salmonella", "cryptosporidiosis" "cryptosporidium", "giardiasis" "giardia"). No language, time or database restrictions were imposed on the searches. For each disease, citations resulting from the database searches were exported into a master library, and duplicates removed based on parameters of identical author, date and title. Full-text versions of the articles that fulfilled our eligibility criteria were obtained and their reference lists were manually searched to identify any further relevant manuscripts. We also examined the bibliographies of narrative reviews and records published on pathogen specific epidemiology to identify additional sources for inclusion in the analysis. Additionally, the websites for the Ministry of Health and the Ministry for Primary Industries were searched for relevant publications.

2.3.2 Study selection

Screening of articles for eligibility involved evaluating the studies using the following *a priori* criteria. Studies were included if: (i) one of the primary outcomes was disease incidence as measured by a laboratory confirmed diagnosis of the enteric pathogen of interest, (ii) one of the primary exposure measures was a relevant climatic or land use variable. A relevant climatic or land use variable was one that was explicitly quantified (e.g. monthly temperature, measure of land use). As the main aim of the study was to evaluate the importance of climatic and agricultural land use variables on disease incidence in humans, literature that assessed pathogen prevalence in different sources but did not relate them to disease incidence in humans were not included. For the same reason, studies that focussed solely on pathogen microbiology, immunology and molecular ecology were excluded. Additionally, (iii) the study had to be published in a peer reviewed journal or be a government commissioned paper; although published reviews were used as a source for additional papers, they were not included, (iv) disease incidence needed to be a measure of sporadic disease as outbreak focussed studies

may not be indicative of the general association with environmental exposures, and (v) if study design was experimental or an intervention trial, then disease incidence needed to be an outcome measure.

2.4 Results

Of the 137 titles and abstracts identified and screened for eligibility from the database search, a total of 16 studies met the selection criteria and contributed to the systematic review. The results of the search strategy and study selection are given in Figure 2.1. Of the 16 articles, six were identified through the databases, seven through the reference lists of eligible articles, one through contacting local experts and two through the government ministry websites. All studies were published in the last ten years and study duration ranged from 12 weeks to 41 years. Table 2.1 records the main research question, description of study exposure and outcome measure, limitations and main findings for each study.

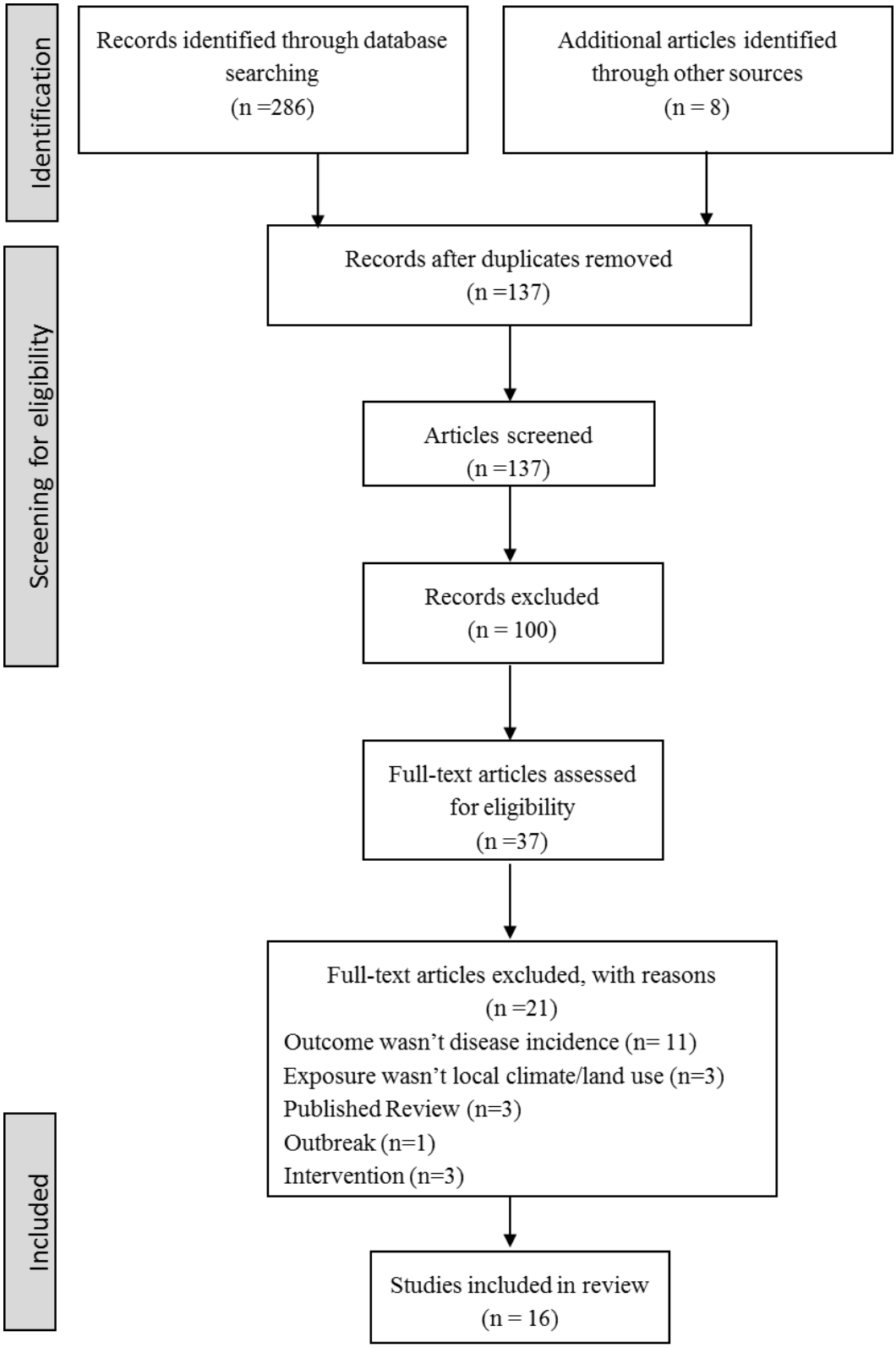


Figure 2.1 Flow diagram illustrating search strategy and selection of studies for final review

2.4.1 Climate

Four studies assessed the influence of weather variables on enteric disease incidence in New Zealand with all four diseases being considered (Table 2.1). For campylobacteriosis, a positive association between warmer winters and an earlier onset of the peak week of infections compared to other countries was reported (Kovats, Edwards et al. 2005, Lloyd, Kovats et al. 2007). For salmonellosis a positive association with temperature was found, with a 15% increase in disease rates projected for every 1°C rise in ambient temperature (Britton, Hales et al. 2010).

Climatic associations with cryptosporidiosis was assessed temporally (monthly) (Lake, Pearce et al. 2008) and spatially at the Census Area Unit (CAU) scale (Britton, Hales et al. 2010). Lake et al (2008) reported a significantly (p> 0.001) positive association with temperature of the current and preceding month in summer-autumn (January to May).

Britton et al (2010) found that for both cryptosporidiosis and giardiasis, the rainfall to evaporation ratio was significantly positively associated with cases. For cryptosporidiosis, better quality drinking water supplies (as categorised by the ESR Water Programme which uses zone code and protozoa compliance to assess public health risk) reduced the effect of rainfall on disease incidence. Cryptosporidiosis was significantly negatively associated with temperature, while giardiasis was marginally positively related to temperature. Rural areas had higher cryptosporidiosis rates, with both diseases having higher notification rates in more affluent locations.

2.4.2 Agricultural land use

Twelve studies across all four diseases examined the influence of agricultural land use variables (Table 2.1). Five studies focussed on dairy cattle as the principal pathogen source (Close, Dann et al. 2008, Gilpin, Scholes et al. 2008, Winkworth, Learmonth et al. 2008, Pearl, Louie et al. 2009). Three of these studies compared human and cattle isolates using molecular techniques (Learmonth, Ionas et al. 2004, Gilpin, Thorrold et al. 2008, Winkworth, Learmonth et al. 2008) without any associated risk factors from human samples, or indications of other environmental sources of infection. This effectively restricted any possible

hypotheses on quantification of risk from dairy cattle or possible transmission mechanisms. Also, as pathogenic potential and principle source can be strain and subgenotype specific (Fearnley, Weinstein et al. 2010), the molecular analysis used here (Gilpin, Scholes et al. 2008, Gilpin, Thorrold et al. 2008, Winkworth, Learmonth et al. 2008, Pearl, Louie et al. 2009) are indicative only of prevalence in livestock.

Four studies evaluated the importance of waterborne transmission of enteric pathogens. Isolation of *Campylobacter* spp. from recreational river water samples found no molecular similarity with human cases, with authors inferring that the river was not a source of human infection (Eyles, Niyogi et al. 2003). A comparison of disease rates over a nine year period in Canterbury in areas with major irrigation schemes to other farming areas found a statistically significantly higher campylobacteriosis, cryptosporidiosis and salmonellosis risk for the former group (Close, Dann et al. 2008). In this study, major irrigation schemes were assumed to be linked to dairy farming. In another study, during times of peak river flow water samples were dominated by livestock strains, while during periods of low flow, wild bird strains dominated samples (McBride, Ball et al. 2011), suggesting that overland flow from livestock is a major source of enteric pathogens. A subsequent study showed a dominance of livestock-associated strains in winter water samples (French, Marshall et al. 2011).

Three studies described spatial associations of disease rates with environmental and demographic factors. One reported a stronger correlation of cryptosporidiosis rates with livestock density as compared to giardiasis (Snel, Baker et al. 2009). A second study showed that campylobacteriosis rates were higher in the South Island and negatively associated with socio-economic deprivation ($p<0.01$) and proportion of the population aged 25–44 years ($p<0.01$) (Rind and Pearce 2010). A study of three regions: Auckland, Canterbury and Manawatu at the meshblock scale by Spencer et al. (2011) found that social deprivation was associated with decreased relative risk in Canterbury (RR 0.96) ($p<0.1$), and Auckland (RR 0.95) ($p<0.05$). In Canterbury, proximity to poultry farms (>1000 birds) (RR 1.02) ($p<0.05$), sheep density (RR 1.03) ($p<0.01$) and dairy cattle density (RR 1.06) ($p<0.05$), were associated with significantly increased risks. In Manawatu, dairy

cattle density (RR 1.16) (p<0.01) was positively associated with disease risk while proximity to poultry farms was inversely related to risk (RR 0.95) (p<0.05).

A case-control study of human salmonellosis showed that *Salmonella* Brandenburg in sheep in spring was associated with increased human cases in spring (Baker, Thornley et al. 2007). Occupational contact with live or dead sheep (p<0.05) was associated with a significant increase in *Salmonella* infection risk.

2.5 Discussion

In New Zealand, climate and agricultural land use have a substantial effect on enteric disease incidence through their influence on environmental pathogen load and transmission pathways. In some regions, environmental pathogen load is considerable. Moreover, this pathogen load is evidently sensitive to ambient physical conditions while transmission and reporting is influenced by environmental and social and demographic factors.

An increase of 1.0°C in average summer temperatures since 1950 (IPCC 2007)and a decreasing trend in the diurnal temperature range (Easterling, Horton et al. 1997) has been noted in New Zealand. Campylobacteriosis and salmonellosis rates in New Zealand show positive associations with temperature (Kovats, Edwards et al. 2005, Britton, Hales et al. 2010). Traditionally food sources, and notably chicken meat, have been implicated in the transmission of these bacterial diseases in New Zealand (Müllner, Collins-Emerson et al. 2010, King, Lake et al. 2011), with similar food borne risk factors for campylobacteriosis in Australia (Stafford, Schluter et al. 2007, Stafford, Schluter et al. 2008). A recent decline in campylobacteriosis coinciding with interventions by the poultry industry (Sears, Baker et al. 2011) and the apparent weakening relationship between temperature and salmonellosis attributed to improved food safety (Britton, Hales et al. 2010) has also been reported. These findings suggest that interventions aimed at known transmission pathways could lessen the potential increase in salmonellosis and campylobacteriosis risk associated with a warming climate.

Although contaminated retail chicken remains the predominant source of campylobacteriosis in New Zealand (Müllner, Collins-Emerson et al. 2010), results from this review suggest that environmental sources of *Campylobacter*

may have been masked by the dominance of chicken. The studies reviewed here show that *Campylobacter* has been detected in cattle and sheep in New Zealand (Gilpin, Thorrold et al. 2008) and in surface and ground water in agricultural areas (Eyles, Niyogi et al. 2003, Close, Dann et al. 2008). Moreover, a spatial association of human infections with pastoral land use (Rind and Pearce 2010) and livestock density (Spencer, Marshall et al. 2011) and detection of campylobacteriosis in humans with occupational livestock contact (Gilpin, Scholes et al. 2008) has been documented. Indeed, for rural populations in New Zealand, ruminants are the leading source of *Campylobacter* infections (Garrett, Devane et al. 2007, Mullner, Shadbolt et al. 2010), with particularly high rates in rural pre-schoolers (McBride, Ball et al. 2011). Catchment scale modelling has shown wild bird strains of Campylobacter during reduced flow periods, with ruminant strains dominating during flooding (McBride, Ball et al. 2011), implicating agricultural runoff as a potential source of pathogens. Finally, detailed typing of *Campylobacter* samples from environmental water has revealed an overlap between ruminant strains and those isolated from human cases suggesting that untreated drinking water contaminated by livestock may be an important source of infection in rural areas (French, Marshall et al. 2011).

Comparatively less research has been done on establishing the environmental load of *Salmonella* and the potential for zoonotic transmission. Recurrent spring peaks in human cases of *S.* Brandenburg in predominantly farming areas has been linked to similar seasonal epidemics occurring in sheep which appear to be the dominant source for this serotype (Clarke and Tomlinson 2004, Baker, Thornley et al. 2007). A recent description of case characteristics has shown significantly higher risks for cases residing in rural areas (Lal, Baker et al. 2011) (Chapter 3). These findings indicate that while campylobacteriosis and salmonellosis in New Zealand are predominantly food borne diseases, the risks associated with environmental sources and transmission is considerable and have the potential to increase under scenarios of environmental change.

The positive association of cryptosporidiosis and giardiasis with rainfall (Lake, Pearce et al. 2008, Britton, Hales et al. 2010) has important implications for water borne transmission of these diseases. Global climate change related sea level rise, increased snow melt and more pronounced disparities in regional precipitation are

projected for New Zealand (IPCC 2007). Accompanying changes such as flooding, high river flow and extreme rainfall events have been linked with increased enteric disease elsewhere (Curriero, Patz et al. 2001, Lake, Bentham et al. 2005, Nichols, Lane et al. 2009). Simulating heavy rainfall events, researchers in New Zealand have shown heavy rainfall can significantly increase runoff of *Cryptosporidium* oocysts over pastoral land (Davies, Ferguson et al. 2004). This increased runoff may affect the quality of surface and ground water drinking water sources, posing a substantial public health risk. Indeed, in New Zealand, Britton et al (2010) showed that drinking water quality modified climate-cryptosporidiosis associations with better quality drinking water supplies having a protective effect. Other studies in New Zealand have reported higher cryptosporidiosis rates in areas with inadequate drinking water supplies as defined by the ESR drinking water programme (Duncanson, Russell et al. 2000) and higher public health risks from water supplies in poor communities (Hales, Black et al. 2003). As hospitalisations for some enteric diseases in New Zealand are already highest in socio-economically disadvantaged populations (Snel, Baker et al. 2009, Snel, Baker et al. 2009) and Māori and Pacific peoples (Lal, Baker et al. 2011), future environmental change may have disproportionately adverse effects on the health of these populations.

Rapid agricultural intensification in recent years (Wilson, Slaney et al. 2011) may have contributed to disease emergence in New Zealand (Derraik and Slaney 2007). Seasonal variations in *Cryptosporidium* strains from human cases suggest zoonotic transmission in spring and human dominated transmission in autumn (Learmonth, Ionas et al. 2004). Similar results from England propose that farming and contact with livestock is a significant risk factor in spring, while urban living and swimming in public pools drive patterns in autumn (Chalmers, Smith et al. 2011). Isolation of *Giardia* spp. from calves and humans in spring (Winkworth, Learmonth et al. 2008) further support the premise that seasonal agricultural practices may be important determinants of disease incidence.

In conclusion, information established to date demonstrates that enteric disease occurrence in New Zealand is influenced by climate variability and agricultural land use. In some regions, there is considerable environmental pathogen load with opportunities for zoonotic transmission. Since environmental processes can also

interact with demographic factors to influence disease patterns, quantifying the disease risk arising from these factors independently, and in combination with population factors is needed. Future climate change could lead to forced population movement and changes in land use patterns, leading to redistribution of disease reservoirs and hosts. As these changes might vary widely across regions, establishing regional differences in environmental influences on disease incidence would provide a useful baseline for disease prediction models. Coupled with evidence from this review, these implications suggest that understanding how concurrent changes in climate and land use may affect zoonotic disease risk in New Zealand should be a research priority.

Table 2.1 Summary of studies selected for review describing the main research question, assessment of exposures and outcomes and main conclusions

Association investigated, reference	Exposure measure	Outcome measure	Limitations	Conclusion
Timing of peak week of campylobacteriosis and seasonal temperature (Kovats, Edwards et al. 2005)	National daily temperature	Cases per week, averaged for 1991-2000 (n=7026)	Temperature variations across years not accounted for	NZ had an earlier onset of peak week of infections associated with warmer winters compared to other countries
Monthly temperature, rainfall, river flow and cryptosporidiosis (Lake, Pearce et al. 2008)	Mean temperature (national), rainfall (average 10 centres) , flow (mean of 7 rivers)	Daily, monthly rate, 1997-2005, foreign travellers excluded	Long term trend and population changes not accounted for	Dominant spring peak. Summer-autumn cases positively associated ($p < 0.001$) with temperatures of current and previous month.
Monthly temperature and salmonellosis (Britton, Hales et al. 2010)	Spatially averaged, monthly mean surface temperature	Monthly salmonellosis count, 1965-2006	Temperature data averaged nationally	Positive association with mean monthly temperature, association weakened over time
Monthly temperature, rainfall and cryptosporidiosis, giardiasis (Britton, Hales et al. 2010)	CAU scale: average annual temperature and rainfall to evaporation ratio, drinking water quality, urban-rural and socio-economic status	CAU scale: total cryptosporidiosis , giardiasis counts 1997-2006	Long term trend, population changes, seasonal patterns and changes in water quality not accounted for	Cryptosporidiosis: positive association with rainfall (modified by water quality), rurality, negative association with temperature. Giardiasis: positive association with rainfall, temperature. Higher incidence in affluent CAUs

Association investigated, reference	Exposure measure	Outcome measure	Limitations	Conclusion
Cryptosporidium strains in humans, dairy cows, calves (Learmonth, Ionas et al. 2001)	*Cryptosporidium* isolates from cows (n=354) and calves (n=302)	*Cryptosporidium* isolates from humans,(n=66)	No information on associated risk factors from human cases	Predominant genotypes isolated in humans was of bovine origin in spring, with the human genotype in autumn
Campylobacter jejuni strains in humans, river water samples (Eyles, Brooks et al. 2006)	*C.* jejuni isolates from river water samples, 10 sites (n=99), 2000-2001	Human samples positive for *C.* jejuni, (n=88)	Human cases assumed to be exposed to pathogens in river	No sufficient overlap between *C.* jejuni in river and human isolates, indicating limited possibility of waterborne transmission
Salmonella Brandenburg in humans and sheep in Southland (Baker, Thornley et al. 2007)	Isolates from sheep, 1995-2002,(n=1621)	*S.* Brandenburg isolates in humans, 2002-2003 (n=671)	Recall and selection bias, inadequate sample size	Simultaneous peaking in human and sheep cases in spring.

Association investigated, reference	Exposure measure	Outcome measure	Limitations	Conclusion
Campylobacter in groundwater and disease incidence in dairying areas with major irrigation schemes to controls (Close, Dann et al. 2008)	*Campylobacter* concentrations in groundwater (n=6 wells) and in cow pats (n=5 at each of the three sites) in Canterbury	Health risk assessment and epidemiology study	Assumption that major irrigation scheme would have greater numbers of cattle	Dairying regions with major irrigation schemes had significantly ($p< 0.05$) higher rates of age-standardised campylobacteriosis, cryptosporidiosis and salmonellosis compared to two control groups.
Campylobacter jejuni strains in humans, dairy cattle (Gilpin, Thorrold et al. 2008)	*C.* jejuni isolates in dairy cattle (n=410), 2000- 2001	*C.* jejuni isolates in humans (n=73)	No other environmental sources of infection tested	Indistinguishable *C.* jejuni isolates from bovine and human samples.
Source of human campylobacteriosis on a dairy farm (Gilpin, Scholes et al. 2008)	Faecal samples from cattle, pets, other residents. Samples from water, milk	Faecal samples from index cases (n=7)	Results indicative of prevalence but not zoonotic transmission	Contact with dairy cattle faeces was likely source of infection for four cases.

Association investigated, reference	Exposure measure	Outcome measure	Limitations	Conclusion
Giardia strains in humans and dairy calves (Winkworth, Learmonth et al. 2008)	Calf isolates (n=40), (Aug-Oct 2005, 2006).	Positive human samples, (n=30)	No risk factors from human cases	Assemblage A, B (human strains) isolated from calves and humans.
Spatial associations of campylobacteriosis with climate, land use and social factors (Rind and Pearce 2010)	TA: Climate, land use, water quality	TA: Cases/100 000, 1997-2007	No account of differences in risk factors in urban-rural areas, deprivation indices aggregated up from finer scale	Significant ($p<0.01$) positive association with affluence, population aged 25–44 years,
Spatial/temporal associations of campylobacteriosis with climate, land use and social factors (Spencer, Marshall et al. 2011)	Meshblock: livestock density (AgriBase), deprivation index, climate	6235 cases, 2001-2007	Individual case information included for one region only	Social deprivation associated with decreased risk; increased risk in high dairy cattle density areas. Temperature not significant.
Campylobacter: food and the environment (McBride, Ball et al. 2011)	Combination of modelling, experimental and molecular techniques		Data and resource intensive- difficult to replicate	Manawatu- cases attributed to livestock in 2008 exceed those attributed to poultry. Higher risk of illness in rural pre-schoolers, water samples dominated by livestock strains during peak flow and wild bird strains during low flow

Association investigated, reference	Exposure measure	Outcome measure	Limitations	Conclusion
Campylobacter in food and the environment (French, Marshall et al. 2011)	Molecular typing of campylobacter is surface water samples, pets, wild birds, ruminants, meat	Molecular typing of human faecal samples	Selected regions of New Zealand	Human cases attributed to poultry. Concentration of campylobacter livestock strains in water was higher in winter.

CHAPTER 3 DESCRIPTIVE EPIDEMIOLOGY OF ENTERIC ZOONOTIC DISEASES IN NEW ZEALAND

3.1 Introduction

In New Zealand, the burden of enteric zoonotic disease in humans is substantial with evidence to suggest that their distribution and incidence could change considerably with future environmental change (Chapter 2). Although there have been published studies describing the epidemiology of these infections in humans (Baker, Thornley et al. 2007, Snel, Baker et al. 2009, Lal, Baker et al. 2011), to date there are no comparisons of patterns of notifications and hospitalisations across all these diseases. Such an analysis would highlight populations that may be at an increased, and potentially disproportionate risk from future environmental and social change.

3.2 Chapter aim

This chapter describes the geographical, seasonal and demographic patterns of campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis notifications and hospitalisations in New Zealand between 1997 and 2008. In doing so, I have highlighted the need to consider spatial and temporal variations in environmental and demographic risk factors when assessing disease risk.

3.3 Methods

3.3.1 Disease data

All notified cases of campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis during 1997-2008 in New Zealand were obtained from the National Notifiable Disease Surveillance system (EpiSurv) which is operated by the Institute of Environmental Science and Research (ESR) for the NZ Ministry of Health. No major changes to reporting practices, surveillance methods, case definitions, and diagnostic approaches were made during 1997-2008. Hospital and mortality data for the same period were obtained from the National Minimum Dataset managed by the Ministry of Health. Population denominator data, including age, sex, ethnicity and Census Area Unit (CAU code), were based on the 2001 National Census of Population and were obtained from Statistics New Zealand. A CAU is a non-administrative, geographical unit defined by Statistics New Zealand, each of which comprises a population of 3000-5000 people.

For notifications, cases were defined as a clinical illness with appropriate laboratory confirmation. For hospitalisations, all discharged cases with a principal diagnosis of *Campylobacter* infection (ICD-9-CM code 008.43 and ICD-10-AM code A04.5), *Salmonella* infection (ICD-9-CM code 003 and ICD-10-AM code A02), *Cryptosporidium* infection (ICD-9-CM code 136.8 and ICD-10-AM code A07.2) and *Giardia* infection (ICD-9-CM code 007.1 and ICD-10-AM code A07.1) were used. The analysis was restricted to overnight or longer admissions and New Zealand residents. In order to include only incident cases, if the same individual was re-admitted with the identical diagnosis within 30 days, only the first record was included. For mortality data, where the underlying cause of death was coded as *Campylobacter*, *Salmonella*, *Cryptosporidium* and *Giardia* infection were used.

3.3.2 Exposure variables

Based on date of notification and hospitalisation, cases were assigned to southern hemisphere seasons as follows: summer (December-February), autumn (March-May), winter (June-August) and spring (September-November).

Cases were assigned to one of the seven categories of rurality based on population number and employment status as defined by Statistics New Zealand (Statistics New Zealand 2000). These categories are: main urban areas, satellite urban areas, independent urban areas, rural areas with high urban influence, rural areas with moderate urban influence, rural areas with low urban influence, and highly rural/remote areas. Average monthly rates for urban and rural areas were calculated by classifying the first three categories as urban and the latter four as rural.

The deprivation index, an area based index, derived from variables important to social and material deprivation (Salmond and Crampton 2002) was used as a socio-economic level indicator. It is constructed on a decile scale with deprivation level 1 representing socio-economically affluent CAUs and level 10 representing the most deprived CAUs. In this study, deprivation levels were grouped into quintiles. Ethnicity was based on Level 1 prioritised ethnicity which divides the population into European, Māori, Pacific, Asian and Other.

3.3.3 Analysis

Rates were calculated using the 2001 Population Census and converted to average rates per 100 000 population per year (hereafter referred to as average annual rates or rates per 100 000 population). Ninety five percent confidence intervals (95% CI) were reported based on average annual rates for the duration of the study period. Rates for ethnic groups were directly age standardised to the age distribution of the national population in 2001; 95% CI were calculated based on the age standardised rates. MS Excel 2010 was used for calculations. ArcGIS v10 was used for mapping.

3.4 Results

3.4.1 Incidence time trends and seasonality

The incidence of campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis notifications, hospitalisations and fatalities was used to assess the public health impact of these diseases in New Zealand (Table 3.1). Among the four diseases, the average annual rate of campylobacteriosis notifications and hospitalisations was the highest (303.01cases/100 000 population and 14.32 cases/100 000 population), followed by salmonellosis (42.88 cases/100 000 population and 3.62 cases/100 000 population), giardiasis (43.55 cases/100 000 population and 0.63 cases/100 000 population) and cryptosporidiosis (22.07 cases/100 000 population and 0.62 cases/100 000 population). The mortality associated with campylobacteriosis and salmonellosis was 0.02 cases/100 000 population, 0.002 cases/100 000 population for giardiasis and there was no cryptosporidiosis associated mortality.

Table 3.1 Number of notifications, hospitalisations and deaths for campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis, 1997–2008

	No. Notified	Rate*	No. Hospitalised	Rate	Deaths	Rate
Campylobacteriosis	135898	303.01	6426	14.32	9	0.02
Salmonellosis	19234	42.88	1624	3.62	9	0.02
Giardiasis	19533	43.55	283	0.63	1	0.00
Cryptosporidiosis	9900	22.07	282	0.62	0	0

*average annual rate per 100 000 population

For all four diseases, the number of notifications and hospitalisations showed a similar temporal pattern to each other over the 12 year period 1997 to 2008 (Figure 3.1 A-D). For campylobacteriosis, incidence was highest in 2006 with 15873 notifications and 791 hospitalisations. For salmonellosis, incidence rose to a peak in 2001 with 2417 notified cases and 178 hospitalisations then declined to a level broadly similar to that at the start of the observation period. Cryptosporidiosis notifications were highest in 2008 (1528 cases) with hospitalisations highest in 2001 (36 cases). Giardiasis hospitalisations peaked in 2006 with 33 cases while notifications showed a tendency to increase after 2006, although the highest number was recorded in 1998 (2183 cases).

Average annual incidence rates for campylobacteriosis notification and hospitalisation rates were highest in summer (96.02 and 4.23/100 000 population) (Table 3.2). For salmonellosis, both notifications and hospitalisation rates peaked in summer (14.42/100 000 population and 1.32/100 000 population respectively), with rates dropping to about half that level over winter (Table 3.3). For giardiasis, notifications were highest in autumn (4.16/100 000), while hospitalisations peaked in winter (0.05/100 000) (Table 3.4). These differences were statistically significant. For cryptosporidiosis, incidence rates were significantly higher in spring for both notifications (12.03/100 000) and hospitalisations (0.37/100 000) (Table 3.4).

Seasonal patterns in campylobacteriosis notifications were similar in both urban (32.04/100 000 population) and rural areas (30.44/100 000 population) with peaks

in summer (December-February) (Figure 3.2). For salmonellosis notifications, seasonality showed a different pattern in rural areas with a marked spring peak (6.4/100 000 population) that was absent in urban populations which only experienced a single peak in summer (4.9/100 000 population) (Figure. 3.2). The monthly average annual incidence of giardiasis notifications showed no apparent difference between urban and rural areas (Figure 3.2). For cryptosporidiosis notifications, seasonality was similar in urban and rural areas, both of which showed a spring increase in average annual incidence. However, the peak in rural (13.31/100 000 population) was almost four times that in urban areas (3.49/100 000 population) (Figure 3.2).

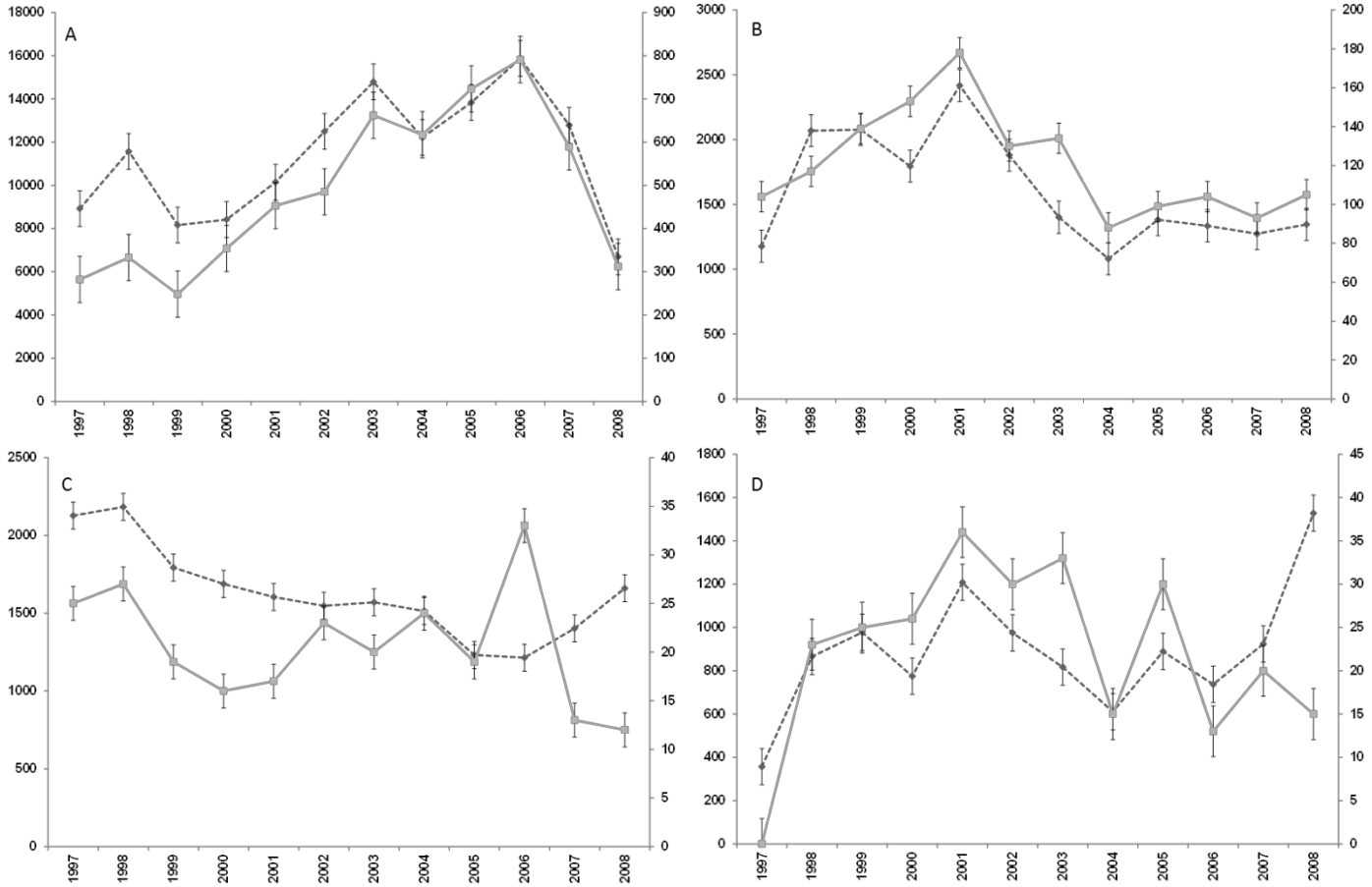


Figure 3.1 Number of notifications and hospitalisations in New Zealand, 1997-2008. (–◆–) Notifications (—■—) Hospitalisations. Standard error bars shown (A) Campylobacteriosis (B) Salmonellosis (C) Giardiasis (D) Cryptosporidiosis

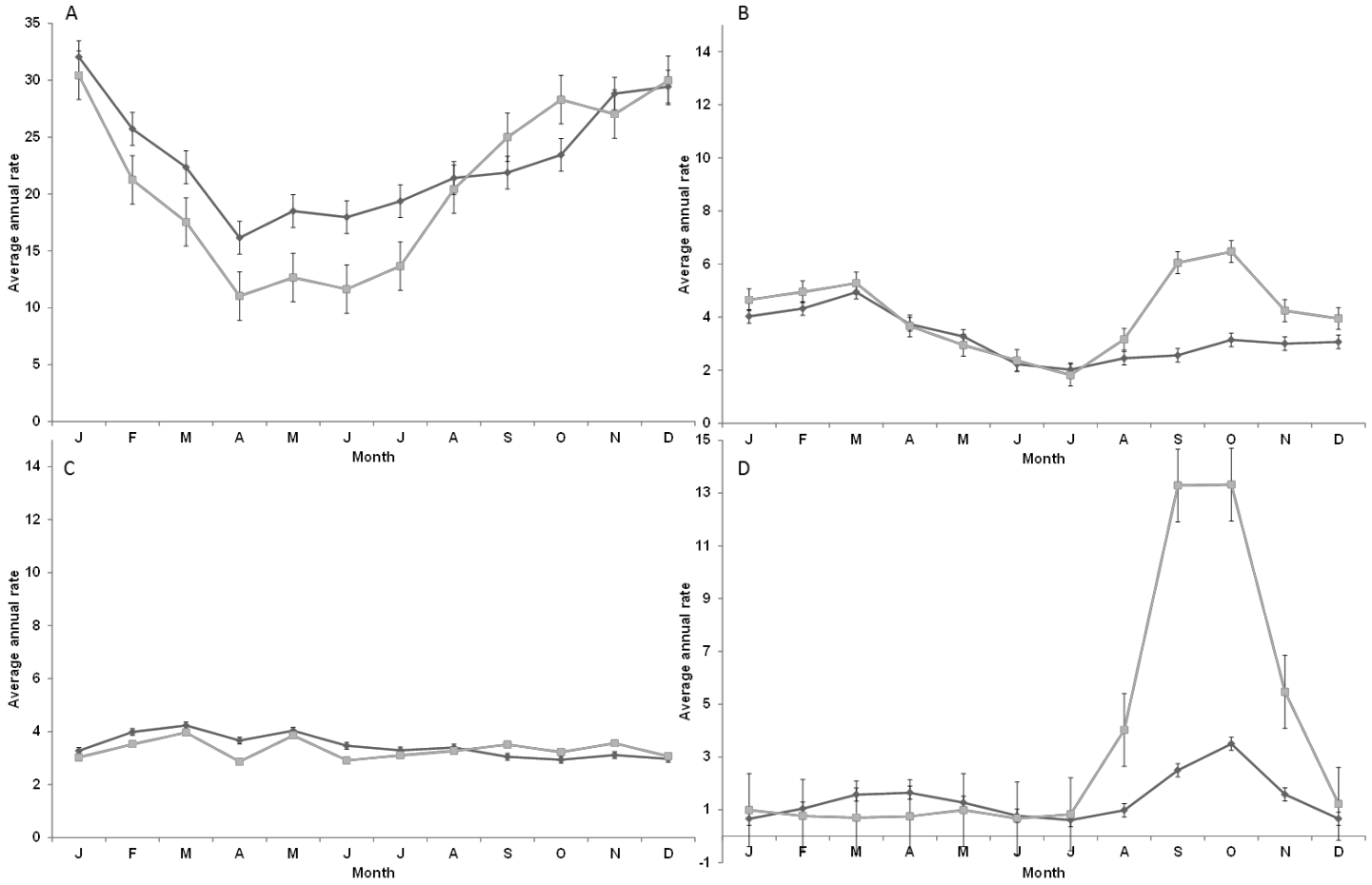


Figure 3.2 Average annual, monthly rate of notification by urban/rural status, 1997-2008. (—◆—) Urban (—■—) Rural. Standard error bars shown. The denominator used to calculate rates was the (A) Campylobacteriosis (B) Salmonellosis (C) Giardiasis (D) Cryptosporidiosis

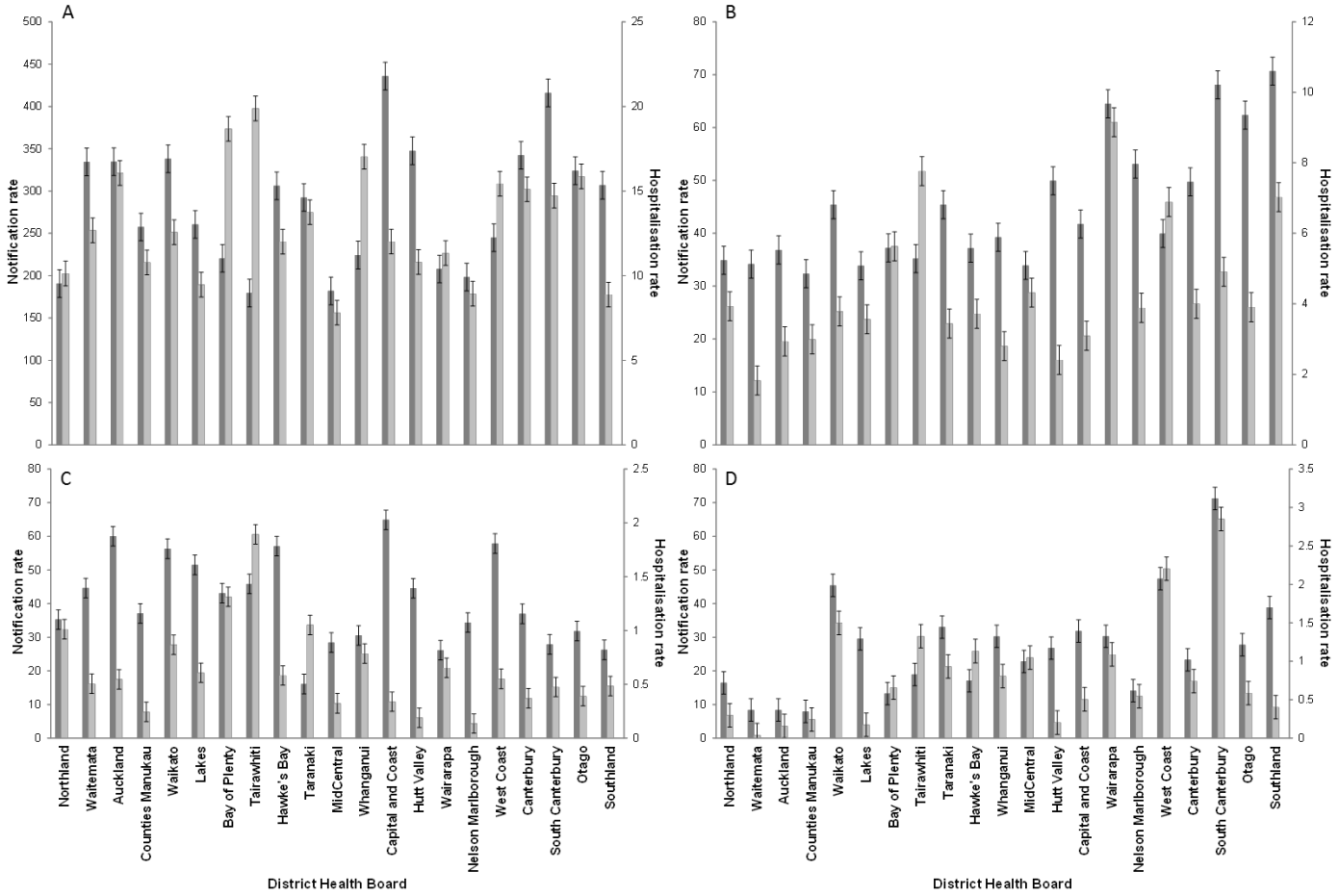


Figure 3.3 Average rate of notifications and hospitalisation by District Health Board (DHB) 1997-2008. (A) Campylobacteriosis (B) Salmonellosis (C) Giardiasis (D) Cryptosporidiosis

3.4.2 Geographical and urban-rural differences

Campylobacteriosis rates tended to be higher in urban areas compared to rural areas (Table 3.2). However, the highest notification rates was seen in remote rural areas (392.30/100 000). Hospitalisations were highest in main urban areas (13.43/100 000). Notifications and hospitalisations rates were highest in the North Island. Notifications were highest in Capital and Coast District Health Board (435.69/100 000), while hospitalisations were highest in Tairawhiti (19.88/100 000) (Figure 3.3).

For both salmonellosis notification and hospitalisation rates, there appeared to be a tendency for increasing incidence rates with increasing grade of rurality (Table 3.3) with rates in remote areas exceeding those in any other category for hospitalisations (5.41/100 000 population). Rates in rural areas with high urban influence had the highest rates for notifications (59.90/100 000 population). However, these rates were not statistically significantly different from the urban category. The Southland District Health Board had the highest notification rate (70.65/100 000), while hospitalisation rates were highest in Wairarapa (9.15/100 000) (Figure 3.3).

Giardiasis notification rates were significantly higher in remote rural areas (50.43/100 000), while hospitalisation rates were highest in satellite urban areas (0.97/100 000) (Table 3.4) were not statistically significant. Similar to campylobacteriosis, notifications and hospitalisations rates were highest in the North Island. Notifications were highest in Capital and Coast District Health Board (64.90/100 000), while hospitalisation were highest in Tairawhiti (1.89/100 000) (Figure 3.3).

Similar to salmonellosis, both notifications and hospitalisations for cryptosporidiosis showed an increase in incidence rates with increasing grade of rurality, with average annual rates for both notifications and hospitalisations being highest in remote rural areas (76.28/100 000 and 1.95/100 000 respectively). The notification rate was statistically significant to all others apart from rates in rural areas with low urban influence. Both notification and hospitalisation rates were highest in the South Island. The South Canterbury District health Board had the

highest notification (71.24/100 000) and hospitalisation rates (2.84/100 000) (Figure 3.3).

3.4.3 Age, sex, ethnicity and deprivation

For all four diseases, average annual notifications and hospitalisation rates varied by age (Table 3.2-3.5). For notified cases across all four diseases, the highest incidence was detected in children aged 0-4, while the lowest incidence was in the ≥ 80 years and this difference was statistically significant. For campylobacteriosis and salmonellosis, high rates were also seen in the 20-29 yr. old age group, while for giardiasis notifications there was a peak in the 30-39 group. While campylobacteriosis and cryptosporidiosis notification rates were slighter lower for males, for salmonellosis and giardiasis average rates in males was slightly higher. Average hospitalisations rates for campylobacteriosis were highest in those ≥80 years (41.51/100 000 population). For salmonellosis, hospitalisation rates were highest in children aged 0-4 (11.33/100 000 population but unlike notification rates had a second peak in older adults aged 70-79 (4.89/100 000 population). For giardiasis and cryptosporidiosis, like notifications average hospitalisation rates were highest in the 0-4 category (1.66 and 2.86/100 000 population respectively). Hospitalisation rates for campylobacteriosis was lower for females, while for salmonellosis, unlike notification rates, hospitalisation rates showed no differences in between sexes. For both giardiasis and cryptosporidiosis, hospitalisations rates in females were higher than that for males.

Average annual incidence rates varied by ethnicity but patterns were very different for notifications and hospitalisations. For campylobacteriosis notifications, Europeans had the highest age standardised rates (288.90/100 000 population), with lower rates for people who identified with Māori ethnicity (92.83/100 000 population), Pacific Island (24.08/100 000 population) populations, Asian (33.32/100 000 population), and ‘Other’ ethnic groups (10.40/100 000 population). However, this pattern differed for hospitalised cases, where the Māori (22.01/100 000 population) had the highest rates, followed by the European (17.30/100 000), ‘Other’ (8.30/100 000 population), Pacific (7.01/100 000) and Asians (3.58/100 000 population) (Table 3.2).

For salmonellosis notifications, Europeans had the highest age standardised rates (42.1/100 000 population), with lower rates for Māori (23.4/100 000 population), Pacific Island (21.8/100 000 population) populations, Asian (15.5/100 000 population), and 'Other' ethnic groups (25.3/100 000 population). However, this pattern was largely reversed for hospitalised cases. The Pacific Island (6.3/100 000 population) and Māori (5.6/100 000 population) people had the highest rates, with Europeans recording the third lowest incidence rate among ethnic groups (3.4/100 000 population) followed by Asians (1.6/100 000 population) and 'Other' (1.0/100 000 population) (Table 3.3.).

For giardiasis notifications, Europeans had the highest age standardised rates (41.70/100 000 population), with lower rates for Māori (14.29/100 000 population), Pacific Island (2.13/100 000 population) populations, Asian (4.49/100 000 population), and 'Other' ethnic groups (2.93/100 000 population). However, this pattern differed for hospitalised cases, where the Māori (1.01/100 000 population) people had the highest rates, followed by the European (0.56/100 000), 'Other' (0.15/100 000 population), Pacific (0.05/100 000) and Asians (0.04/100 000 population) (Table 3.4).

For cryptosporidiosis notifications, Europeans had the highest age standardised rates (24.16/100 000 population), with lower rates for Māori (6.75/100 000 population), Pacific Island (1.19/100 000 population) populations, Asian (1.39/100 000 population), and 'Other' ethnic groups (0.25/100 000 population). Hospitalisations followed the same general pattern, recording the highest rates for Europeans (0.66/100 000), followed by Māori (0.42/100 000 population) 'Other' (0.07/100 000 population), and Pacific (0.01/100 000) and Asians (0.01/100 000 population) (Table 3.5).

For all four diseases, notification and hospitalisation rates varied by deprivation status, with contrasting patterns for notifications and hospitalisations (Table 3.2-3.5). Average annual campylobacteriosis notification rates in the least deprived CAUs were higher (360.37/100 000 population) compared with the most deprived CAUs (177.10/100 000 population). Hospitalisation rates were reversed with higher rates recorded for the most deprived CAUs (15.07/100 000 population)

compared with the most affluent CAUs (10.72/100 000 population). For salmonellosis, notification rates were higher in the affluent CAUs (37.2/100 000 population) compared with the most deprived CAUs (25.20/100 000 population). Hospitalisation rates were higher for the most deprived CAUs (5.7/100 000 population) compared with the most affluent CAUs (2.6/100 000 population). For giardiasis, notification rates in the affluent CAUs was 51.06/100 000 population compared with the most deprived CAUs (29.04/100 000 population). Hospitalisation rates were higher for the most deprived CAUs (0.87/100 000 population) compared with the most affluent CAUs (0.37/100 000 population). For cryptosporidiosis, notification rates in the affluent CAUs was 25.70/100 000 population compared with the most deprived CAUs (11.77/100 000 population). Hospitalisation rates were higher for the most deprived CAUs (0.63/100 000 population) compared with the most affluent CAUs (0.43/100 000 population).

3.5 Discussion

Trends in average annual notifications and hospitalisations rates for campylobacteriosis, salmonellosis, giardiasis and cryptosporidiosis in New Zealand continue to be high. The spatial, temporal and demographic characteristics of cases indicate that the dominant drivers of incidence vary across the diseases. While notifications and hospitalisations for all four diseases showed a similar temporal trend from 1997 to 2008, they differed substantially with regard to the demographic characteristics of cases. All four diseases showed marked ethnic and socioeconomic inequalities in disease distribution with higher hospitalisation rates for Māori and Pacific peoples and those living in more deprived neighbourhoods. While campylobacteriosis and giardiasis tended to be higher in urban areas, salmonellosis and cryptosporidiosis rates were generally higher in rural areas with a distinct spring peak that was absent in urban populations.

3.5.1 Incidence time trends and seasonality

The reported incidence for all four diseases in New Zealand is relatively high by international standards. For example, salmonellosis rates in comparable countries are 35.8/100 000 in Australia (Sumner, Raven et al. 2004), 9.9/100 000 in the US

(Arshad, Wilkins et al. 2007) and 25.9/100 000 in Canada (Keegan, Majowicz et al. 2009). Similarly, for cryptosporidiosis, rates in New Zealand (23.8/100 000) are markedly higher as compared to the UK (8.5/100 000), US (2.8/100 000) and Germany (1.6/100 000) (Snel, Baker et al. 2009). Such high incidence rates suggest an incomplete understanding of the complex epidemiology of these diseases. However, for campylobacteriosis, there has been a substantial reduction in cases after 2006 (Figure 3.1), a drop largely attributed to poultry industry interventions (Sears, Baker et al. 2011).

Distinct temporal variations in incidence suggest seasonal exposure to high pathogen loads and subsequent transmission. The summer peak noted for campylobacteriosis and salmonellosis is similar to that observed in other countries (Kovats, Edwards et al. 2004). In the case of salmonellosis, such a peak may be attributed to the effect of ambient environmental conditions on bacterial survival and multiplication. The causes of this summer peak in campylobacteriosis are less clear. International travel can affect seasonal patterns in enteric infections, particularly with respect to the geographic variations in the genotypes isolated (Mughini-Gras, Smid et al. 2013). For the current study, the history of recent international travel for cases and strain specific information was not available. Nonetheless, given the distinct seasonal patterns in disease incidence, clarifying the influence of climatic variables on enteric disease incidence would be helpful to assess the potential health impacts due to climate change in New Zealand.

3.5.2 Geographical and urban-rural differences

Distinct spatial associations of infection rates with climatic factors have been previously noted in New Zealand (Rind and Pearce 2010), and Australia (Bi, Cameron et al. 2008), with seasonal patterns varying regionally in New Zealand (Hearnden, Skelly et al. 2003). Findings from this chapter show varying seasonal patterns in urban and rural populations. For salmonellosis, spring rates were strongly influenced by rural populations which experienced a dominant spring peak in addition to one in summer, unlike urban populations which had a single peak in summer. This difference probably reflects greater local exposures to environmental pathogen reservoirs and opportunities for pathogen-human contact

due to seasonal host activities. A study in Scotland reported a spring peak in human salmonellosis cases, with pronounced infection rates in the farming community, as compared to higher rates in late summer-early autumn in the general community (Sharp, Paterson et al. 1980). In New Zealand, Salmonella Brandenburg, associated with the lambing season has been implicated in spring peaks in rural cases in southern New Zealand (Baker, Thornley et al. 2007).

Similarly, cryptosporidiosis in rural populations showed a spring peak nearly four times larger than the incidence reported for urban populations in spring. Moreover, incidence rates were significantly higher in spring for both notifications (12.03/100 000) and hospitalisations (0.37/100 000) (Table 3.5). A dose-response relationship between human cryptosporidiosis rates and increasing rurality has been reported in previous studies (Snel, Baker et al. 2009). Additionally, cryptosporidiosis outbreaks due to farm visits (Stefanogiannis, McLean et al. 2001), and molecular analysis implicating livestock as a major source of human cryptosporidiosis in spring (Learmonth, Ionas et al. 2001) have been documented. This has important implications for rural population health in New Zealand as livestock reservoirs are expected to grow. Future work focussing on these seasonal reservoirs and their transmission mechanisms could support disease prevention measures in these populations.

3.5.3 Age, sex, ethnicity and deprivation

Consistent with published studies, strong age associations in disease incidence were identified across all four diseases. For both notifications and hospitalisations, the 0-4 age group had the highest rates. Additionally, hospitalisation rates for campylobacteriosis and salmonellosis were also high for the elderly. This vulnerability at both ends of the age range is seen for infectious diseases generally (Baker, Barnard et al. 2012). Contributing factors could include increased contact with infection sources (Doorduyn, Van den Brandhof et al. 2006), susceptibility to infection due to inadequate immunity or a greater probability of seeking treatment (Koehler, Lasky et al. 2006). Higher rates in the elderly has also been related to increased proton pump inhibitor use as the drugs may increase vulnerability to *Campylobacter* (Nichols, Richardson et al. 2012).

There is less comparable literature on ethnic and socio-economic patterns in enteric infections. Interestingly, the notification and hospitalisation data presented here show opposite patterns with regard to ethnicity and deprivation. For campylobacteriosis, salmonellosis and giardiasis, notification rates for Europeans were the highest, while hospitalisation rates were highest for Māori and Pacific populations. For all four diseases, a similar reversal is shown for socio-economic deprivation; while notification rates showed that the socio-economically advantaged areas had the highest rates, hospitalisation rates indicated the reverse. Other studies have reported comparable patterns in cryptosporidiosis and giardiasis notification data (Snel, Baker et al. 2009), with similar patterns in ethnic differences between notifications and hospitalisations for campylobacteriosis (Baker, Sneyd et al. 2007) and salmonellosis (Lal, Baker et al. 2011) (paper based on results of this chapter). It has been suggested that such inconsistent patterns could be due to poorer access to health resources resulting in lower rates of reported cases (Baker, Sneyd et al. 2007). Higher rates for certain ethnic groups could also indicate cultural differences relating to food preparation and handling, apparently unrelated to deprivation status (Dixon, Donnison et al. 2007). Using notified, hospitalised and fatal cases over a 12 year period (1997-2008) to describe the epidemiology of enteric diseases in New Zealand highlights the importance of using multiple data sources as demographic disparities could be masked when using single sources. Results showed that while incidence was highest in the 0-4 age group, ethnic and socio-economic patterns showed contrasting patterns for notifications and hospitalisations. Hospitalisations showed higher rates for Māori and Pacific populations compared to European, and those living in more deprived areas, whereas notifications showed the reverse, implying that notifications are influenced by health seeking behaviours.

For a developed country, enteric zoonotic infection rates in New Zealand have remained consistently high suggesting more work is needed to investigate, control and prevent these diseases.

Table 3.2 Numbers and rates (average rate per 100 000 population per year) of campylobacteriosis notifications and hospitalisation population) by season, rural–urban domicile, age group, sex, ethnicity, and deprivation level, 1997–2008

	Notifications			**Hospitalisations**		
Category	No[a]	Rate*	RR (95% CI)†	No	Rate	RR (95% CI)
Season						
Summer	43066	96.02	1	1900	4.23	1
Autumn	27318	60.91	0.63 (0.63-0.63)	1059	2.36	0.55 (0.54-0.57)
Winter	28016	62.46	0.65 (0.64-0.65)	1236	2.75	0.65 (0.63-0.66)
Spring	37498	83.61	0.87 (0.86-0.87)	1663	3.70	0.87 (0.87-0.88)
Urban-Rural						
Main urban	96411	302.59	1	4282	13.43	1
Satellite urban	3369	252.96	0.85 (0.83-0.84)	161	12.08	0.89 (0.88-0.91)
Independent urban	11941	227.47	0.75 (0.74-0.75)	652	12.42	0.92 (0.91-0.92)
Rural, high urban	3480	273.57	0.90 (0.90-0.90)	136	9.59	0.71 (0.67-0.74)
Rural, mod urban	4333	305.67	1.01 (1.00-1.01)	124	9.74	0.72 (0.69-0.76)
Rural, low urban	6588	217.53	0.71 (0.71-0.72)	268	8.84	0.65 (0.63-0.68)
Remote rural	2606	392.30	1.29 (1.28-1.31)	73	10.98	0.81 (0.78-0.85)
Age group						
0-4	15961	491.53	1.84 (1.82-1.86)	318	9.79	1.11 (1.10-1.12)
5-9	6567	191.34	0.71 (0.71-0.72)	151	4.39	0.50 (0.46-0.54)
10-19	15180	227.69	0.85 (0.85-0.85)	740	11.09	1.26 (1.23-1.28)
20-29	26090	447.33	1.67 (1.66-1.69)	1051	18.02	2.05 (1.92-2.18)
30-39	20266	293.18	1.10 (1.09-1.10)	660	9.54	1.08 (1.07-1.09)
40-49	17158	266.38	1	566	8.78	1
50-59	14770	294.56	1.10 (1.10-1.10)	559	11.14	1.26 (1.24-1.29)
60-69	9843	290.66	1.09 (1.08-1.09)	571	16.86	1.91 (1.77-2.06)
70-79	6384	250.22	0.93 (0.93-0.94)	696	27.27	3.10 (2.61-3.58)
≥80	2801	212.98	0.79 (0.79-0.80)	546	41.51	4.72 (3.24-6.20)
Sex						
Male	71739	327.93	1	3090	14.12	1
Female	61882	269.38	0.82 (0.82-0.82)	2768	12.04	0.85 (0.84-0.85)
Ethnicity‡						
European	90427	288.90	1	5417	17.30	1
Māori	5724	92.83	0.32 (0.31-0.32)	1004	22.01	1.27 (1.25-1.29)
Pacific	1500	24.08	0.08 (0.07-0.08)	341	7.01	0.40 (0.38-0.42)
Asian	3441	33.32	0.11 (0.11-0.11)	205	3.58	0.20 (0.20-0.22)
Other	681	10.40	0.03 (0.03-0.03)	305	8.30	0.48 (0.47-0.50)
Deprivation						
1-2	32301	360.37	1	961	10.72	1
3-4	27268	310.31	0.86 (0.85-0.86)	1054	11.99	1.11 (1.11-1.12)
5-6	24068	282.00	0.78 (0.78-0.78)	1227	14.37	1.34 (1.31-1.36)
7-8	20544	245.97	0.68 (0.67-0.68)	1300	15.56	1.45 (1.41-1.48)
9-10	14810	177.10	0.49 (0.48-0.49)	1261	15.07	1.40 (1.37-1.43)
Total	135898	303.01	n.a.	6426	3.62	n.a.

Table 3.3 Numbers and rates (average rate per 100 000 population per year) of salmonellosis notifications and hospitalisation population) by season, rural–urban domicile, age group, sex, ethnicity, and deprivation level, 1997–2008

	Notifications			**Hospitalisations**		
Category	No[a]	Rate*	RR (95% CI)†	No	Rate	RR (95% CI)
Season						
Summer	6469	14.42	1	596	1.32	1
Autumn	4348	9.69	0.67 (0.66-0.67)	323	0.72	0.54 (0.51-0.57)
Winter	3647	8.13	0.56 (0.55-0.57)	285	0.63	0.48 (0.45-0.51)
Spring	4770	10.63	0.73 (0.73-0.74)	420	0.93	0.70 (0.68-0.72)
Urban-Rural						
Main urban	13680	42.93	1	965	3.02	1
Satellite urban	519	38.96	0.90 (0.90-0.91)	60	4.50	1.49 (1.30-1.67)
Independent urban	1668	31.77	0.74 (0.73-0.74)	269	5.12	1.69 (1.55-1.83)
Rural, high urban	762	59.90	1.39 (1.35-1.43)	37	2.90	0.96 (0.95-0.97)
Rural, moderate urban	773	54.53	1.27 (1.24-1.29)	45	3.17	1.05 (1.03-1.06)
Rural, low urban	1377	45.46	1.05 (1.05-1.06)	141	4.65	1.54 (1.40-1.67)
Remote rural	347	52.23	1.21 (1.18-1.24)	36	5.41	1.79 (1.32-2.26)
Age group						
0-4	5009	154.25	5.11 (4.53-5.69)	368	11.33	5.75 (2.95-8.54)
5-9	1601	46.64	1.54 (1.50-1.58)	105	3.05	1.55 (1.38-1.71)
10-19	2065	30.97	1.02 (1.02-1.02)	186	2.78	1.41 (1.33-1.50)
20-29	2771	47.51	1.57 (1.54-1.60)	205	3.51	1.78 (1.59-1.97)
30-39	2265	32.76	1.08 (1.08-1.09)	177	2.56	1.29 (1.24-1.35)
40-49	1942	30.15	1	127	1.97	1
50-59	1491	29.73	0.98 (0.98-0.98)	144	2.87	1.45 (1.34-1.56)
60-69	987	29.14	0. 96 (0.96-0.96)	138	4.07	2.06 (1.69-2.43)
70-79	574	22.49	0.74 (0.73-0.76)	125	4.89	2.48 (1.83-3.13)
≥80	238	18.09	0.60 (0.56-0.63)	49	3.72	1.89 (1.41-2.36)
Sex						
Male	9910	45.36	1	808	4.03	1
Female	9033	39.35	0.86 (0.86-0.86)	816	4.03	1 (1.00-1.00)
Ethnicity‡						
European	13193	42.14	1	1069	3.41	1
Māori	1521	23.47	0.55 (0.54-0.56)	282	5.69	1.66 (1.55-1.78)
Pacific	513	21.85	0.51 (0.49-0.53)	118	6.35	1.86 (1.60-2.11)
Asian	592	15.53	0.36 (0.34-0.39)	52	1.66	0.48 (0.41-0.55)
Other	105	25.33	0.60 (0.54-0.65)	5	1.07	0.31 (0.07-0.56)
Deprivation						
1-2	3339	37.25	1	217	2.64	1
3-4	2905	33.05	0.88 (0.88-0.89)	270	3.35	1.26 (1.22-1.31)
5-6	2671	31.29	0.84 (0.83-0.84)	310	3.96	1.5 (1.41-1.58)
7-8	2433	29.13	0.78 (0.77-0.78)	365	4.76	1.8 (1.65-1.95)
9-10	2108	25.20	0.67 (0.66-0.68)	439	5.72	2.16 (1.93-2.40)
Total	19234	42.88	n.a.	1624	3.62	n.a.

Table 3.4 Numbers and rates (average rate per 100 000 population per year) of giardiasis notifications and hospitalisation population) by season, rural–urban domicile, age group, sex, ethnicity, and deprivation level, 1997–2008

	Notifications			**Hospitalisations**		
Category	No[a]	Rate*	RR (95% CI)†	No	Rate	RR (95% CI)
Season						
Summer	4804	3.57	1	55	0.04	1
Autumn	5598	4.16	1.16 (1.16-1.17)	62	0.04	1.12 (1.09-1.16)
Winter	4750	3.53	0.98 (0.98-0.98)	70	0.05	1.27 (1.19-1.35)
Spring	4381	3.25	0.91 (0.90-0.91)	61	0.04	1.10 (1.07-1.13)
Urban-Rural						
Main urban	13774	43.23	1	146	0.45	1
Satellite urban	515	38.66	0.89 (0.88-0.90)	13	0.97	2.13 (0.82-3.43)
Independent urban	1633	31.10	0.71 (0.70-0.72)	33	0.62	1.37 (1.19-1.54)
Rural, high urban	578	45.43	1.05 (1.04-1.05)	8	0.62	1.37 (1.01-1.72)
Rural, moderate urban	672	47.40	1.09 (1.08-1.10)	12	0.84	1.84 (0.96-2.73)
Rural, low urban	960	31.69	0.73 (0.72-0.73)	26	0.85	1.87 (1.24-2.50)
Remote rural	335	50.43	1.16 (1.14-1.18)	4	0.60	1.31 (0.90-1.71)
Age group						
0-4	4542	139.87	3.71 (3.42-4.00)	54	1.66	3.96 (0.82-7.10)
5-9	1610	46.91	1.24 (1.23-1.26)	13	0.37	0.90 (0.85-0.95)
10-19	852	12.77	0.33 (0.32-0.35)	17	0.25	0.60 (0.49-0.72)
20-29	2218	38.02	1.01 (1.00-1.01)	32	0.54	1.30 (1.16-1.44)
30-39	4756	68.80	1.82 (1.78-1.87)	36	0.52	1.24 (1.14-1.34)
40-49	2425	37.64	1	27	0.41	1
50-59	1553	30.92	0.82 (0.81-0.82)	29	0.57	1.37 (1.18-1.57)
60-69	984	29.05	0.77 (0.76-0.78)	22	0.64	1.54 (1.19-1.90)
70-79	373	14.61	0.38 (0.36-0.41)	13	0.50	1.21 (1.07-1.35)
≥80	120	9.12	0.24 (0.20-0.27)	5	0.38	0.90 (0.83-0.98)
Sex						
Male	9818	44.88	1	116	0.53	1
Female	9375	40.81	0.90 (0.90-0.91)	132	0.57	1.08 (1.06-1.09)
Ethnicity‡						
European	13054	41.70	1	178	0.56	1
Māori	1007	14.29	0.34 (0.32-0.35)	45	1.01	1.78 (1.44-2.13)
Pacific	163	2.13	0.05 (0.04-0.05)	6	0.05	0.09 (0.005-0.18)
Asian	529	4.49	0.10 (0.10-0.11)	5	0.04	0.07 (-0.01-0.15)
Other	239	2.93	0.07 (0.06-0.07)	9	0.15	0.27 (0.21-0.39)
Deprivation						
1-2	4577	51.06	1	34	0.37	1
3-4	3644	41.46	0.81 (0.80-0.81)	47	0.53	1.41 (1.24-1.57)
5-6	3529	38.18	0.74 (0.74-0.75)	38	0.44	1.17 (1.10-1.23)
7-8	3086	36.94	0.72 (0.71-0.73)	54	0.64	1.70 (1.38-2.02)
9-10	2429	29.04	0.56 (0.55-0.57)	73	0.87	2.30 (1.61-2.98)
Total	19533	43.55	n.a.	283	0.63	n.a.

Table 3.5 Numbers and rates (average rate per 100 000 population per year) of cryptosporidiosis notifications and hospitalisation population) by season, rural–urban domicile, age group, sex, ethnicity, and deprivation level, 1997–2008

	Notifications			**Hospitalisations**		
Category	No[a]	Rate*	RR (95% CI)†	No	Rate	RR (95% CI)
Season						
Summer	1154	2.57	1	31	0.06	1
Autumn	2011	4.48	1.74 (1.68-1.80)	27	0.06	0.87 (0.82-0.91)
Winter	1336	2.97	1.15 (1.14-1.16)	38	0.08	1.22 (1.13-1.31)
Spring	5399	12.03	4.68 (4.22-5.14)	170	0.37	5.48 (1.78-9.18)
Urban-Rural						
Main urban	5054	16.94	1	100	0.31	1
Satellite urban	262	20.50	1.21 (1.17-1.24)	3	0.22	0.71 (0.48-0.94)
Independent urban	1255	25.02	1.47 (1.43-1.51)	73	1.29	4.43 (0.94-7.91)
Rural, high urban	508	41.56	2.45 (2.14-2.76)	7	0.55	1.75 (0.77-2.73)
Rural, moderate urban	690	51.48	3.03 (2.57-3.49)	11	0.77	2.47 (0.32-4.62)
Rural, low urban	1606	58.99	3.48 (3.05-3.90)	53	1.75	5.57 (0-12.44)
Remote rural	472	76.28	4.50 (3.07-5.92)	13	1.95	6.23 (0-23.98)
Age group						
0-4	4286	131.99	17.78 (8.84-26.72)	93	2.86	14.19 (0-52.23)
5-9	1432	41.72	5.62 (4.27-6.96)	49	1.42	7.07 (0-19.10)
10-19	1073	16.09	2.16 (2.01-2.32)	29	.43	2.15 (1.24-3.06)
20-29	978	16.76	2.25 (2.08 -2.43)	34	.58	2.88 (1.05-4.72)
30-39	1038	15.01	2.02 (1.89-2.14)	24	.34	1.72 (1.22-2.21)
40-49	478	7.42	1	13	.20	1
50-59	253	5.04	0.68 (0.65-0.70)	12	.23	1.18 (1.06-1.31)
60-69	157	4.63	0.62 (0.58-0.66)	4	.11	0.58 (0.34-0.82)
70-79	60	2.35	0.31 (0.26-0.37)	4	.15	0.77 (0.60-0.94)
≥80	26	1.97	0.26 (0.19-0.34)	4	.30	1.50 (0.75-2.25)
Sex						
Male	4839	22.12	1	105	0.47	1
Female	4942	21.51	0.97 (0.97-0.97)	161	0.70	1.46 (1.35-1.56)
Ethnicity‡						
European	7563	24.16	1	213	0.66	1
Māori	703	6.75	0.27(0.26-0.29)	40	0.42	0.64 (55-0.72)
Pacific	107	1.19	0.04(0.03-0.05)	2	0.01	0.02 (-0.02-0.06)
Asian	153	1.39	0.05(0.05-0.06)	1	0.01	0.01 (-0.06-0.06)
Other	3	0.25	0.01(0.008-0.01)	9	0.07	0.11 (0.04-0.2)
Deprivation						
1-2	2304	25.70	1	39	0.43	1
3-4	1920	21.84	0.85 (0.84-0.85)	64	0.72	1.67 (1.39-1.95)
5-6	1538	18.02	0.70 (0.69-0.71)	46	0.53	1.23 (1.15-1.32)
7-8	1346	18.02	0.62 (0.61-0.63)	63	0.75	1.73 (1.41-2.04)
9-10	985	11.77	0.45 (0.44-0.47)	53	0.63	1.45 (1.27-1.63)
Total	9900	22.07	n.a.	282	0.62	n.a.

SECTION I: KEY FINDINGS

1. A review of the global literature on the environmental and social determinants of enteric zoonoses indicates that global environmental change, particularly changes in climate and agricultural land use patterns will have a considerable influence on enteric zoonotic disease risk. Furthermore, the response and resilience of humans to such change will be strongly mediated by population characterises.

2. In New Zealand, a review of the evidence characterising the association between climatic factors, agricultural land use and enteric disease incidence suggests that this aspect of infectious disease research is undervalued. Review findings indicated that the potential for large scale climatic and agricultural land use variables to influence environmental pathogen load, transmission potential and ultimately human disease risk is substantial.

3. The reported incidence of campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis in New Zealand is relatively high when compared to other developed countries. An analysis of epidemiological characteristics of notifications and hospitalisations in New Zealand from 1997-2008 highlighted inequalities in disease burden. Infants and the elderly, Māori and Pacific Peoples, rural populations and those residing in socio-economically deprived areas were more severely and disproportionately affected by these diseases. Disease rates were also seasonal, with campylobacteriosis showing a summer peak for both urban and rural populations, while both cryptosporidiosis and salmonellosis notification rates were distinctly higher in rural areas with a dominant spring peak.

SECTION II: CHAPTER 4 SEASONALITY IN ENTERIC ZOONOTIC DISEASES: A SYSTEMATIC REVIEW

4.1 Introduction

Seasonality is characteristic of many infectious diseases (Fisman 2007, Naumova, Jagai et al. 2007). Enteric diseases typically exhibit seasonal patterns which tend to be more pronounced in temperate countries (Chapter 3) and display seasonal peaks alternating with low background levels of infection (Checkley, Epstein et al. 2000, Kelly-Hope, Alonso et al. 2008). Campylobacteriosis and salmonellosis peak in summer and decrease in winter (Kovats, Edwards et al. 2004, Kovats, Edwards et al. 2005, Keegan, Majowicz et al. 2009). Among protozoan diseases, cryptosporidiosis has a definite seasonality, with spring peaks reported in the United Kingdom and New Zealand and summer-autumn peaks in the United States and Canada (Naumova, Chen et al. 2000, Callaghan, Cormican et al. 2009, Snel, Baker et al. 2009). In contrast, giardiasis is markedly less seasonal, albeit with an early autumn peak in some countries (Odoi, Martin et al. 2003).

To date, international comparisons of enteric zoonotic diseases have been restricted to a single disease (Nylen, Dunstan et al. 2002, Laupland, Schonheyder et al. 2010) or pathogen groups (Hörman, Korpela et al. 2004), associations with weather variables (Bi, Cameron et al. 2008), other specific risk factors (Ravel, Smolina et al. 2010), outbreaks (Karanis, Kourenti et al. 2007) or the burden of non-pathogen specific diarrhoeal disease (Prüss, Kay et al. 2002, Kosek, Bern et al. 2003). Multi-pathogen studies are generally limited to detailed analyses of regional data (e.g. (Naumova, Jagai et al. 2007, Denno, Keene et al. 2009)). There exists no compiled evidence documenting seasonality across enteric zoonotic diseases in temperate, developed countries. Such a cross-country, multi-disease approach may be especially informative when integrating trans-boundary issues such as human health and environmental change.

4.2 Chapter Aim

In this chapter, I used a systematic review of the literature and statistical summaries of temporal distribution to establish: (i) the existence (or absence) of a consistent, pattern of disease incidence and quantify the overall magnitude of

temporal inequality for each pathogen; and, (ii) compare monthly disease patterns among regions by applying a seasonality index.

4.3 Methods

Focusing on regions governed by similar climate mechanisms would be useful to identify environmental and population influences underlying seasonal variations in disease (Altizer, Dobson et al. 2006). Consequently, this study was confined to temperate regions. It is equally important to also account for dominant non-climatic differences among countries that may mask seasonal patterns (Jagai, Castronovo et al. 2009). This was achieved by limiting this review to OECD (Organisation for Economic Co-operation and Development) member states; countries that have relatively similar economies, public health infrastructure, population dynamics and disease reporting standards.

4.3.1 Systematic Review

4.3.1.1 Search strategy

Using three electronic databases, PubMed, Web of Science and Embase, we searched publications across the 1960-2010 period that quantified the temporal patterns of campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis in humans. The keywords used were: (“season”, “seasonality” “temporal”), AND (“campylobacteriosis” “campylobacter”, “salmonellosis”, “salmonella”, “cryptosporidiosis” “cryptosporidium”, “giardiasis” “giardia”). No language or database restrictions were imposed on the searches. For each disease, citations resulting from the database searches were exported into a master library, and duplicates removed based on parameters of identical author, date and title. Full-text versions of the articles that fulfilled the eligibility criteria were obtained and their reference lists were manually searched to identify any further relevant manuscripts. The bibliographies of reviews published on pathogen specific epidemiology were also examined to identify additional sources for inclusion in the analysis.

4.3.1.2 Study selection

Screening of articles for eligibility consisted of two steps. The first step aimed to exclude papers not relevant to the review and consisted of (i) identifying papers where research was conducted in non-OECD or tropical regions or polar regions (studies conducted outside of 23.5°N - 66.5°N and 23.5°S - 66.5°S) and, (ii) assessing the residual citations using the question "Does the title, and/or abstract and text explicitly describe data relating to the temporal and/or seasonal variation in the disease of interest in humans?" (O'Connor, Denagamage et al. 2008). Here, an explicit description of seasonal variation consisted of text and/or graphics documenting the number or percentage of cases or incidence rates over the study duration.

The second stage involved critically evaluating the studies using the following *a priori* established criteria. Studies were included if (i) they had been conducted continuously for a minimum of a full year to cover all seasons, (ii) the primary outcome was a laboratory confirmed diagnosis of the enteric pathogen of interest, (iii) the study reported case data temporally (day, week, month) (iv) the study was written in English and published in a peer reviewed journal and, (v) study design did not include intervention trials.

Studies that satisfied the inclusion conditions but failed to be representative of the general population were excluded. These comprised studies that were (i) conducted in institutions (e.g. day-care centres, rest homes), (ii) directed at specific demographic groups (e.g. children, elderly) and groups with certain characteristics (immune-compromised, travellers), (iii) studies focussed solely on outbreaks as these studies were generally of a shorter duration and can reflect patterns that may not be typical of disease seasonality generally, (iv) studies looking at broader gastro-enteric outcomes (GI) or infectious intestinal disease (IID), (v) studies focussed on the microbiological and immunological characteristics and molecular ecology of the pathogen, (vi) clinical studies, (vi) review articles, although these were used as a source for additional papers.

4.3.1.3 Data abstraction

All data used here were taken from the papers, either directly from the tables or extracted from graphs using DigitizeIt software (Levy, Hubbard et al. 2009) or in four cases, by contacting authors.

4.3.1.4 Study characteristics

For each pathogen, the relevant studies were examined in detail and the following information recorded: authors and year of publication, location and study duration, study design and sample size, temporal resolution of case data, age range of population, and the timing of the peak number of cases reported.

4.3.2 Seasonality

Based on geographical and political boundaries studies were assigned to the following regions: United Kingdom (UK) which includes Ireland, Scotland and Wales; Continental Europe which includes studies in mainland Europe; North America (USA); Canada; Oceania (Australia and New Zealand); and the Asian region. As a majority of the data came from countries in the northern hemisphere, data from the southern hemisphere countries were adjusted by six months for the opposite season (i.e. January in the northern hemisphere was aligned with July in the southern hemisphere) (Laupland, Schonheyder et al. 2010). Seasons were defined based on their occurrence in the Northern hemisphere: Winter (December-February), spring (March-May), summer (June-August) and autumn (September-November).

Disease patterns were assessed using the Gini coefficients (Gini 1912) and a monthly seasonality index. Study-specific monthly averages were obtained by dividing the total number of cases for each month by the number of relevant months in the study. For example, to calculate the average for January over January 1992- December 1995, the number of cases in each month were added together and divided by the number of relevant months in the study (in this case, four). Next, an annual average for each study was calculated by dividing by the number of monthly averages (e.g. January average + February average …… ÷ 12 = annual average). Study-specific monthly averages were divided by the annual average and thus converted to proportions (e.g. January average ÷ annual average

= January proportion) (Tierney, Waller et al. 1999). These proportions were used for the calculation of the Lorenz curve, Gini coefficient and the monthly seasonality index.

4.3.2.1 Lorenz curve and Gini coefficient

In order to characterize seasonality for each disease Lorenz curve models (Lorenz 1905) were developed for each disease and the corresponding Gini coefficients determined (Gini 1912). In this study, the Lorenz curve is a graphical representation of the cumulative distribution of disease incidence as a function of proportion of the year. If incidence is equally distributed across the year, the Lorenz curve is represented by a straight 45° diagonal line (no heterogeneity). The 'concavity' of the curve represents the concentration of cases through the year. To calculate and plot the Lorenz curve, the study-specific proportions were ranked by ascending order of incidence. The ranked cumulative incidence was plotted against the cumulative proportion of the year.

For this study, a higher Gini coefficient indicated a more uneven distribution of cases through the year. With the same ranked data used to plot the Lorenz curve, Gini Coefficients, (G), were calculated for each study using the formula presented by Lee (Lee 1997). To take into account variation in each individual study, using the program R (v. 2.12.2) (R Development Core Team 2012), a Gini Coefficient and its error structure was estimated for each study. For each disease, an overall Gini Coefficient and associated variance was estimated by bootstrapping (Llorca and Delgado-Rodriguez 2002). These measures have previously been extensively applied to demonstrate socio-economic inequality, and more recently in infectious disease epidemiology to assess seasonality (Green, Krause et al. 2006) and allow easily interpretable comparisons across diseases (Elliott, Blanchard et al. 2002).

4.3.2.2 Monthly seasonality index

For each disease, a monthly seasonality index (Tierney, Waller et al. 1999) was applied to describe both overall and regional variations in seasonal patterns. To create overall monthly seasonality indices for each disease, the study-specific monthly proportions were averaged and converted to percentages. For example, if

March had a value of 173, it would mean that the proportion of cases in March was 73% higher than the 12 month average. A plotted confidence interval of plus and minus one standard deviation accompanied each overall monthly index.

To obtain region specific monthly indices, the study-specific monthly proportions from each region were averaged and plotted. The strength of this index is that this method reduces the variability that may occur from combining data from years with high number of cases to years with low annual numbers, because it focuses on the relative monthly incidence (Tierney, Waller et al. 1999). The index allows a visual comparison of monthly seasonal patterns across diseases and among regions. It also describes where (region) seasonality is evident and when (months) incidence is highest.

4.4 Results

4.4.1 Systematic review

The results of the search strategy and study selection for each of the four pathogens are given in Figure 4.1. Across all the diseases, a total of 3652 titles and abstracts were screened for eligibility. Of these, 74 studies from 19 countries conducted across 1960-2010 met the selection criteria and contributed to the systematic review and subsequent analyses (Appendix 1).

4.4.2 Seasonality

4.4.2.1 Lorenz curve and Gini coefficient

For all diseases, the Lorenz curve and corresponding Gini coefficient indicated the departure from uniformly distributed incidence through the year. The Lorenz curve for campylobacteriosis, salmonellosis and giardiasis was even with the giardiasis curve being a little shallower. Cryptosporidiosis showed a sharp skew in the curve indicating a clear, narrow peak in temporal incidence. The corresponding Gini coefficients were as follows: campylobacteriosis 0.22 (0.18-0.28), salmonellosis 0.22 (0.18-0.26), cryptosporidiosis 0.39 (0.33-0.45), giardiasis 0.18 (0.14-0.24) (Figure 4.2).

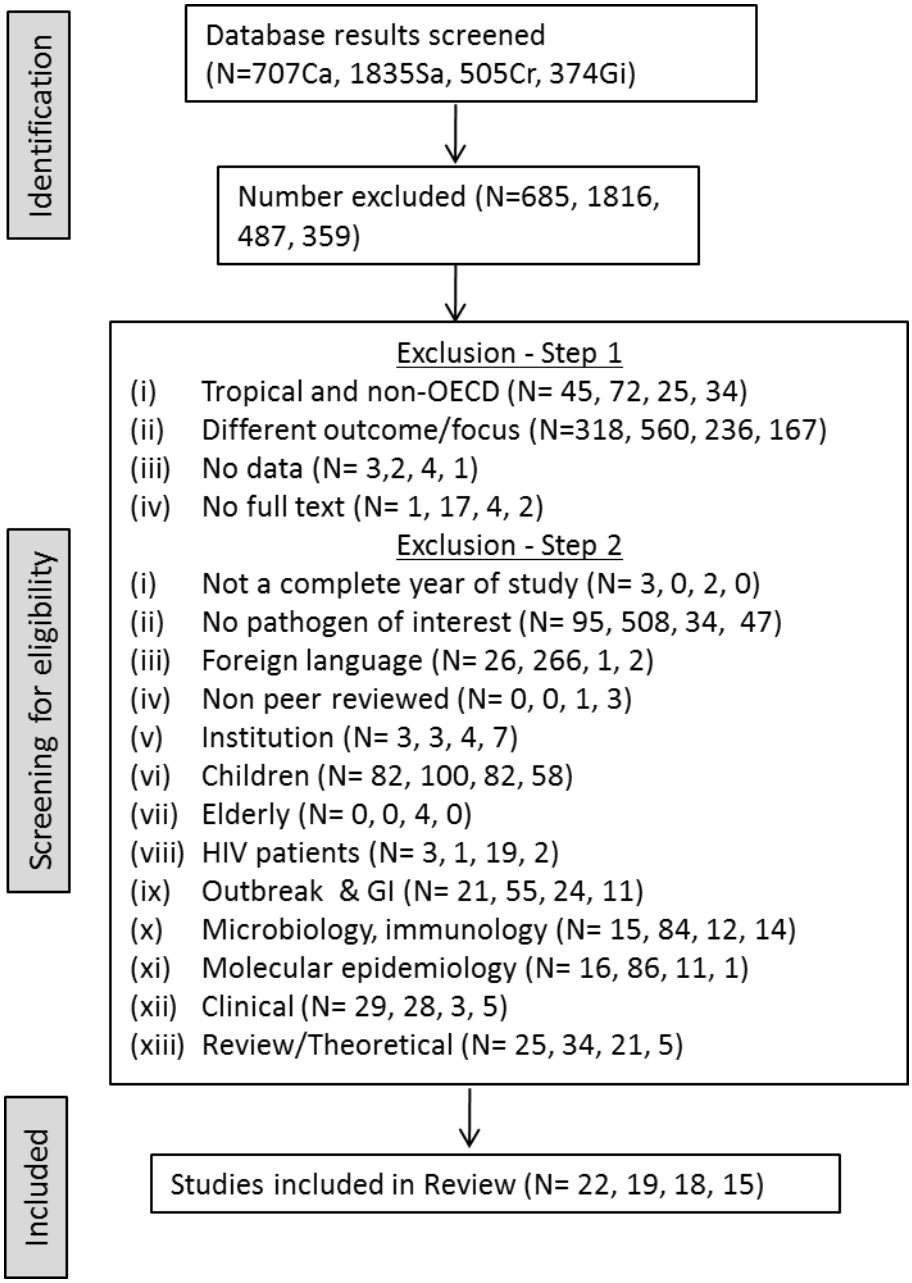


Figure 4.1 Flow chart illustrating criteria for study selection. The grey boxes represent the three major steps relating to article selection process. N is the total number of papers found across all three database searches; the suffixes represent the disease (Ca-Campylobacteriosis, Sa-Salmonellosis, Cr-Cryptosporidiosis, Gi-Giardiasis). This order is maintained throughout the diagram

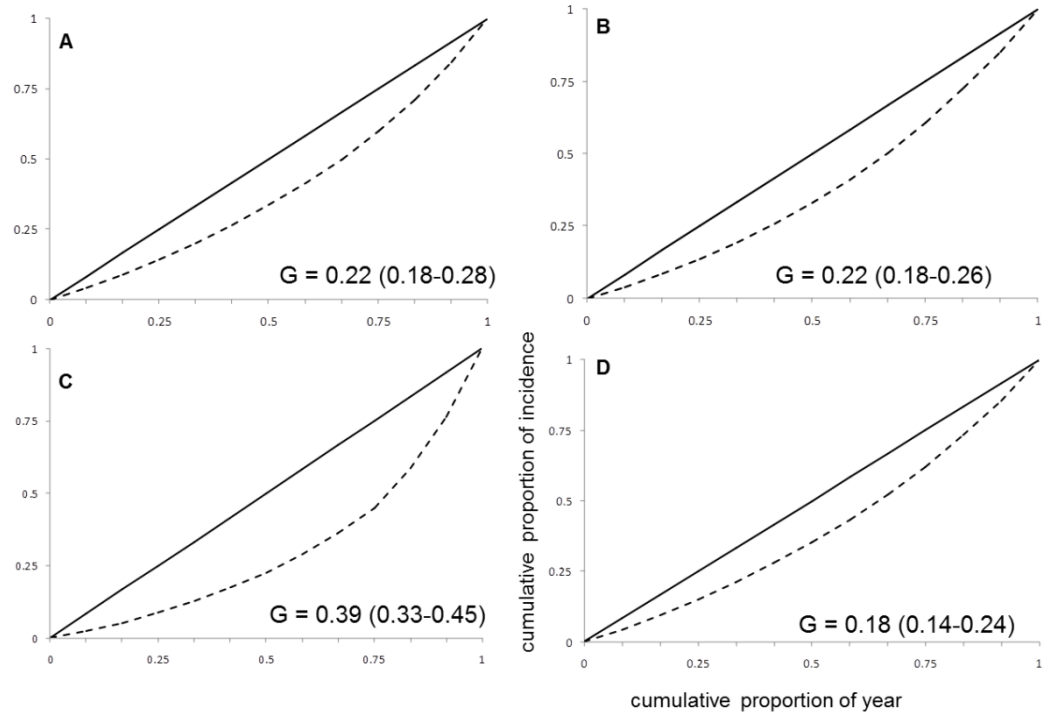


Figure 4.2 The Lorenz curves and corresponding Gini co-efficient (95% confidence intervals) for each disease. Disease curves showing cumulative distribution of disease incidence as a function of proportion of the year. The solid black line represents equal incidence through the year, and the dotted line represents the cumulative incidence. (A-campylobacteriosis, B-salmonellosis, C-cryptosporidiosis, D-giardiasis)

4.4.2.2 Monthly seasonality index

When disease incidence was pooled up to the multi-national scale, seasonal patterns were distinct. Regional variations in these patterns were evident for all the diseases (Figure 4.3).

Campylobacteriosis

The overall monthly seasonality index for campylobacteriosis peaked in summer (July-August) (Figure 4.3A). Regionally, North America, UK, Europe and Canada peaked between June-August with the UK peaking the earliest in June and Canada the latest in August. When adjusted for northern hemisphere seasons, the Oceanic region showed two seasonal peaks, once in May and again in September (Figure 4.3A).

Salmonellosis

The overall monthly seasonality index curve for salmonellosis was wider, spreading from summer-early autumn (June-September) (Figure 4.3B). US peaked first in June-July followed by Canada and Europe in July, and then the UK and Asia in August (Figure 4.3B). The disease incidence in these countries exhibited a decrease through the rest of the year. Adjusted for the northern hemisphere season, the Oceanic region showed a peak in spring (February-March) and a relatively small increase over autumn (October-November).

Cryptosporidiosis

The overall monthly index for cryptosporidium indicated a clear bi-modal peak, in spring (April) and late summer-early autumn (August-September), with the latter being considerably larger (Figure 4.3C). Separately, all countries considered here had one major peak (Figure 4.3C). The adjusted incidence in Oceanic countries (Australia, New Zealand) together with the UK exhibited a strong spring peak (April) with an additional second smaller autumn peak (September) shown by the Oceanic countries. North America, Canada, and the rest of Europe displayed a late summer peak, with Canada showing a small spring peak. In all countries represented, the lowest number of cases was recorded in winter.

Giardiasis

The monthly seasonality index for giardia showed a small summer peak (Figure 4.2D). Here, Oceania, Europe and Canada displayed a small spring peak (March-May), while the US, UK and Canada showed a larger summer peak (July-September) (Figure 4.3D). The UK and Canada peaked first around July, followed by US in August and Europe in September.

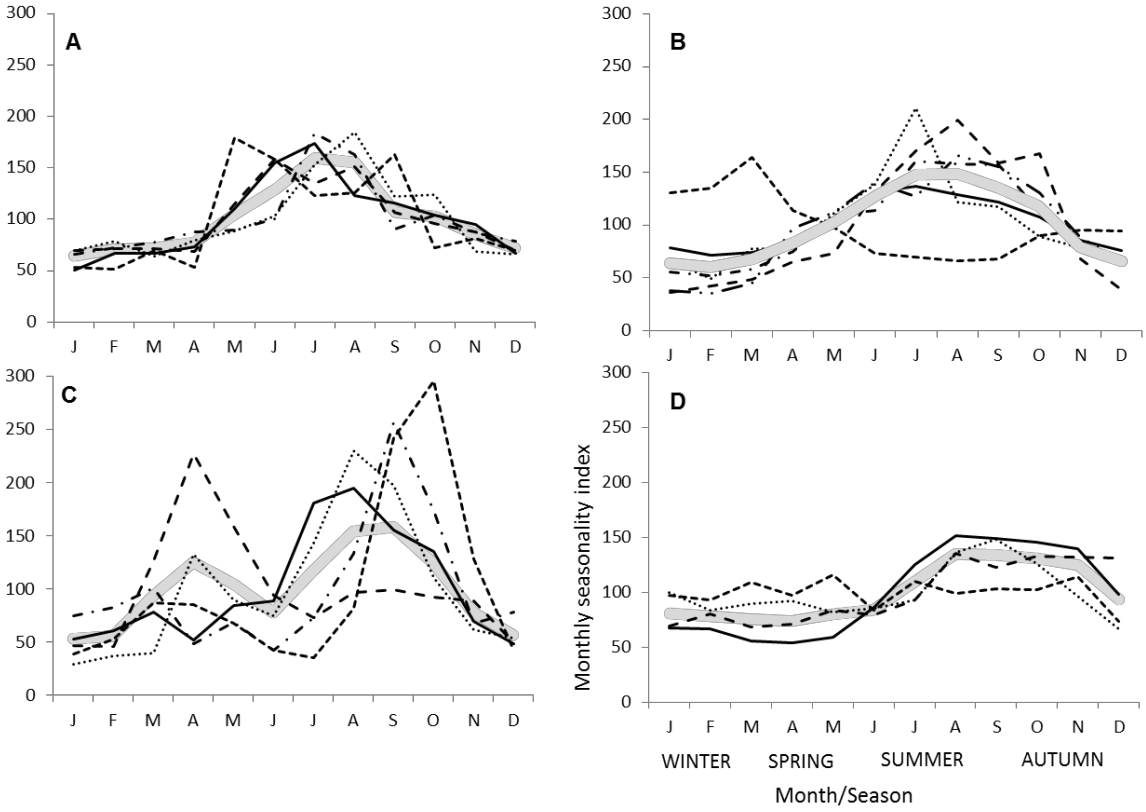


Figure 4.3 Disease specific, regional monthly seasonality indices. Months and seasons shown refers to month/seasons of the northern hemisphere (i.e. January = month 1) and adjusted by six months for the southern hemisphere (i.e. January = month 7). Seasons are December, January, February (winter), March, April, May (spring), June, July, August (summer), September, October, November (autumn). Regional seasonal patterns (——) Overall, (– – –) United Kingdom, (——) USA, (.....) Canada, (– · –) Europe, (– – – –) Oceania, (— · ·) Asia. CI of plus and minus one standard deviation is plotted. (A-campylobacteriosis, B-salmonellosis, C-cryptosporidiosis, D-giardiasis)

4.5 Discussion

Based on data from 74 studies, regular, cyclical patterns were observed for all enteric zoonotic diseases, with campylobacteriosis, salmonellosis, and cryptosporidiosis displaying distinct season associated peaks. This review used easily interpretable measures of seasonality across diseases to compare monthly incidence patterns among major regions. Although global reviews of general seasonality in these diseases have typically focussed on the climate-disease association (Kovats, Edwards et al. 2005, Jagai, Castronovo et al. 2009) and these

results are not strictly comparable with these studies, they are largely consistent with literature published on individual diseases.

There are several potential mechanisms proposed to explain seasonal patterns in enteric diseases. Although attributing causal mechanisms for seasonal patterns is beyond the scope of this study, the discussion of seasonality in these diseases is centred on two principal mechanisms believed to significantly influence disease patterns globally: (i) environmental influences on pathogen occurrence and pathogen-host interactions and (ii) population behaviour and characteristics.

Findings showed that seasonal variation in enteric zoonotic diseases is ubiquitous. The consistent summer peak in bacterial diseases suggests the direct effect of a large-scale environmental influence on a shared exposure route. Although the spring peak in salmonellosis in the oceanic region may be due to a seasonal exposure such as livestock as shown in New Zealand (Clarke and Tomlinson 2004) , unlike other regions this line represents a single study (D'Souza et al. 2004), making generalisation difficult. As food is the dominant vehicle for transmission of these pathogens in many countries (Kessel, Gillespie et al. 2001), it is probable that higher temperatures associated with summer increase the risk of food borne transmission (D'Souza, Becker et al. 2004). For example, a study undertaken across six European countries reported a strong association between average monthly temperature and *Campylobacter* incidence in both broiler chickens and humans (Jore, Viljugrein et al. 2010). For food borne illnesses, sustained warmer temperatures could increase length of transmission seasons, enhancing opportunities for food related, seasonal enteric disease outbreaks (Tirado, Clarke et al. 2010). Additionally, summer highs of campylobacteriosis in temperate countries have been hypothesised to occur as a result of summer increases in house fly density (Nichols 2005), with flies acting as mechanical vectors of transmission, thereby enhancing seasonal prevalence (Ekdahl, Normann et al. 2005), although further studies are needed.However, it has also been shown that in New Zealand (Britton, Hales et al. 2010) and the United Kingdom (Lake, Gillespie et al. 2009) the association of bacterial enteric disease with climatic

variables has weakened over time, suggesting that targeted health policies and obligatory industrial regulations were effective. Therefore, a proactive multidisciplinary approach to disease control and prevention could mitigate some of these impacts expected with future environmental change, particularly for predominantly food borne pathogens.

Regional variations in seasonal patterns provide an insight into the complex hierarchical and nonlinear nature of interactions between environmental, pathogen and host specific factors and transmission opportunities (Figure 4.2). For cryptosporidiosis, all represented regions had a prominent seasonal peak, commonly with a second smaller peak (bi-modal seasonal pattern), suggesting important regional variations in disease drivers. For example, both New Zealand and the UK displayed a prominent spring peak along with a smaller one in autumn for New Zealand.Young livestock are a significant reservoir of enteric pathogens (Atwill, Johnson et al. 1999), and synchronisation of agricultural practices such as calving take place in both New Zealand and the UK in spring (Verkerk 2003, Grinberg, Pomroy et al. 2005). In New Zealand the majority of human cases in spring have been attributed to the bovine strain with peaks in autumn due to the human strain (Learmonth, Ionas et al. 2001, Learmonth, Ionas et al. 2004). Analogously, the UK has reported similar seasonal shifts in *Cryptosporidium* strains affecting humans, with zoonotic sources hypothesised to dominate in spring and anthroponotic sources in autumn (Chalmers, Smith et al. 2011).

Spring peaks in cryptosporidiosis incidence may also be related to contamination of water supplies through heavy rainfall events. A study in North West England showed that in areas with marked seasonal patterns, cryptosporidiosis in spring was associated with increased rainfall (Naumova, Christodouleas et al. 2005). In the same geographic region, a significant association between maximum river flows and cryptosporidiosis cases in spring were found, suggesting that increased seasonal pathogen load coupled with heavy rainfall could result in seasonally high disease rates (Lake, Bentham et al. 2005).

Results for giardiasis indicated minimal inequality in incidence through the year as suggested by the Gini coefficient and seasonality index. Giardiasis incidence and spread is thought to be mainly a result of anthroponotic risk factors and transmission (Kettlewell, Bettiol et al. 1998, Hoque, Hope et al. 2003). So, the slightly elevated summer highs shown in the US, UK and Canada may imply transmission in warmer months as a consequence of outdoor activities (Welch 2000) and exposure to untreated water sources (Greig, Michel et al. 2001). Thus, both periodic oscillations in environmental factors and host characteristics are important seasonal forcing mechanisms driving epidemiological patterns in enteric diseases.

Although few studies have documented interactions between environmental and population factors, these effects are not mutually exclusive. For example, although a positive association between temperature and *Salmonella* incidence in retail chicken and human cases in Canada was found, it was summer barbequing and gardening that were identified as primary risk factors (Ravel, Smolina et al. 2010). In New Zealand, population drinking water quality was found to modify the positive association between rainfall and cryptosporidiosis, with better quality drinking water having a protective effect (Britton, Hales et al. 2010).

Understanding disease specific seasonal patterns is important for improving existing disease surveillance methods, generating appropriate prevention strategies, developing valid prediction models, and enhancing cross-border cooperation. Although an individual level focus is often necessary to infer causality (Hill 1965), assessing population level patterns allows ecological processes, which typically function at international scales, to be integrated into the public health framework (Eisenberg, Desai et al. 2007). This perspective is particularly important for those diseases where trans-boundary environmental change plays a pivotal role in disease incidence (Patz, Daszak et al. 2004), which may not be measurable at the individual scale. Regional variations in seasonal patterns provide an insight into the climatic and non-climatic seasonally mediated factors acting at different spatio-temporal scales, and interacting along a

continuum of influence. These finer scale patterns highlight regions that follow the expected pattern and those that are outliers, which is crucial information to establish region specific determinants of disease variability.

This review highlights the regionally and seasonally varying, context dependant, inter-relationships between environmental processes, pathogen physiology and intrinsic population attributes as drivers of enteric disease patterns. Nonetheless, this study has certain shortcomings. First, as this study aimed to assess seasonal patterns in zoonotic diseases in the general population, it did not focus on host characteristics and seasonal patterns for particular demographic groups (such as children, the elderly or immune suppressed), possibly resulting in a simplification of seasonal patterns (e.g. (George and Manges 2010)). Second, as a consequence of the keywords used and concentration on studies conducted in English, it is possible that this search strategy missed some relevant studies. However, by searching three different databases and checking reference lists of all relevant articles and reviews, I believe the majority of the appropriate literature was identified. Third, as the primary aim of this study was to describe seasonal patterns, studies using different designs and methodologies were included (e.g.(Jagai, Castronovo et al. 2009)), assuming differences would be independent of seasonal trends over time (Nylen, Dunstan et al. 2002, Naumova, Jagai et al. 2007). Fourth, although seasonal variations may be due to differences in reporting systems across countries, relevant data on reporting delays were generally not available. Reporting variations will introduce changes in the annual timing of seasonal peaks, but this will not affect the pattern on seasonal timescales, assuming that systems are nationally consistent.

The Lorenz curve and Gini coefficients are influenced by sample variability and length of study, and high values may not be indicative of actual seasonality. Although data were standardised to a monthly scale, it is accepted that the studies being of varying duration could affect interpretation of results. The current approach was validated by excluding studies conducted for a year and since no significant change was found, they were included in the final review. While

recognising the limitations of this method, when taken together with the seasonality index and the seasonal patterns documented by the individual authors (Appendix 1), the Gini coefficient remains useful as a relative indicator of potentially seasonally associated variation and warrants further research. Combining data from geographically and climatically diverse areas implies that subtle differences in seasonal patterns among countries may have been lost, although an attempt to reduce this effect by selecting studies from temperate areas only was made. Finally, the monthly seasonality index was biased towards countries with presumably more established research settings (Carneiro, Roca-Feltrer et al. 2010). However, regional grouping also highlighted potential gaps in the availability of comparable, published data (e.g. salmonellosis in New Zealand) (Tucker and Gilliland 2007).

The objective of this chapter was to evaluate whether enteric zoonotic diseases exhibited patterns coincident with season and to review the results in the light of two primary mechanisms thought to influence global enteric disease patterns. It was assumed that if the studies were reasonably representative of the general population, study duration was sufficient, and reporting systems and target populations did not vary greatly between years, existing seasonal patterns would be cyclical and distinguishable. Based on these results, it is concluded that large scale environmental influences and associated host demographics will determine seasonal enteric disease patterns through their effect on host pathogen load, transmission opportunities and spread (McMichael 2001, Plowright, Sokolow et al. 2008).

CHAPTER 5 CLIMATE VARIABILITY AND ENTERIC DISEASE INCIDENCE IN NEW ZEALAND: TIME SERIES ANALYSIS USING AUTO-REGRESSIVE INTEGRATED MOVING AVERAGE (ARIMA) MODELS

5.1 Introduction

Global climate change is projected to increase the frequency and intensity of extreme climatic events such as floods, droughts and cyclones (IPCC 2007, IPCC 2012). These climatic conditions have been associated with increased enteric disease risk (Checkley, Epstein et al. 2000, Curriero, Patz et al. 2001, Hall, D'Souza et al. 2002, Naumova, Jagai et al. 2007). Moreover, atypical weather known to accompany climatic phenomena such as *El Niño* have been implicated in enteric disease outbreaks worldwide (Jofre, Blanch et al. 2010). Despite this evident association with climatic factors, our understanding of the impacts of regional climate variability on infectious disease risk is driven primarily by research focussed on malaria (Poveda, Rojas et al. 2001), dengue (Earnest, Tan et al. 2012), cholera (Cash, Rodó et al. 2010) and influenza (Shaman and Lipsitch 2013). Examining the associations between regional climate linked to the *El Niño*/Southern Oscillation (ENSO) and enteric disease will develop our understanding of climatic triggers for enteric infections.

The effect of the ENSO on global climate, through inter-annual fluctuations in temperature, precipitation and atmospheric circulation at distant locations is termed teleconnection. The climate in New Zealand shows a strong teleconnection to the ENSO, with cooler and drier conditions during the *El Niño* phase and warmer and wetter conditions during the *La Niña* phase (Gordon 1985). Associations between temperature and salmonellosis (Britton, Hales et al. 2010) and rainfall and cryptosporidiosis and giardiasis (Lake, Pearce et al. 2008, Britton, Hales et al. 2010) and distinct seasonal patterns (Lal, Hales et al. 2012) (Chapter 3 and 4) suggest that investigating the effect of region wide climatic variability may help improve predictions of enteric disease responses to regional climate change.

5.2 Chapter aim

In this chapter I investigated the role of regional climate variability and local weather variations on enteric disease incidence. Seasonal Auto-Regressive Moving Average (SARIMA) models were built to analyse monthly incidence of campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis in relation to

the Southern Oscillation Index (SOI) and average monthly temperature and rainfall.

5.3 Methods

5.3.1 Disease data

All notified cases of campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis during the period 1997-2008 in New Zealand were obtained from the National Notifiable Disease Surveillance system (EpiSurv), operated by the Institute of Environmental Science and Research (ESR) for the NZ Ministry of Health. Cases were defined as a clinical illness with appropriate laboratory confirmation which requires isolation of the pathogen (*Campylobacter* spp., *Salmonella* spp., *Cryptosporidium* spp., *Giardia* spp.) from a clinical specimen (Ministry of Health 2012). To better evaluate lagged effects, only cases with a reported onset date were used. In total, 79193 cases of campylobacteriosis, 14084 cases of (non-typhoidal) salmonellosis, 8092 cases of cryptosporidiosis and 10424 cases of giardiasis were included in the analysis.

Using onset date, cases were aggregated into counts by month over the study period. National incidence rates were calculated using the monthly number of cases as the numerator and the 2001 census population as the denominator (Statistics New Zealand 2010). To lessen the effect of extreme values (e.g. outbreaks) on model outcomes and to normalise the data, the natural logarithm of monthly incidence rates were used.

5.3.2 Climate data

For 1997-2008, daily surface average temperature (°C) and average rainfall (millimetres) were obtained from surface temperature and precipitation time series records constructed from gridded climate data and spatially averaged over New Zealand as specified by latitude (35.25S) to (47.75S) and longitude (166.25E) to (177.75E) (IRI/LDEO 2007). These values were aggregated monthly.

The SOI is the most commonly used index to measure the intensity of an ENSO event. It is based on the differences in atmospheric pressure between Tahiti in the eastern equatorial Pacific and Darwin, Australia in the west Pacific, expressed as a standard deviation from the norm. Negative anomalies are generally associated with El Niño events and positive anomalies with La Niña events. The monthly SOI for 1997-2008 was obtained from the Australian Bureau of Meteorology.

5.3.3 Data analysis

All climate variables that showed a cross correlation with disease incidence up to a lag of two months were included in the model. These cross correlations were tested using STATA v11.1 (StataCorp LP, College Station, TX, USA). multivariate seasonal autoregressive integrated moving average (SARIMA) model was used to examine the combined effect of climatic variables on enteric disease incidence for each of the diseases separately. As both the dependent and independent variables exhibited periodicity, they were seasonally differenced before analysis (as described below).

5.3.4 Model specification

Using incidence data from 1997-2007, a SARIMA model was fitted to disease data and used to predict incidence rates for each of the four diseases in 2008 (Luz, Mendes et al. 2008). To check for seasonal effects, the time series plot of monthly incidence was examined and an Augmented Dickey-Fuller (ADF) test was used. To achieve a stationary time series, monthly incidence was seasonally differenced by replacing each observation by the difference between itself and the observation a year ago. The climatic variables were also seasonally differenced.

To examine the independent contribution of climatic variables to enteric disease incidence a Seasonal ARIMA model that includes seasonality, referred to as SARIMA(p, d, q)(P, D, Q), where p denotes the AR order, d the differencing order and q the MA order was used. P, D and Q denote the seasonal order of AR, differencing, and MA, respectively. Akaike's Information Criterion (AIC) was used to assist model selection (Akaike 1974). To check for seasonal effects, and help identify the model parameters, the Autocorrelation function (ACF) and

partial autocorrelation function (PACF) were analysed. The residuals were further examined for autocorrelation using ACF and PACF.

Goodness of fit was examined through Portmanteau test for white noise (Ljung and Box 1978) in residuals and a scatter plot of residuals versus fitted values. The Portmanteau test is a test for autocorrelation in the residuals of a model: the null hypothesis is that there is no serial correlation in the residuals. Furthermore, the disease dataset was divided into two: one (1997-2007) was used for the model fitting process (parameter estimation), and another for prediction (2008). To verify model fit, the predictive ability of both models (with and without climatic variables) was assessed using the Diebold- Mariano test (Diebold and Mariano 2002), which tests the null hypothesis of equal accuracy using Mean Absolute Percentage Error (MAPE) and Mean Absolute Error (MAE). Lower MAPE and MAE values indicate a better fit of the data. Finally, a plot of time series on the cumulative sums of actual and predicted values was used to assess model validity. All analyses were conducted using STATA v11.1 (StataCorp LP, College Station, TX, USA).

5.4 Results

5.4.1 Descriptive analyses

Descriptive statistics for the notification and weather variables are presented in Table 5.1. Correlations between the differenced independent variables indicate that relationships between surface temperature, rainfall and SOI were neither strong nor statistically significant at the monthly scale (Table 5.2). Cross correlations co-efficient between seasonally differenced disease incidence and lag periods showed that campylobacteriosis was correlated with temperature two months previously (R^2=0.15), salmonellosis was positively correlated with temperature of the current (R^2=0.46), the previous (R^2=0.21) and previous two months (R^2=0.32) temperature. Salmonellosis was also positively correlated with SOI of the current (R^2=0.31), the previous (R^2=0.30) and previous two months (R^2=0.32). Cryptosporidiosis was positively correlated with temperature of the current (R^2=0.27), the previous (R^2=0.20) and previous two months (R^2=0.16)

temperature. Cryptosporidiosis was negatively correlated with current months rainfall (R^2=-0.15) and positively associated with SOI (R^2=0.24) two months previously. Giardiasis was positively with temperature of the current month (R^2=0.13) and SOI of the previous two months (R^2=-0.24), and inversely correlated to the rainfall of the current month (R^2=-0.12).

5.4.2 Model specification

The log transformed and differenced time series shows less periodicity than the original monthly incidence, with no apparent trend (Figure 5.1). The Augmented Dickey-Fuller (ADF) test (Dickey and Fuller 1981) for unit root was compared with the 1%, 5%, and 10% critical values to indicate rejection of the null hypothesis. For all diseases, t_α values were less than the critical values and hence the time series was considered stationary (Table 5.3).

For campylobacteriosis, the best model was SARIMA (1, 0, 0) $(2, 0, 0)_{12}$ (Log-likelihood = 23.63, AIC =-37.26) (Table 5.4). Campylobacteriosis incidence was positively associated with the temperature of the previous two months, but there was no relationship with precipitation or SOI (Table 5.5). The model estimated without the climatic variables was a slightly better fit than the model with these variables (Table 5.4).

For salmonellosis, a SARIMA (1, 0, 0) $(1, 0, 0)_{12}$ model was the best fit (Log-likelihood = -20.37, AIC =48.74) (Table 5.4). The temperature and SOI of the current month, and lagged by 1 and 2 months were associated with incidence, but there was no relationship with precipitation (Table 5.5). The model estimated with the climatic variables was a better fit than the model without these variables (i.e. the log-likelihood increased, while AIC decreased) (Table 5.4).

For cryptosporidiosis, the best fitting model was SARIMA (1, 0, 0) $(1, 0, 0)_{12}$ (Log-likelihood = -78.53, AIC =165.06) (Table 5.4). Temperature and precipitation of the current month, temperature (lagged by 1 and 2 months) and the SOI (lagged by 2 months) were each associated with cryptosporidiosis onset

(Table 5.5). The model estimated with the climatic variables was a better fit than the model without these variables (Table 5.4).

For giardiasis, the best model was SARIMA (1, 0, 0) $(1, 0, 1)_{12}$ (Log-likelihood = -20.37, AIC =48.74) (Table 5.4). The temperature and precipitation of the current month and SOI of the previous 2 months were associated with disease (Table 5.5). The model estimated without the climatic variables was a better fit than the model without these variables (Table 5.4).

For all four diseases, the plots of the ACF and PACF of the residuals of the chosen models showed no significant temporal correlation between residuals at different lags (Figure 5.2) and the scatter plot of the predicted values against the residuals showed no discernible pattern (Figure 5.2). Portmanteau Q statistics for campylobacteriosis, salmonellosis, cryptosporidiosis, and giardiasis of 51.22, 53.09, 51.22 and 41.85, respectively. For all four diseases, we failed to reject the null hypothesis of no serial correlation between residuals.

5.4.3 Validation model

Out-of-sample predictions for the year 2008 were compared with the observations. The chosen models (SARIMA (1, 0, 0) $(2, 0, 0)_{12}$ for campylobacteriosis, SARIMA (1, 0, 0) $(0, 0, 1)_{12}$ for salmonellosis, SARIMA (1, 0, 0) $(1, 0, 0)_{12}$ for cryptosporidiosis and SARIMA (1, 0, 0) $(1, 0, 1)_{12}$ for giardiasis) were realistically appropriate models for forecasting incidence (Figure 5.3). Results of the Diebold-Mariano test for forecasting accuracy indicated that for salmonellosis and cryptosporidiosis the multivariate models were better, while values for the unadjusted and multivariate models for campylobacteriosis and giardiasis were not significantly different from each other (Table 5.6). Finally, a plot of the predicted and actual rates along with the cumulative sums of actual and predicted values for disease incidence showed that the models were a reasonable fit (Figure 5.3).

Table 5.1 Descriptive statistics for the disease and climatic variables in New Zealand, during 1997-2008

Variable	Mean ±SD	Minimum	Maximum
Campylobacteriosis‡	14.90±5.88	4.84	34.33
Salmonellosis‡	2.85±1.24	0.96	6.74
Cryptosporidiosis‡	1.64±1.43	0.24	5.94
Giardiasis‡	1.93±0.48	0.96	3.48
Rainfall (mm)	142.16±35.50	63.00	240.39
Temperature (°C)	10.71±3.46	4.63	17.62
SOI	1.98±14.79	-37.70	42.90

‡Average monthly incidence /100 000 population

Table 5.2 Spearman's correlation coefficients between independent climatic variables

Variable	Temperature (°C)	SOI
Rainfall (mm)	0.13	0.007
Temperature (°C)		0.01

Table 5.3 Results of the Augmented Dickey-Fuller test for examining stationarity of the transformed, seasonally differenced time series for all four diseases

Variable†	Dickey-Fuller test for unit root			
	t_α	1%	5%	10%
Campylobacteriosis	-3.97*	-3.50	-2.88	-2.57
Salmonellosis	-5.39**	-3.50	-2.88	-2.57
Cryptosporidiosis	-4.18**	-3.50	-2.88	-2.57
Giardiasis	-10.00**	-3.50	-2.88	-2.57

† Log-transformed and seasonally differenced monthly incidence /100 000 population

* $p<0.05$

** $p<0.01$

*** $p<0.001$

Table 5.4 Regression coefficients (β) and standard error (SE) of the chosen SARIMA models (with and without climatic predictors) on the monthly incidences of campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis in New Zealand

Variable	**Model without climate variables** [abcd]		**Model with climate variables** [efgh]	
	β	SE	β	SE
Campylobacteriosis				
Autoregression	0.79***	0.05	0.79***	0.06
Seasonal autoregression (1)	-0.73***	0.09	-0.73***	0.10
Seasonal autoregression (2)	-0.28**	0.10	-0.28**	0.10
Temperature -2months previous			0.01	0.01
Salmonellosis				
Autoregression	0.71***	0.07	0.63***	0.07
Seasonal autoregression	-0.50***	0.06	-0.48**	0.07
Temperature current month			0.11***	0.02
SOI current month			0.005*	0.002
SOI previous month			0.005*	0.002
Cryptosporidiosis				
Autoregression	0.75***	0.04	0.73***	0.05
Seasonal autoregression	-0.56***	0.08	-0.61***	0.08
Temperature previous month			0.13**	0.04
SOI -2months previous			-0.008*	0.004
Giardiasis				
Autoregression	0.44***	0.08	0.39***	0.08
Seasonal autoregression	-0.24*	0.11	-0.24	0.13
Seasonal moving average	-0.85***	0.23	-0.78***	0.18
Temperature current month			0.02	0.01
Precipitation current month			-0.0004	0.0003
SOI -2months previous			-0.001	0.001

[a] Campylobacteriosis, log-likelihood = 23.63, AIC =-37.26
[b] Salmonellosis, log-likelihood = -20.37, AIC =48.74
[c] Cryptosporidiosis, log-likelihood = -78.53 AIC = 165.06
[d] Giardiasis, log-likelihood = 39.10 AIC = -68.20
[e] Campylobacteriosis, log-likelihood = 23.39, AIC =-34.79
[f] Salmonellosis, log-likelihood = -4.65, AIC = 29.31
[g] Cryptosporidiosis, log-likelihood = -68.00, AIC = 154.00
[h] Giardiasis, log-likelihood = 39.48 AIC = -62.97
* $p<0.05$
** $p<0.01$
*** $p<0.001$

Table 5.5 Spearman's rank cross correlation coefficients of (seasonally differenced) disease incidence and climatic variables in New Zealand

Variable	Lag0	Lag1	Lag2
Campylobacteriosis			
Temperature	-	-	0.15
Rainfall	-	-	-
SOI	-	-	-
Salmonellosis			
Temperature	0.46	0.21	0.32
Rainfall	-	-	-
SOI	0.31	0.30	0.32
Cryptosporidiosis			
Temperature	0.27	0.20	0.16
Rainfall	-0.15	-	-
SOI	-	-	0.24
Giardiasis			
Temperature	0.13	-	-
Rainfall	-0.12	-	-
SOI	-	-	0.24

Table 5.6 Forecasting accuracy of SARIMA unadjusted and multivariate (with climatic predictors) models for all four diseases

	Unadjusted		Multivariate	
	MAPE	MAE	MAPE	MAE
Campylobacteriosis	1.29	0.16	1.28	0.16
Salmonellosis	1.01	0.21	0.90	0.19*
Cryptosporidiosis	1.17	0.31	1.14*	0.33*
Giardiasis	1.41	0.14	1.33	0.14

*$p<0.05$

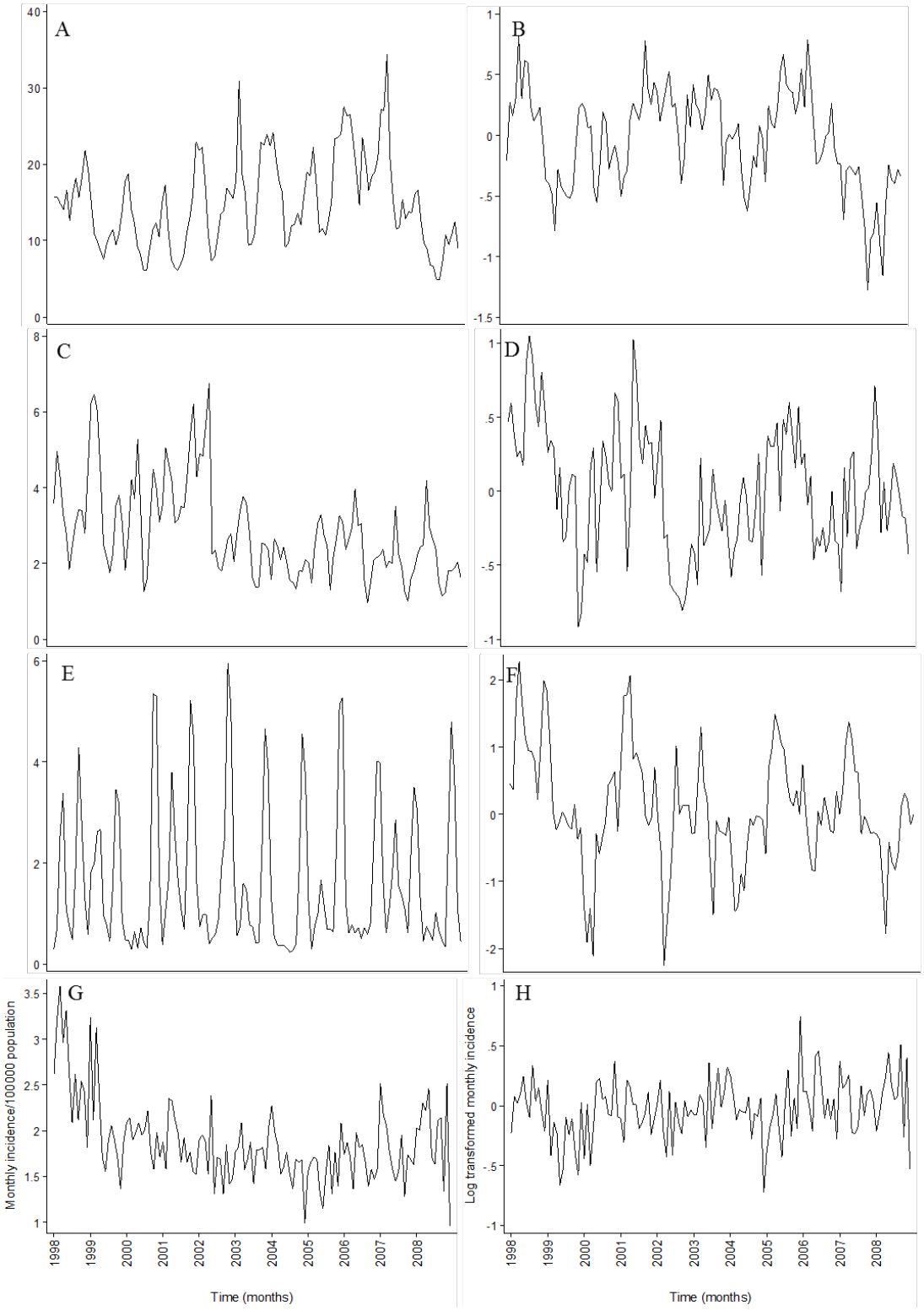


Figure 5.1 Time series of raw and log transformed monthly incidence (after seasonal differencing) of campylobacteriosis (A-B), salmonellosis (C-D), cryptosporidiosis (E-F), and giardiasis (G-H) in New Zealand, 1997-2008

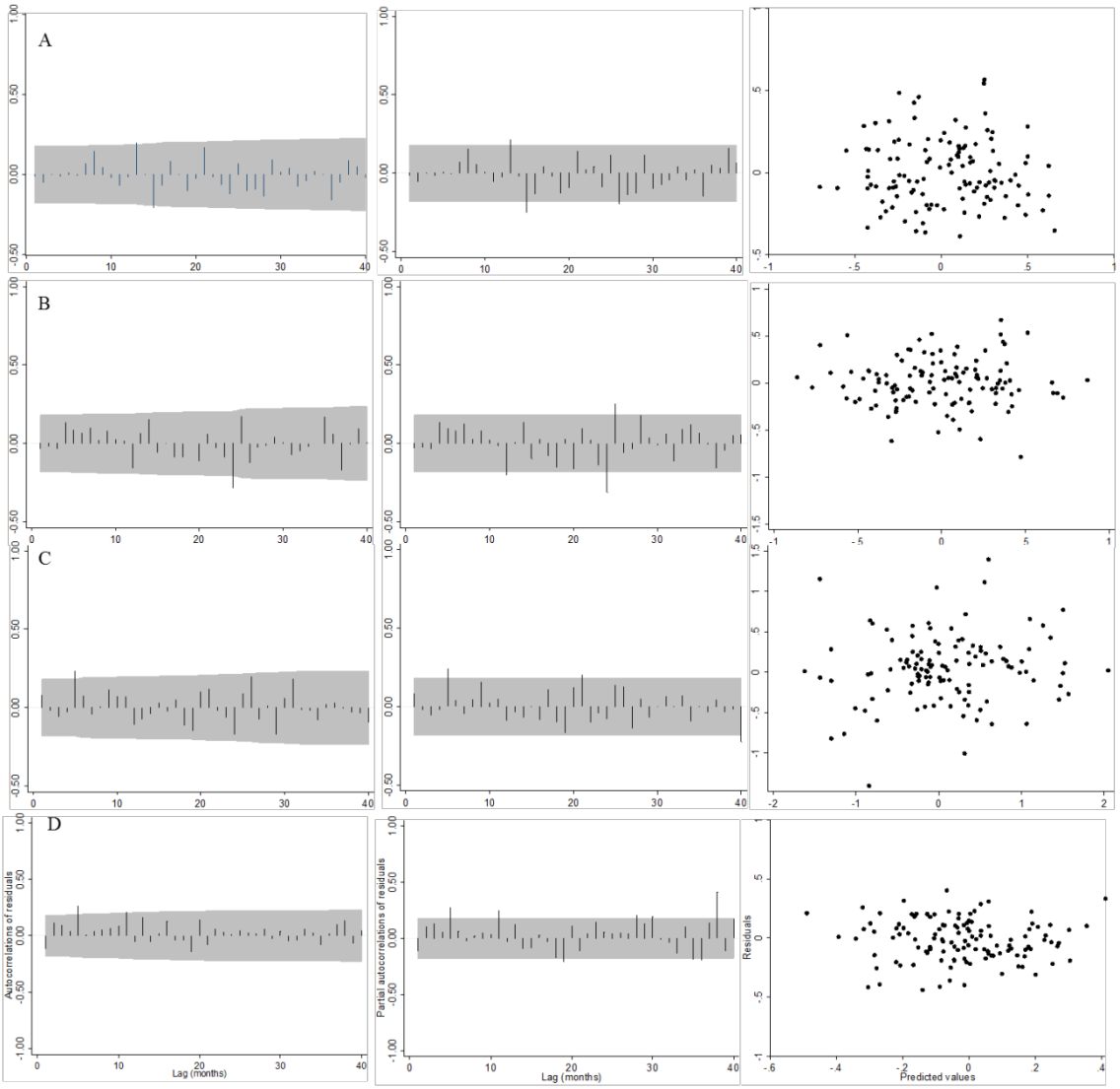


Figure 5.2 Autocorrelation plots, partial autocorrelation plots of the residuals and scatter plot of residuals against the predicted values of the seasonal autoregressive moving average SARIMA model fitted to the natural logarithm differenced disease incidence. Campylobacteriosis SARIMA (1, 0, 0) $(2, 0, 0)_{12}$ (A-C), salmonellosis SARIMA (1, 0, 0) $(1, 0, 0)_{12}$ (D-F), cryptosporidiosis SARIMA (1, 0, 0) $(1, 0, 0)_{12}$ (G-I), giardiasis SARIMA (1, 0, 0) $(1, 0, 1)_{12}$ (J-L). The x-axis gives the number of lags in months and the grey shaded areas represent the 95% confidence interval

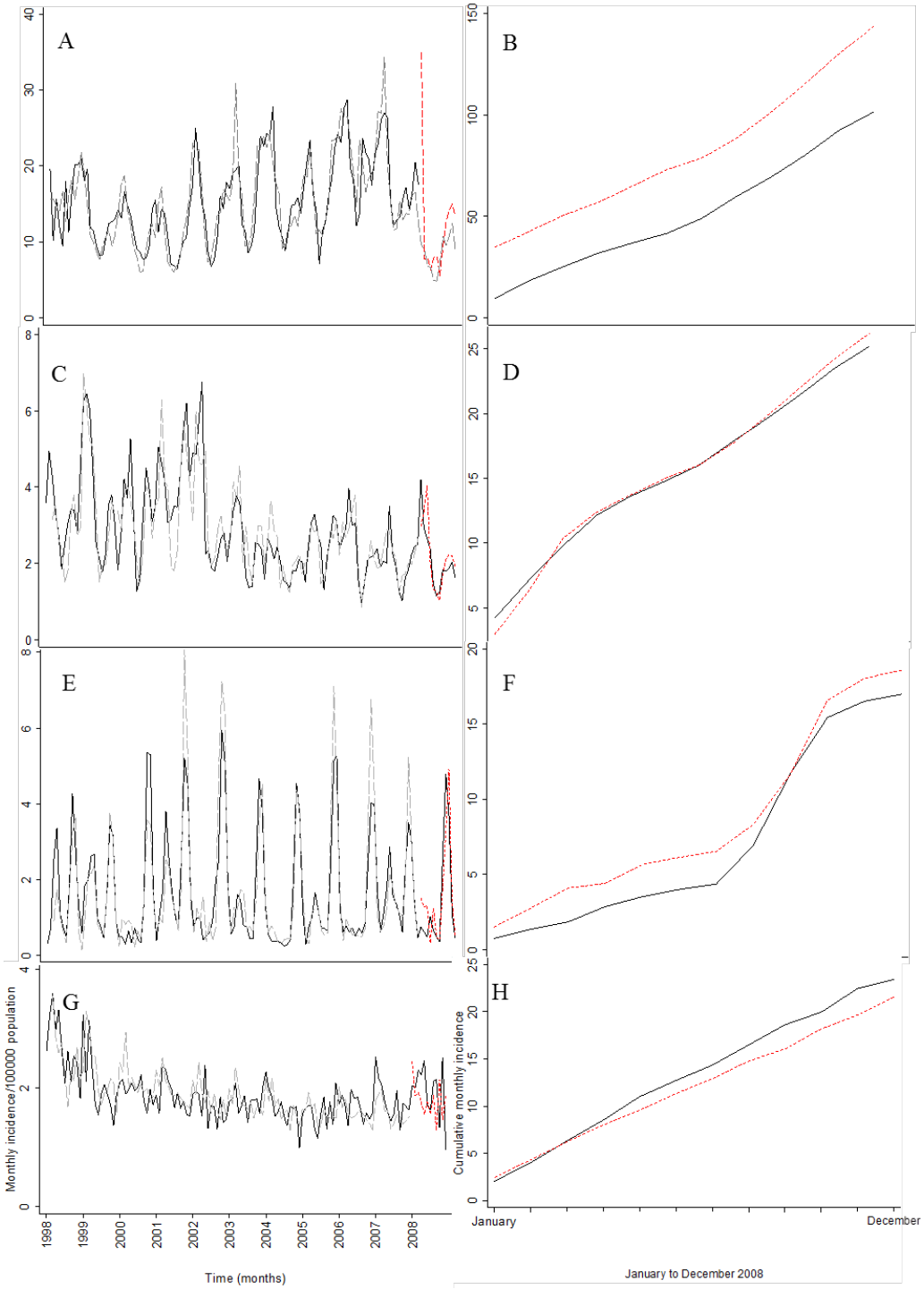


Figure 5.3 (A-C-E-G) Actual monthly incidence /100 000 population (black line), rates predicted by the chosen SARIMA models for each disease (grey dashed line) and rates predicted for the validation period (January to December 2008) (red dashed line). (B-D-F-H) Cumulative monthly incidence /100 000 population of the actual rates (black line) and rates predicted by the chosen SARIMA models for each disease (red dashed line) from January to December 2008 (validation period). Campylobacteriosis (A-B), salmonellosis (C-D), cryptosporidiosis (E-F), giardiasis (G-H). The y axis gives the monthly incidence and the x axis represents time in months

5.5 Discussion

The findings from this chapter suggest that inter annual climate variability, indicated by the ENSO phenomenon (measured by the SOI) in association with regional temperature and precipitation has a general influence on enteric disease incidence. In particular, regional climatic factors are significant predictors of salmonellosis and cryptosporidiosis but not campylobacteriosis or giardiasis.

Temperature and SOI of the current month and SOI of the previous month were positively and significantly associated with monthly salmonellosis incidence, with a dominant summer peak in cases (Figure 5.1B). These results are consistent with previous research, globally (Kovats, Edwards et al. 2004) and in New Zealand (Britton, Hales et al. 2010). Due to the ENSO driven teleconnection patterns for New Zealand, positive SOI or *La Niña* like conditions in New Zealand are typically characterised by anomalous north-easterly airflows (Gordon 1986), bringing warmer, wetter weather to most of the country (Salinger and Mullan 1999). Given the thermophilic nature of *Salmonella* spp. (Mackey and Derrick 1987), warmer temperatures would allow enhanced *Salmonella* survival and proliferation (Phungamngoen, Chiewchan et al. 2011). This increased pathogen load could subsequently be easily spread through food (Sumner, Raven et al. 2004), water (Franklin, Fielding et al. 2009) or contaminated environments (Ravel, Smolina et al. 2010). As food is the dominant source of *Salmonella* in many countries (Kessel, Gillespie et al. 2001, Doorduyn, Van den Brandhof et al. 2006), it is probable that higher temperatures increase the risk of food borne transmission in summer. There may be a substantial temporal lag between climate variation and increase in disease notification where contamination is related to food production or distribution (D'Souza, Becker et al. 2004). Sustained warmer temperatures could increase length of transmission seasons, enhancing opportunities for food handling errors leading to enteric disease outbreaks (Tirado, Clarke et al. 2010). Indeed, enhanced food hygiene regulations over time may be partly responsible for recent weakening of the relationship of salmonellosis with temperature in New Zealand (Britton, Hales et al. 2010).

Livestock are also an important enteric pathogen reservoir in New Zealand with salmonellosis (*Salmonella* Brandenburg) incidence in humans related to the lambing season (Clark, Fenwick et al. 2004). Therefore, it is plausible that agricultural runoff and subsequent contamination of drinking water supplies has a role to play in disease transmission. Private well water, prone to contamination has been associated with increased salmonellosis risk (Uhlmann, Galanis et al. 2009). Such a transmission pathway would also result in a delayed disease response. Interestingly, despite the distinct epidemiologies of different *Salmonella* serotypes (Pires and Hald 2010), broad associations with regional climate were detected in our study. The delayed effect found here is similar to those reporting positive lagged relationships between salmonellosis and temperature in England and Wales (Bentham and Langford 2001, Kovats, Edwards et al. 2004), Canada (Fleury, Charron et al. 2006) and Australia (Zhang, Bi et al. 2010).

Analysis of long term data in New Zealand shows a 0.5°C warming since 1950 (Fitzharris 2007), a decrease in the diurnal temperature range (Easterling, Horton et al. 1997), fewer days with temperatures below 0°C and an increase in the number of days with temperatures above 30°C in warmer locations (Plummer, Salinger et al. 1999). Although sub national patterns in the intensity and range of these effects are acknowledged, based on the results of the present study, increasing temperatures in New Zealand could favour higher *Salmonella* loads in the environment due to the well-established link between bacteria and temperature. At the same time, warmer temperatures could also affect social habits such as increased outdoor activity, potentially enhancing opportunities for *Salmonella* transmission. In New Zealand, a 15% increase in salmonellosis for every 1°C rise in average monthly temperature has been predicted (Britton, Hales et al. 2010). Similarly, in Australia, climate and demographic change are estimated to result in a significant increase in salmonellosis (Zhang, Bi et al. 2012). Taken together, these findings suggest the potential for salmonellosis to become a major public health concern as a consequence of climatic changes in New Zealand.

For cryptosporidiosis, average temperature of the previous month was positively associated with monthly incidence, while SOI two months previously was inversely related with incidence. A similar positive association with temperature of the previous month has been reported in the United States (Naumova, Jagai et al. 2007), Australia (Hu, Tong et al. 2007) the United Kingdom (Lake, Bentham et al. 2005) and previously in New Zealand (Lake, Pearce et al. 2008). In the latter study, authors suggested that recreational activities such as swimming and outdoor camping may be important in driving transmission in autumn (time of year when an association with temperature was reported) (Lake, Pearce et al. 2008). Although the lagged response may be attributed to reporting delays, I attempted to minimise this bias by using the case onset date rather than reporting date.

A spring peak in cryptosporidiosis (Figure 5.1E-F) is thought to be associated with agricultural practices, notably the birth of livestock (Learmonth, Ionas et al. 2001). There is a strong association between calves infected with *C. parvum* and the occurrence of diarrhoea and scours (Trotz-Williams, Jarvie et al. 2005), providing ample opportunities for spread. In addition, increased exposure due to close handling of new-born livestock by children is likely a risk factor for infection (Gormley, Little et al. 2011) .In New Zealand, significantly higher cryptosporidiosis rates in rural areas (Britton, Hales et al. 2010) and outbreaks linked to farm visits support this (Stefanogiannis, McLean et al. 2001). Thus, the positive association with temperature could be due to an indirect effect of climate, whereby seasonal exposure to high pathogen loads typically takes place in warmer conditions. Conversely, the spring season is when the strongest linear relationship between the state of the Southern Oscillation (measured by the SOI) and New Zealand temperature and precipitation anomalies is seen (Mullan 1995).

The negative association of cryptosporidiosis with SOI in this study suggests a link between incidence and *El Niño* like conditions, which, in New Zealand, are typically characterised by an increased frequency of cold south-westerly airflows (Salinger and Mullan 1999), leading to decreased temperatures and drier than

usual conditions (Basher and Thompson 1996). Negative values of the SOI are linked to reduced peak flow and flood frequency in major river systems in New Zealand (Mosley 2000). This finding could have important implications for the predominantly waterborne *Cryptosporidium* spp. In England and Wales, 20% of waterborne disease outbreaks in the twentieth century were due to extended periods of low rainfall, as opposed to 10% of outbreaks associated with heavy rainfall (Nichols, Lane et al. 2009). A global analysis of diarrhoeal incidence in children found a negative linear association with rainfall (Lloyd, Kovats et al. 2007), consistent with the results of a cross-sectional study in the Pacific Islands (Singh, Hales et al. 2001). In Australia, a negative relationship between weekly rainfall, relative humidity, and cryptosporidiosis incidence, and a positive association with temperature, suggest that extended dry periods may also affect transmission (Hu, Mengersen et al. 2010). Droughts or prolonged dry periods can lead to greater effluent pathogen concentration in water sources which can be flushed out by subsequent periods of rainfall. Such conditions have been known to overwhelm water supply infrastructure in the past leading to cryptosporidiosis outbreaks (Atherton, Newman et al. 1995, Curriero, Patz et al. 2001). Such a transmission pathway may also partly explain the lag between SOI and disease incidence found here.

Consistent with global trends attributed to anthropogenic or human dominated climate change, increased variability in rainfall patterns and increased drought intensity have been observed in New Zealand (Plummer, Salinger et al. 1999). Moreover, relationships between river flow regimes and interdecadal climatic changes (McKerchar and Henderson 2003) as well as a relationship between SOI and water quality (independent of changes in flow linked to rainfall variability) (Scarsbrook, McBride et al. 2003) have been reported. Such changes may be influential in driving future patterns of waterborne cryptosporidiosis. However, the effect of rainfall on disease incidence can be modified by the quality of drinking water supplies, with better quality drinking water providing a protective effect (Britton, Hales et al. 2010).

Changes in rainfall patterns could also have important consequences for New Zealand pasture production (Zhang, Valentine et al. 2007). Given the importance of zoonotic transmission from livestock (Learmonth, Ionas et al. 2001), changing pasture production could result in geographical shifts in agricultural systems/practices with follow on effects for health. Exploring the influence of interactions between climatic and land use processes on enteric disease risk would provide a useful baseline for future zoonotic disease projections.

The lack of an apparent relationship of climatic factors with campylobacteriosis is in keeping with the literature which shows mixed results. For example, in Australia an inverse relationship between weekly temperature and campylobacteriosis cases in Adelaide was shown, while a positive relationship was reported in Brisbane (Bi, Cameron et al. 2008). Previous research in New Zealand examining the spatial determinants of campylobacteriosis found that climate was not significantly associated with the rate of human infections (Rind and Pearce 2010, Spencer, Marshall et al. 2011). A detailed examination of campylobacteriosis seasonality in New Zealand and other European countries found that the seasonal peak in New Zealand was the most variable (Nylen, Dunstan et al. 2002), indicating a seasonal trigger that may be unrelated to climate. One possible reason for this finding is that historically, retail poultry has been the dominant source of *Campylobacter* infection in humans (Mullner, Shadbolt et al. 2010), with infections being positively associated with consumption of inadequately cooked chicken (Eberhart-Phillips, Walker et al. 1997), fast food outlet density (Rind and Pearce 2010) and urban residence (Spencer, Marshall et al. 2011). This suggests that the summer peak seen here may be more reasonably related to activities such as summer barbequing and consumption of undercooked chicken (Doorduyn, Van Den Brandhof et al. 2010), or contamination rates in chicken flock (Jore, Viljugrein et al. 2010). As a significant decline in campylobacteriosis in New Zealand following industry led interventions has been noted (Sears, Baker et al. 2011), it is likely that strengthening food production practices and food hygiene may be an adequate adaptation to reduce campylobacteriosis risk with climate change (Lake, Gillespie

et al. 2009). The drastic 54% decline in campylobacteriosis cases in 2008 compared with previous years (Sears, Baker et al. 2011) may also indicate why the model forecasts in this study did not perform that well (Figure 5.3A).

The absence of a relationship between climate and giardiasis rates seen here is in contrast to an earlier study in which spatial patterns in giardiasis notifications were positively, albeit weakly, associated with temperature (Britton, Hales et al. 2010). In New Zealand, high disease rates in urban areas (Hoque, Hope et al. 2002) and a significant increase in infection risk linked to changing baby diapers has been reported (Hoque, Hope et al. 2001). This evidence coupled with the relatively small late summer-early autumn increase in cases (Figure 5.1G-H) suggest that human activity may be primary drivers of giardiasis incidence (Lal, Hales et al. 2012) (Chapter 1 and Chapter 3).

Counter-intuitively, it has been documented that large scale climate indices, of which the SOI is one, can outperform local climatic factors when predicting species' dynamics (Hallett, Coulson et al. 2004). While local measures of climate may fail to capture the complexity of the relationships between local weather and ecological processes, climate indices may reflect these associations better, although incompletely (Hallett, Coulson et al. 2004). Moreover, as climate indices represent a composite of climatic variables it has been argued that they are better indicators of natural climate variation than single weather variables (Panackal 2012). In New Zealand, ENSO related variations in atmospheric circulation are dominant drivers of regional temperature and precipitation patterns (Salinger and Mullan 1999). Indeed, large-scale variations in atmospheric circulation in the Southern Hemisphere (represented by the SOI) have a significant influence on local weather characteristics in New Zealand through their effects on rainfall extremes (Ummenhofer and England 2007), river flow (Mosley 2000), temperature and mean sea level pressure (Mullan 1998) and annual snowlines on glaciers (Clare, Fitzharris et al. 2002). Thus, there is a growing body of evidence showing a link between regional weather response and atmospheric circulation.

This study has implications for development of adaptation strategies in response to predicted climates as adaptation responses are more likely to occur at a regional scale. Although the link between atmospheric circulation and regional temperature and precipitation is widely acknowledged, this chapter highlights the limited understanding of interactions between the two in driving disease patterns. This relationship may be critical to understanding the environmental conditions that lead to enteric disease outbreaks. Although preliminary, this chapter provides key considerations for regional climate change adaptation options in New Zealand. By analysing historical disease patterns, such investigations can enhance disease prediction models (Ford, Colwell et al. 2009), identify diseases that are potentially useful markers of changes in global climate or local weather (Patz 2002) and contribute to the development of climate based, early warning systems.

CHAPTER 6 RATE OF RUNOFF AND ENTERIC DISEASE INCIDENCE: TIME SERIES ANALYSIS USING DISTRIBUTED LAG NON-LINEAR (DLNM) MODELS

6.1 Introduction

Given the considerable zoonotic transmission of the selected pathogens (Gradel, Schønheyder et al. 2008, Chalmers, Smith et al. 2011), agricultural runoff is cited as an important transmission pathway (Tong and Chen 2002, Collins and Rutherford 2004). Indeed, increased concentration of enteric pathogens in runoff following extreme rain events has been documented (Atherholt, LeChevallier et al. 1998), indicating the potential for subsequent increases in disease incidence through waterborne transmission of pathogens.

Although the SARIMA models used in Chapter 5 highlighted the importance of lagged climatic effects, the method assumed a linear association between the predictor and the outcome, indicating strong assumptions about the exposure-response shape. In contrast, distributed lag non-linear (DLNM) models specifically model the non-linear exposure-response relationship which is more biologically likely. DLNM models can simultaneously describe non-linear and lagged associations (Gasparrini, Armstrong et al. 2010, Gasparrini and Armstrong 2011). Moreover, modelling the lagged effect of weather variables offers an insight into the short term and long term effects and the possible existence of thresholds beyond which climate-disease relationships might vary (Guo, Barnett et al. 2010, Goldberg, Gasparrini et al. 2011).

6.2 Chapter aim

In this chapter, I used distributed lag non-linear (DLNM) models controlling for seasonal and long term trends without making *a priori* assumptions about the lag relationship between runoff and incidence to association between runoff rate and the weekly incidence of campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis.

6.3 Methods

6.3.1 Disease data

All cases of campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis notified in New Zealand during the period 1997-2008 were obtained from the

National Notifiable Disease Surveillance system (EpiSurv), operated by the Institute of Environmental Science and Research (ESR) for the New Zealand Ministry of Health. For notifications, cases were defined as a clinical illness with appropriate laboratory confirmation. In total, 135898 cases of campylobacteriosis, 19234 cases of salmonellosis, 9900 cases of cryptosporidiosis and 19533 cases of giardiasis were included in the analysis. Using the report date, cases were aggregated into counts by week over the study period.

6.3.2 Climate data

Runoff rate is the the flow of water, from rain, snow melt, or other sources, over land (volume or mass of water per unit area and time). For 1997-2008, daily surface average temperature (°C) and average runoff rate ($kg/m^2/s$) were obtained from time series records constructed from gridded climate data and spatially averaged over New Zealand as specified by latitude (35.25S) to (47.75S) and longitude (166.25E) to (177.75E) (IRI/LDEO 2007). These were aggregated weekly.

6.3.3 Data analysis

For each of the four diseases, weekly counts of cases and weekly runoff rate and temperature were linked by date. A Poisson regression model combined with a distributed lag non-linear model (DLNM) was used to simultaneously describe non-linear and delayed dependencies in the association between incidence and runoff rate after adjusting for the effect of temperature (Armstrong 2006, Gasparrini, Armstrong et al. 2010). Briefly, the DLNM allows the effect of an exposure event (in this case, runoff rate) to be distributed over a specific period of time, simultaneously estimating the different non-linear associations with runoff rate at each lag period and also estimating the non- linear effects across lags, thus providing a comprehensive picture of the exposure-response relationship (Gasparrini, Armstrong et al. 2010). A “natural cubic spline” DLNM with a maximum lag of 6 weeks was used to quantitatively estimate the cumulative effects of runoff rate over the current week and the previous 5 weeks. To estimate the effect of runoff rate after adjusting for the effect of temperature, a two week lag was chosen for temperature and models were centred on the mean

temperature. Previous studies studying climatic variations and campylobacteriosis and salmonellosis have reported a lag that persists for upto 5-6 weeks (Kovats, Edwards et al. 2004, Fleury, Charron et al. 2006).

Degrees of freedom (df) for the predictor and lag were tested to determine the optimal df for each disease specific function, in which each predictor and lag was chosen based on the minimum Akaike Information Criterion (AIC) value. To plot the relationship between runoff rate and campylobacteriosis, I used a DLNM with 3 df and applied 2 df for the lag space for runoff rate, 2 df for temperature and 1df for the lag space for temperature (AIC 9520.52). To plot the relationship between runoff rate and salmonellosis, I used a DLNM with 5 df and applied 2 df for the lag space for runoff rate and 2 df for temperature and 3df for the lag space for temperature (AIC 4694.82). For cryptosporidiosis, I used a DLNM with 4 df and applied 2 df for the lag space for runoff rate and 5 df for temperature and 2 df for the lag space for temperature (AIC 5415.61). For giardiasis, I used a DLNM with 2 df and applied 2 df for the lag space for runoff rate and 4 df for temperature and 3 df for the lag space for temperature (AIC 4384.73). I incorporated natural smooth functions of time, with 2 df to remove the effect of seasonal and long term trend over the time period.

Model fit was evaluated using AIC values. All analyses were performed using R software (version 2.15.1) (R Development Core Team 2012). The “dlnm” package was used to create DLNM models (Gasparrini and Armstrong 2011).

6.4 Results

6.4.1 Descriptive statistics

The annual average of weekly temperature was 14.42°C and runoff rate was 0.36 kg/m^2. On average there were 217 campylobacteriosis, 31 salmonellosis, 15 cryptosporidiosis, and 31 giardiasis notifications per week. Spearman’s rank correlation coefficients between weekly runoff rate, average annual weekly temperature and cases are presented in Table 6.1.

Table 6.1 Spearman's Rank Correlation between environmental variables and enteric disease

Variable	Spearman's Rank Correlation	
	Weekly Runoff rate (kg/m/s)	Weekly Average temperature (°C)
Weekly Runoff rate	1	0.66**
Campylobacteriosis‡	-0.13*	0.09*
Salmonellosis‡	-0.36*	0.53*
Cryptosporidiosis‡	0.06	-0.26*
Giardiasis‡	-0.13*	0.24*

*$p<0.05$
**$p<0.001$
‡Average weekly incidence /100 000 population

6.4.2 Estimated effects of runoff rate

Figure 6.1 is a contour plot showing the relationship between runoff rate and disease specific relative risk at all lags. The estimated effect of runoff rate was non-linear for all diseases with higher relative risks at lower runoff rate for salmonellosis, cryptosporidiosis and giardiasis and higher relative risk at higher runoff rates for campylobacteriosis. For campylobacteriosis, an increased risk at 5-6 weeks was associated with a higher runoff rate of about 0.8 kg/m^2. For salmonellosis, there was a bimodal peak at 0.2 kg/m^2 and 0.6 kg/m^2. Cryptosporidiosis incidence appeared to be positively associated with a lower runoff rate (up to 0.6 kg/m^2) across the entire lag period, while giardiasis incidence showed an effect of a narrow range of runoff (0.4-0.6 kg/m^2) at a lag of less than a week.

Figure 6.2 shows the estimate effect of mean runoff rate over 6 weeks on disease incidence with 95% confidence intervals. For all diseases, there was a concave relationship between mean runoff rate and incidence. For campylobacteriosis, a runoff rate of about 0.8 kg/m^2 was associated with increased incidence while for salmonellosis, it was lower at about 0.3 kg/m^2. For cryptosporidiosis a runoff rate of 0.2 kg/m^2 was associated with relatively high risk while the estimated relative risks for giardiasis was marginally higher than 1.0 with runoff at 0.3 kg/m^2.

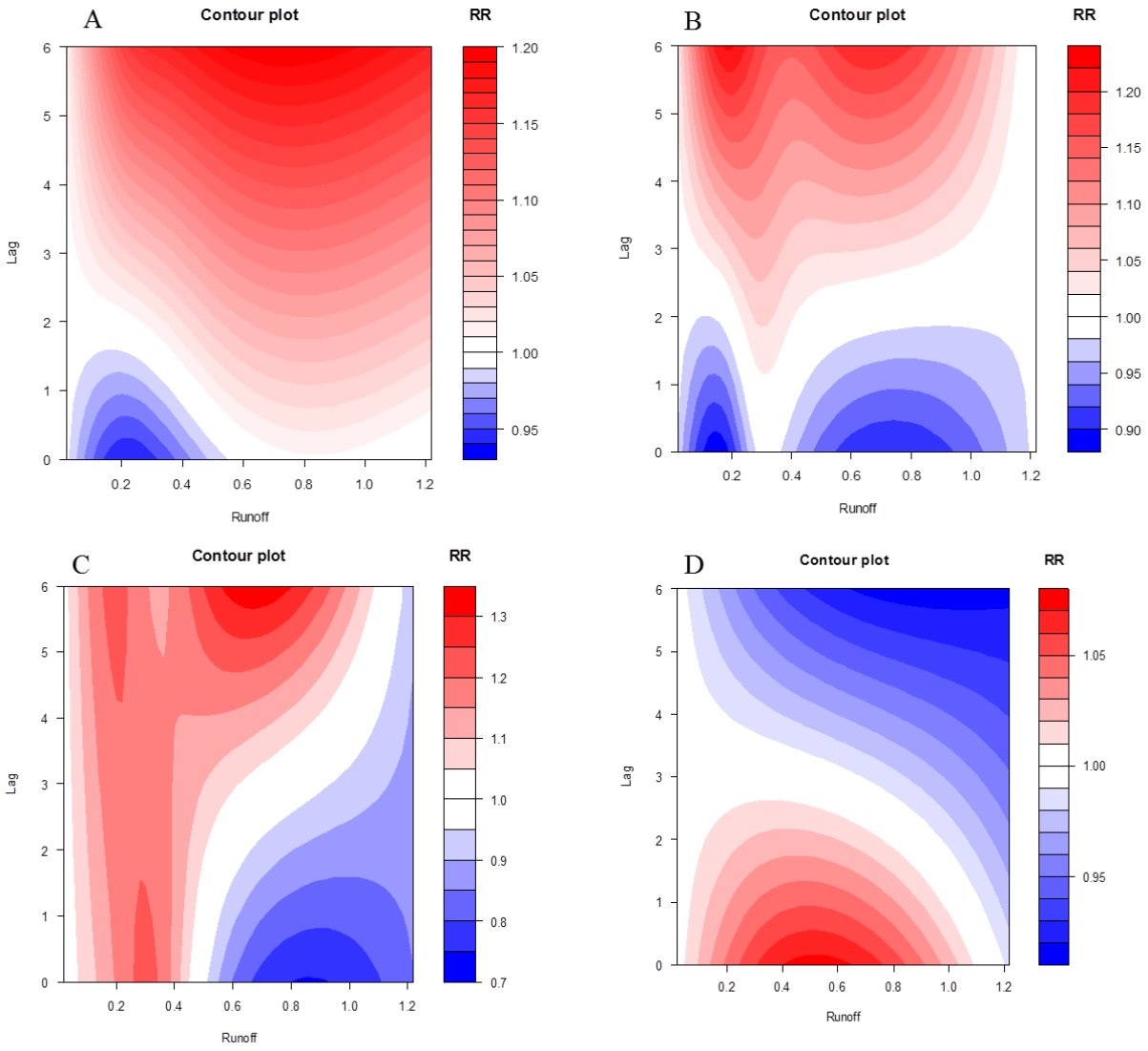
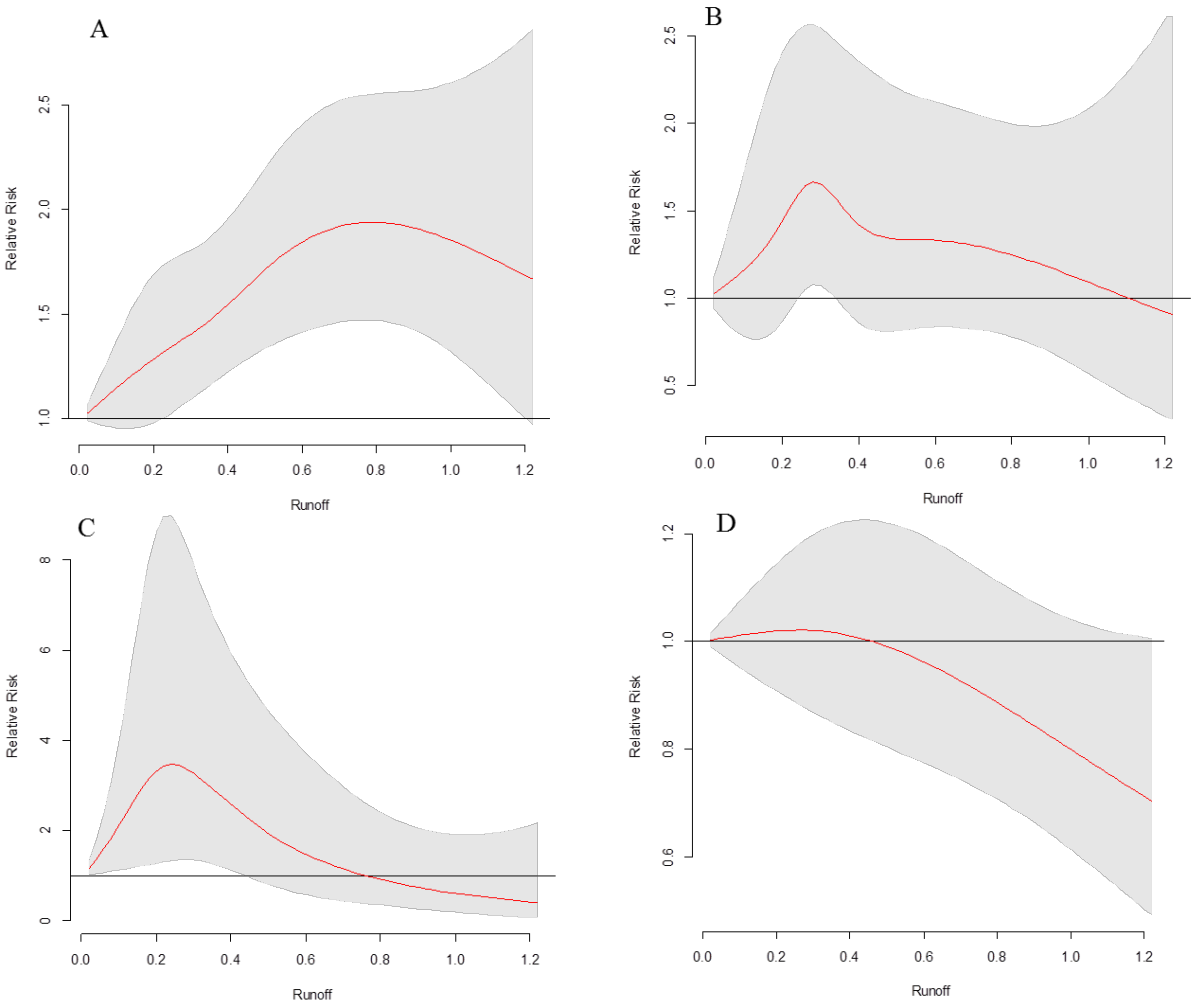


Figure 6.1 Estimated effect of weekly runoff rate on disease incidence fitted with distributed lagged nonlinear model adjusted for mean temperature, seasonal variation and inter-annual variation. The different hue intensities of the colours red and blue represent elevated and decreased relative risk, respectively. (A) campylobacteriosis (B) salmonellosis (C) cryptosporidiosis (D) giardiasis



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Figure 6.2 Estimated overall effect of runoff rate over a 6 week lag using a distributed lagged nonlinear model adjusted for mean temperature, seasonal variation and inter-annual variation. The red lines are the mean relative risks and the grey regions are 95% confidence intervals. (A) campylobacteriosis (B) salmonellosis (C) cryptosporidiosis (D) giardiasis

6.5 Discussion

While disease risk from zoonotic enteric pathogens is substantial and agricultural runoff is acknowledged as an important transmission pathway, this is the first study to quantify the non-linear and lagged effects of runoff rate on the incidence of zoonotic enteric diseases. Although preliminary, results highlight the disease specific, non-linear and lagged nature of the runoff-disease relationship in New Zealand. For campylobacteriosis and salmonellosis, a longer lag period of 5-6 weeks and a higher runoff rate increased disease risk. For cryptosporidiosis, disease risk was highest at a lower runoff rate with a more immediate effect, while for giardiasis, there was no strong relationship with amount or timing of runoff.

Rate of runoff is an important determinant of the pathogen load entering waterways, and may be influenced by pathogen characteristics, land management practices, physical features of the land and ambient environmental conditions (Pachepsky, Sadeghi et al. 2006, Miller, Lewis et al. 2008). In this study, relative risk of campylobacteriosis was highest at a high rate of runoff. This finding could be due to pathogen ecology, whereby efficient pathogen transport over land requires a high rate of runoff (Pachepsky, Sadeghi et al. 2006). Prolonged heavy rainfall has been associated with increased *Campylobacter* presence in surface water samples (Jokinen, Edge et al. 2012), indicating that climatic extremes may have an important effect on pathogen load in water sources. A study of *Salmonella* load in surface water sources found an absence of the pathogen preceding rainfall events but significant pathogen load subsequent to precipitation, suggesting a non-point pollution source such as agricultural runoff (Gaertner, Garres et al. 2009).

The lagged relationships between runoff rate and bacterial disease incidence described here is an indicator of the potential mechanisms by which changing rainfall patterns may affect future disease incidence in an increasingly agricultural landscape. Rainfall can transport faecal bacteria to surface water sources for at least 28 days after deposition (Donnison and Ross 2009) suggesting a delay between time of contamination and transport. This may partly explain the long lag

time (5-6 weeks) between runoff and increased campylobacteriosis and salmonellosis risk. Additionally, foodborne outbreaks related to consumption of shellfish and produce exposed to water contaminated by agricultural runoff has been reported (Rose, Epstein et al. 2001). Such a transmission pathway would also result in a delay between runoff rate and disease occurrence.

In contrast to the bacterial diseases, a high relative risk of cryptosporidiosis with a comparatively lower rate of runoff was noted. This pattern is in keeping with pathogen characteristics, whereby it is predominantly waterborne and requires a low infectious dose to cause disease (Rose, Huffman et al. 2002, Fayer 2004). This association also suggests that for *Cryptosporidium*, low rate of runoff may be effective at maintaining an endemic level of disease. This premise is further supported by the finding that the relative risk of cryptosporidiosis at a low runoff rate remained high even at a lag of 6 weeks. Although increased runoff rate is an inevitable consequence of increased rainfall, increased runoff may also follow extended dry periods, which may facilitate pathogen runoff into surface water sources due to unsaturation of land. Low flows may promote pathogen concentration, resulting in a higher pathogen load (Boxall, Hardy et al. 2009), leading to increased disease. The relatively short lag time (2-3 weeks) between runoff rate and peak cryptosporidiosis support its status as a primarily waterborne pathogen and is keeping with its average incubation period of around 7 days (Chin and American Public Health Association 2000).

While extreme rainfall is strongly associated with sporadic enteric disease and waterborne enteric outbreaks (Curriero, Patz et al. 2001, Drayna, McLellan et al. 2010), neglecting the considerable variation during such events may misrepresent the overall effect (Signor, Roser et al. 2005). For example, a study of faecal indicator-runoff relationships in North Carolina showed that within the first 30% of creek storm volume, the mean cumulative load of faecal bacteria was less that 50%, suggesting that these creeks did not show the ‘first flush’ scenario commonly assumed to result from heavy rainfall events (Stumpf, Piehler et al. 2010). Moreover, the rate of recovery of faecal bacteria from storm-water runoff

has been shown to be more frequent during prolonged rains, than during short, intense rain storms (Van Donsel, Geldreich et al. 1967), indicating that both the duration and the amount of rainfall are important. Although faecal indicator bacteria may not be an appropriate surrogate for enteric pathogens, results from this study suggest that the amount of runoff in conjunction with the timing is important to consider when assessing the effect of extreme climatic events. Results illustrate that traditional time series methods of describing associations between environmental influences and disease incidence may not adequately capture the important non-linear and lagged effects. It is important to understand that disease response to multiple interacting environmental and demographic variables are dynamic and seldom linear. Assuming a linear exposure-response relationship may limit our understanding of the mechanisms by which future environmental change may affect disease risk.

Both Chapter 5 and 6 were limited by data quality, as notification data may vary in space and time due to under ascertainment and other disease surveillance artefacts (as highlighted in Chapter 3). However, no major changes were made regarding the surveillance of these notifiable diseases from 1997-2008 suggesting that the completeness of reporting is likely to have remained the same over this time period. Although notified cases represent only a portion of actual incidence in the community (Lake, Adlam et al. 2010), the main aim of this study was to study the temporal association between disease incidence and climate. It seems unlikely that there were substantial seasonal variations in reporting which might have introduced bias. Although the patterns reported here could differ by pathogen strain (McCarthy, Gillespie et al. 2012), strain specific information was not available for this study. Second, as the analyses were done nationally, spatial heterogeneity in climate could not be accounted for. While data aggregated monthly as used in Chapter 5 have been used for similar studies , it is recognised that weekly data might be more appropriate, particularly to establish effects of heavy runoff as shown here. Finally, population factors influencing disease incidence like demographics, socio-economic characteristics and immunity status and pathogen level factors like reservoirs and virulence were not considered.

While disease incidence is mediated by a variety of interacting factors, hygiene practices and socio-economic factors do not generally vary on a monthly or weekly timescale and so cannot confound the temporal associations reported here.

Increased agricultural runoff due to rainfall extremes is identified as a key factor in the contamination of recreational and surface water sources leading to increased zoonotic enteric disease (De Magny, Murtugudde et al. 2008). Although other factors were not accounted for, this chapter highlights for the first time, the disease specific, lagged and nonlinear nature of the association between runoff rate and enteric zoonotic disease incidence in New Zealand. Understanding the influence of runoff is an important first step toward clarifying how projected variability in rainfall patterns could affect future zoonotic disease risk in areas with intensified agriculture.

SECTION II: KEY FINDINGS

1. A systematic review of global seasonal patterns in campylobacteriosis, salmonellosis, cryptosporidiosis and giardiasis using published literature from 1960-2010 resulted in the review of 74 studies across the four diseases. Findings showed consistent seasonal patterns across transnational boundaries, albeit with regional variations. The bacterial diseases, campylobacteriosis and salmonellosis had a pronounced summer peak. Cryptosporidiosis displayed a bi-modal pattern with spring and summer peaks, while giardiasis was the least seasonally variable.

2. Regional climate variability as indicated by the SOI, in association with local temperature and precipitation has a broad influence on enteric disease incidence. In particular, *La Niña* related warmer, wetter climates were positively associated with monthly salmonellosis incidence, while *El Niño* related cooler, drier conditions favoured cryptosporidiosis transmission. Regional climatic factors did not significantly influence campylobacteriosis and giardiasis incidence patterns.

3. The influence of runoff rate on weekly enteric disease incidence is non-linear and temporally lagged. Campylobacteriosis and salmonellosis risk was associated with a higher runoff rate and a lag of 5-6 weeks. Cryptosporidiosis risk was related to a more immediate effect of runoff at a low runoff rate while the association with giardiasis was not significant.

SECTION III: CHAPTER 7 SPACE-TIME CLUSTERS OF CRYPTOSPORIDIOSIS AND GIARDIASIS IN NEW ZEALAND

7.1 Introduction

Space-time clustering methods can be used to identify emerging areas of increased risk (Ogden, Bouchard et al. 2010), link disease patterns to point sources of contaminants (Van Den Wijngaard, Dijkstra et al. 2011), and highlight outbreaks retrospectively and prospectively through routine disease surveillance (Huang, Yokoe et al. 2010, Hughes and Gorton 2013). These methods can also be used to monitor the effectiveness of a public health intervention (Ali, Asefaw et al. 2005).

The apparent contrast in the epidemiological characteristics of cryptosporidiosis and giardiasis cases (Chapter 3) and their temporal associations with weather and climate variables (Chapter 5 and 6) suggest that, in New Zealand, the dominant factors driving the transmission of these diseases are likely to be quite different. Detecting areas with recurrent disease clusters may identify seasonally and spatially varying risk factors that merit additional research.

The Kulldorf space-time scan statistic is a simple and effective tool for preliminary analysis of routine disease surveillance data (Kulldorff 1997). It offers multiple advantages in that it identifies circular clusters of any size, situated anywhere within the study region, while adjusting for multiple hypothesis testing (Boscoe, McLaughlin et al. 2003). This scan statistic determines which clusters warrant further investigation and those that are possibly random occurrences (Kulldorff, Athas et al. 1998). It also identifies clusters that are not defined by administrative boundaries, minimising pre-selection bias (Kulldorff, Heffernan et al. 2005). Finally, it is theoretically straightforward with the software freely available, making it accessible to a wide range of users (Robertson and Nelson 2010).

7.2 Chapter aim

By performing a retrospective spatial and temporal cluster analysis of cryptosporidiosis and giardiasis incidence using disease notification data, this chapter attempted to identify risk factors for these diseases.

7.3 Methods

7.3.1 Disease data

Notified cases of cryptosporidiosis and giardiasis in New Zealand from January 1, 1997 to December 31, 2008 were included in the analysis. The cases excluded those identified as being part of a known outbreak, that is, only 'sporadic' cases were used in this analysis. The report date of cases were used was used for this analysis.

7.3.2 Population data

Population denominator data and Census Area Unit (CAU) boundaries for the 2006 National Census were obtained from Statistics New Zealand. The centroid for each CAU was calculated using ArcGIS v10 (ESRI 2011).

7.3.3 Analysis

7.3.3.1 Empirical Bayes Smoothing

Disease rates from low population areas can be unstable, resulting in large changes in estimated rates following the addition or subtraction of a few cases. In such cases, Empirical Bayes (EB) smoothing stabilises these rates using information from surrounding areas to adjust the estimated incidence. This method is recommended for studies where data are grouped into small geographical areas such as CAUs. EB estimates of average annual incidence rates per 100 000 population for cryptosporidiosis and giardiasis at the CAU level were calculated using the spatial dependence (SPDEP) package (Bivand, Bernat et al. 2005) available in the R software (version 2.15.1) (R Development Core Team 2012).

7.3.3.2 Spatial and temporal clusters

A scan statistic implemented in SaTScan v9.0 software was used to identify space-time clusters of cryptosporidiosis and giardiasis in New Zealand (Kulldorff 1997, Kulldorff, Heffernan et al. 2005). Specifically, cryptosporidiosis and giardiasis count data were examined for high disease rate space-time clusters using a retrospective space-time permutation model to detect space-time clusters across three separate time periods. The analysis was carried out at the CAU level with aggregated, unadjusted count data.

In this method, a cylindrical window, with a circular base centred on each location (the radius varying from zero to a user pre-defined limit) and with height corresponding to time (adjusted from zero to a predetermined maximum) was used to detect space-time clusters as the "centre" of each window moves across the study area. As the window moves, for each location it also scans each possible time period, thus highlighting spatio-temporal clusters of possible cases. High risk clusters were detected by comparing the observed number of cases within the window to the expected number. Spatio-temporal clusters were therefore identified if a significant excess of cases had been observed in a geographic zone during a particular period. The default setting of no geographic overlap was used, so secondary clusters would not overlap the most significant cluster.

The Monte Carlo method was used to test the statistical significance of the detected clusters. A *p*-value was obtained by ranking the likelihood of an observed cluster in a dataset over the maximum likelihoods acquired by generating 999 randomly produced datasets. The null hypothesis of no cluster was rejected when the simulated *p*-value was less than, or equal to 0.1.

As one of the limitations of SaTScan is that, over a long time period, clusters detected may be due to the effect of changes in population in certain areas, the time period in this study was divided into three segments (i) 1997-2000, (ii) 2001-2004, (iii) 2005-2008, under the assumption that the space-time clusters detected in such short time periods were more likely to be true clusters rather than the effect of changes in population. A maximal geographical cluster size of 50% of

the population was chosen as a conservative estimate of the population at risk and to avoid pre-selection bias in choosing areas. Kulldorf (1997) recommends a maximum temporal cluster size that is 50% of the length of the study period, which would represent a maximum temporal cluster size of 730 days as the analysis was carried out separately for each time period specified above. A maximum temporal cluster size of 60 days was chosen for this study as the objective was to identify relatively short periods of time that may indicate localised and/or seasonal exposure. For the same reason, 50km was chosen as the radius of the cylindrical window used to scan across the study region. For each disease, SaTScan required three data files: one file with the geographic coordinates of the centre of each CAU; one with the population of each CAU; and one with case data.

The output from SaTScan was input into STATAv11 (StataCorp 2009) to develop a cluster dataset which was then exported to ArcGIS v10.1 (ESRI 2011) as a new geodatabase for mapping. For each time period, all clusters with $p < 0.01$ and $p < 0.05$ were mapped.

7.4 Results

7.4.1 Incidence rates

Smoothed annual average rates of giardiasis and cryptosporidiosis (1997-2008) are shown in Figure 7.1. For giardiasis, visual inspection of Figure 7.1 indicates a relatively high incidence rate across the country with possible spatial clusters in the lower central portion of the South Island. For cryptosporidiosis, average annual incidence rates were more heterogeneous, with no obvious spatial clusters.

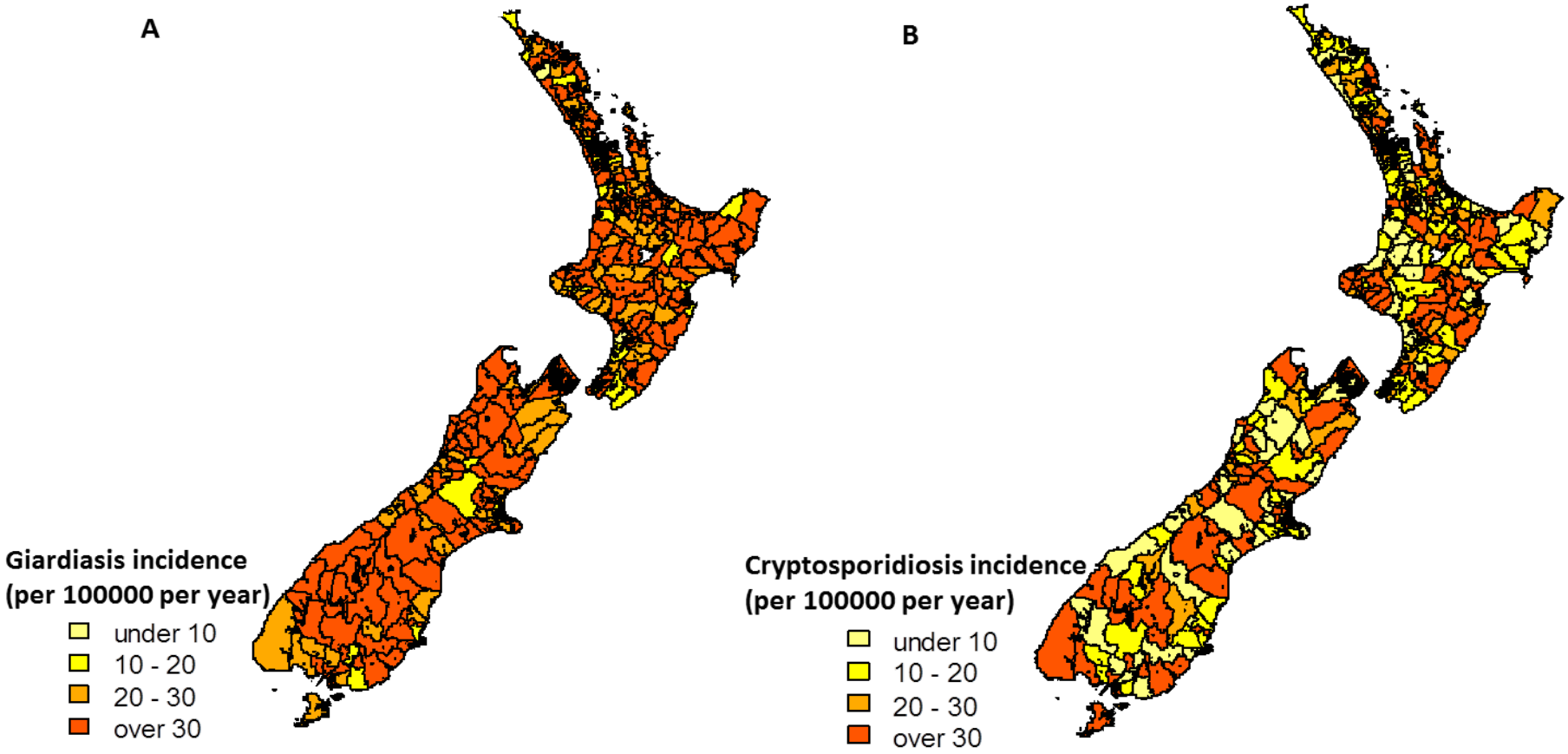


Figure 7.1 Empirical Bayes Smoothed incidence rates for (A) giardiasis (B) cryptosporidiosis in New Zealand (1997-2008) at the Census Area Unit level (CAU)

7.4.2 Space-time clusters

The most likely cluster identified in each time period was indicated in red, while all identified clusters with a *p*-value of <0.05 were denoted in yellow (Figure 7.2 and 7.3). For giardiasis the most likely cluster identified in 1997-2000 was in the Waihou-Valley Hupara CAU in the upper North Island where a cluster of 12 cases as compared to the expected 0.24 was observed and occurred from 14th July 1997 to the 27th July 1997. A total of 30 significant ($p<0.05$) clusters were identified during this time period. In 2001-2004 the most likely cluster was in the Eastbourne CAU in lower North Island where a cluster of 11 cases was observed compared to an expected 0.29 and lasted from 17th August 2002 to 6th of September 2002. A total of 20 significant ($p<0.05$) clusters were identified during this time period. In the 2005-2008 period, the most likely giardiasis cluster was in the upper South Island in the Nelson region, where 40 cases were observed as compared to the expected 3.25 and lasted from 19th April 2007 to the 13th of June 2007. A total of 61 significant ($p<0.05$) clusters were identified during this time period. Recurrent giardiasis clusters were detected in the northern half of the South Island in the Nelson/Golden Bay region. In 1997-2000 this cluster occurred between 13th January 1997 and the 9th February 1997, with 10 cases as compared to the expected 0.58 (Cluster 12 Appendix 2). In 2001-2004 this cluster occurred between 21st July 2001 and the 31st August 2001, with 14 cases as compared to the expected 1.74 (Cluster 13 Appendix 2). In 2005-2008 this cluster also covered the most likely cluster detected in Nelson (April-June2007) and occurred between 4th August 2008 and the 24th August 2008, with 9 cases as compared to the expected 0.29 (Cluster 18 Appendix 2).

For cryptosporidiosis, the most likely cluster identified in 1997-2000 was in the Wellington region in the lower North Island where a cluster of 136 cases as compared to the expected 28.78 was observed and occurred from 16th March 1998 to the 10th May 1998. A total of 20 significant ($p<0.05$) clusters were identified during this time period. In 2001-2004 the most likely cluster was in the Auckland region in central North Island where a cluster of 91 cases was observed compared to an expected 22.38 and lasted from 10th March 2001 to 4th of May 2001. A total

of 8 significant ($p<0.05$) clusters were identified during this time period. In the 2005-2008 period, the most likely cryptosporidiosis cluster was in the Palmerston North region, where 24 cases were observed as compared to the expected 1.24 and lasted from 8th June 2006 to the 14th of June 2006. A total of 14 significant ($p<0.05$) clusters were identified during this time.

Recurrent clusters were detected in the southern half of the South Island in the Southland region. In 1997-2000 the Southland cluster occurred between 19th October 1998 and the 15th November 1998, with 24 cases as compared to the expected 3.6 (Cluster 7 Appendix 3). In 2001-2004 the Southland cluster occurred between 6th October 2001 and the 30th November 2001, with 27 cases as compared to the expected 6.91 (Cluster 4 Appendix 3). In 2005-2008 this cluster occurred between 16th October 2008 and the 3rd December 2008, with 14 cases as compared to the expected 2 (Cluster 9 Appendix 3).

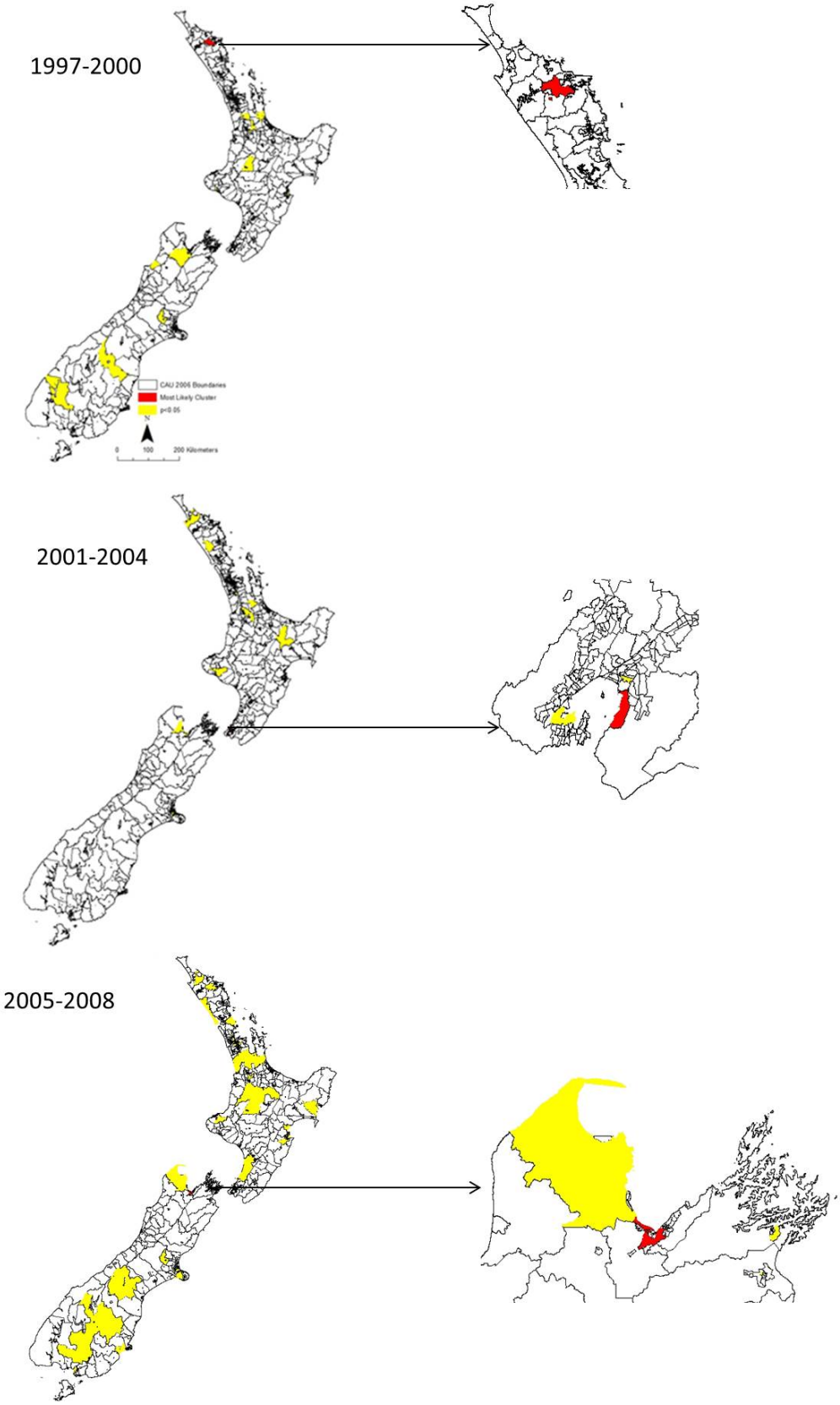


Figure 7.2 Space-time clusters for giardiasis in New Zealand (1997-2008) at the CAU level as identified by the spatial scan statistic in SatScan v. 9.0. The red regions are the most likely space-time clusters and the yellow regions are the significant secondary space-time clusters (p<0.05) identified

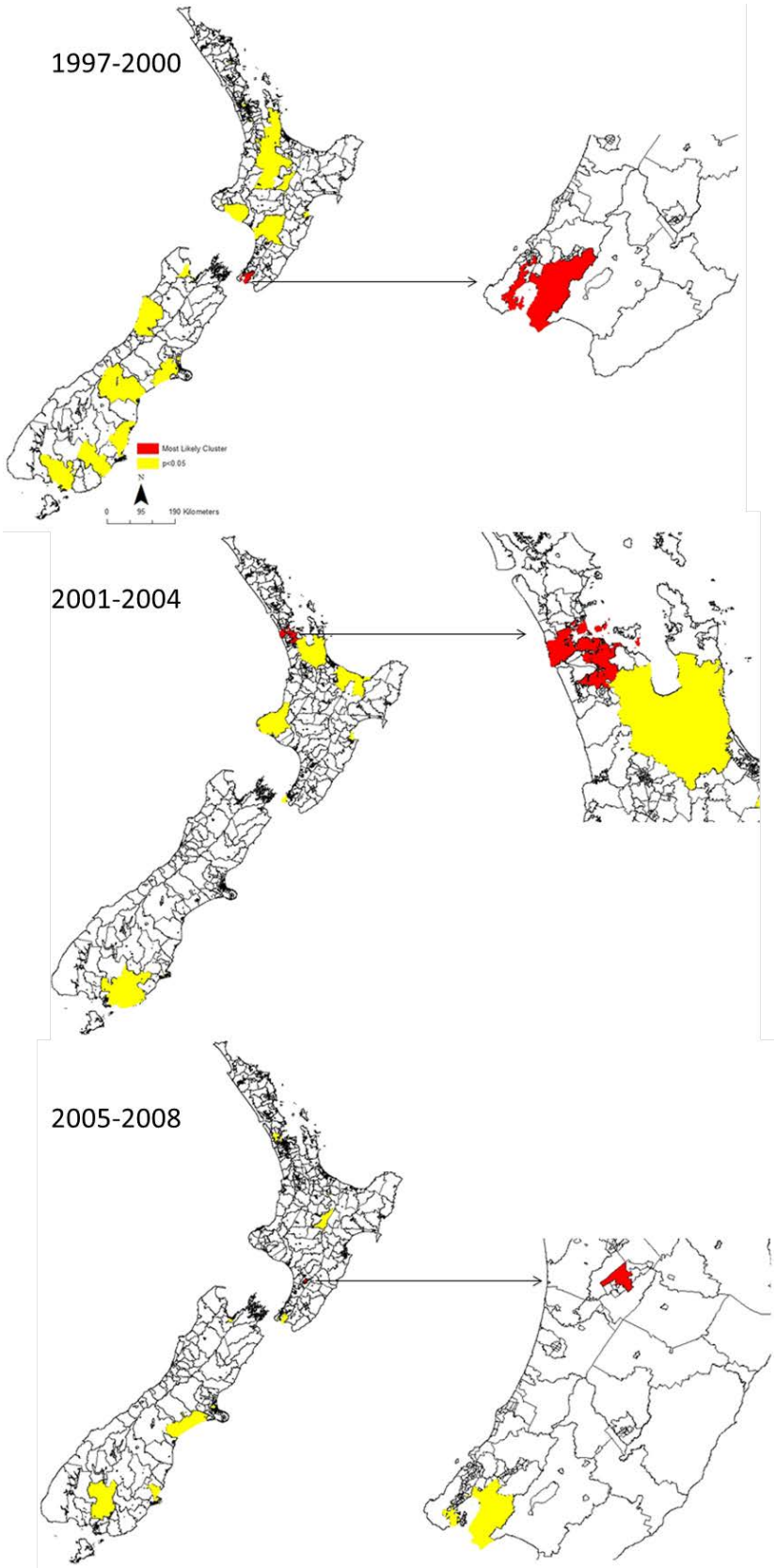


Figure 7.3 Space-time clusters for cryptosporidiosis in New Zealand (1997-2008) at the CAU level as identified by the spatial scan statistic in SatScan v. 9.0. The red regions are the most likely space-time clusters and the yellow regions are the significant secondary space-time clusters (p<0.05) identified

7.5 Discussion

Combining GIS techniques and SaTScan statistics was useful to visualise spatio-temporal patterns in disease risk and identify areas of high case counts using routine surveillance data (Lian, Warner et al. 2007). In New Zealand, this is the first attempt to compare the spatio-temporal distribution of cryptosporidiosis and giardiasis notifications. Results revealed significant clusters that did not follow the distribution of disease incidence rates at the CAU level, with recurrent space-time clusters being detected. As these were notified as sporadic cases, the clusters identified here represent clusters not previously identified as outbreaks. These findings highlighted potential causal mechanisms that may be further investigated using advanced statistical and experimental approaches.

7.5.1 Incidence rates

The heterogeneity in cryptosporidiosis and giardiasis incidence at the CAU level provides a baseline pattern against which the location of space-time clusters may be compared (Odoi, Martin et al. 2003). While giardiasis rates were particularly high in the lower half of the South Island, cryptosporidiosis rates were far more heterogeneous, suggesting site specific environmental and population exposures. Although these rates have been smoothed to stabilise high rates in sparsely populated areas, on their own they do not shed much light on possible risk factors as they are based on pre-decided, administrative boundaries (Pearl, Louie et al. 2009). Nevertheless, they emphasise inequalities in cryptosporidiosis and giardiasis incidence and identify areas that may merit further attention.

7.5.2 Space-time clusters

7.5.2.1 Giardiasis

Recurrent clusters of giardiasis were identified in the northern half of the South Island, in a primarily urban area. It is possible that, in this region, person-to-person transmission is dominant. Results of a case-control study in Auckland suggest that toddler diaper changing is a significant risk factor (Hoque, Hope et al. 2003) with descriptive studies showing increased risk in the age group 30-39 years (Snel, Baker et al. 2009) and in females (Hoque, Hope et al. 2004), which

may be attributed to a closer association with young children. Indeed, attendance at day care centres has been frequently cited as a common risk factor for *Giardia* infections in children (Sagebiel, Weitzel et al. 2009). Although overseas travel has also been noted as an important risk factor for acquiring *Giardia* infections (Swaminathan, Torresi et al. 2009), travel related cases could not be distinguished in this study.

As *Giardia* spp. are easily transmitted through water (Baldursson and Karanis 2011), waterborne transmission may also play a role in the geographical structuring of incidence patterns. In New Zealand, endemic giardiasis associated with reticulated drinking water supplies has been reported (Fraser and Cooke 1991), with improvements in municipal drinking water supplies suggested to result in decreased enteric disease incidence in local populations (Duncanson, Russell et al. 2000). Therefore, it is possible that the clusters identified in this region could be a result of a compromised water supply. However, as the Nelson/Golden Bay region is a popular recreational area, swimming in public pools and water bodies may also be an important risk factor in this region (Hoque, Hope et al. 2003, Stuart, Orr et al. 2003).

7.5.2.2 Cryptosporidiosis

In contrast, for cryptosporidiosis recurrent disease clusters were detected in the southern half of the South Island, an area of intensified livestock farming. Furthermore, these clusters showed a consistent seasonal spring peak. As suggested in Chapter 2, new-born livestock in spring may be an important infection source of *Cryptosporidium* infection in humans (Learmonth, Ionas et al. 2001, Learmonth, Ionas et al. 2003, Learmonth, Ionas et al. 2004). Such an analysis could form the basis of an early warning system for an imminent increase in incidence based on known agricultural activities unique to these respective areas.

However, spring clusters could also be due to rainfall patterns as suggested by a study in North West England where in areas with marked seasonal patterns, peaks in spring rainfall preceded those in cryptosporidiosis (Naumova, Christodouleas et

al. 2005). In the same geographic region, a significant association between maximum river flows and cryptosporidiosis cases in spring were found, suggesting that increased seasonal pathogen load coupled with heavy rainfall could result in seasonally high disease rates (Lake, Bentham et al. 2005). In New Zealand, increased contamination of water sources from livestock following extreme rainfall events has been documented (Davies-Colley, Lydiard et al. 2008). Moreover, recreational water contact has been emphasized as a significant risk factor for cryptosporidiosis outbreaks (Lake, Pearce et al. 2008). As water bodies in rural areas are also popular swimming spots, it is plausible that recreational contact with water carrying heavy pathogen loads could result in higher disease rates. Alternatively, rainfall associated runoff may exacerbate drinking water related risk. As groundwater contamination as a result of agricultural activities has also been associated with increased risk of cryptosporidiosis (Close, Dann et al. 2008) (Chapter 2), it is possible that spring peaks in rainfall could result in contamination of the drinking water source. The clusters identified here support previous spatial analyses of cryptosporidiosis patterns in New Zealand, where disease incidence was strongly associated with rural areas and environmental factors (Britton et al. 2010).

As has been widely documented, the limitations of using passive surveillance data to assess disease distribution include case ascertainment (Lian, Warner et al. 2007) and incorrect allocation of cases to geographic areas (Skelly, Black et al. 2002). For example, in this analysis, reporting location is based on home domicile address may not be an accurate reflection of actual exposure due to commuting and travel patterns. However, such data deficiencies are likely to affect purely spatial analyses, as clusters in both space and time also require a temporal variation. Secondly, demographic differences were not considered in this analysis. Studies that include the effect of socio-economic and demographic variables could result in different clusters. Thirdly, as a circular window was used to scan across the region for this analysis, it is possible that non-circular clusters, for example those along a river bank may have been missed. Such extensions may be of interest when investigating a specific hypothesis such as a point source of

contamination in a catchment. It is also likely that using onset date rather than notification data would have improved results as onset date is closer to the time of acquiring the infection. However, for this study reporting date was used. Also, some of the identified clusters were fairly large, indicating a potentially inaccurate inclusion of some areas (Odoi, Martin et al. 2003). However, specific CAUs showed clusters in more than one time period, suggesting that despite these shortcomings, SaTScan was useful for recognising areas of repeated high incidence and providing a rationale for subsequent analysis.

In conclusion, exploratory tools such as SaTScan provide a resource efficient method for public health authorities to detect prioritise and monitor high risk areas. In this chapter, space-time clusters provided supplementary information to area based incidence rates highlighting possible spatial and temporal variations in disease drivers. Results suggest that while giardiasis clusters tended to recur in predominantly urban areas, repeated cryptosporidiosis clusters were identified in primarily agricultural, livestock dominated areas.

CHAPTER 8 SPATIAL AND TEMPORAL ANALYSIS OF CRYPTOSPORIDIOSIS AND GIARDIASIS IN NEW ZEALAND

8.1 Introduction

Space-time interactions, which consider the extent to which cases are spatially and temporally related, can be used as an indicator of underlying infectious processes. The spatial scan statistic proposed by Kulldorff is one of the most commonly used methods to detect disease clusters (Kulldorff 1997, Kulldorff, Heffernan et al. 2005) (Chapter 7). However, as used in Chapter 7, this method employs a circular window to identify the most likely cluster, making it difficult to correctly detect clusters that are not circular.

In this chapter, a Bayesian approach is used to analyse spatial and temporal patterns in the disease data (Spencer, Marshall et al. 2011). The advantage of this method is that it generates a relative risk for each individual spatial unit that can be easily visually interpreted. This is in contrast to the SaTScan method (Chapter 7), which just identified high risk areas. Furthermore, for each spatial unit, over the entire period of interest the model used in this chapter calculates an outbreak probability for all observed cases, highlighting phases of unusually high incidence that may benefit from further investigation. While the SaTScan method identifies the start and end dates of detected clusters, it does not consider cases not belonging to an identified cluster, limiting the interpretation of space-time patterns to detected clusters only. A visual assessment of spatial and temporal variations in disease risk across the country allows an easier detection and comparison of patterns at a national scale.

8.2 Chapter aim

This chapter aimed to identify spatial and temporal variations in disease risk by examining the underlying spatial and temporal trends in cryptosporidiosis and giardiasis notification data. I used a Bayesian model to estimate spatial patterns in relative risk and temporal outbreak probability.

8.3 Methods

8.3.1 Disease data

All notified cases of cryptosporidiosis (n=9848) and giardiasis (n=19553) during 1997-2008 in New Zealand with corresponding CAU code based on home address were extracted. Population denominator data, including CAU code, were based on the 2006 National Census of Population and were obtained from Statistics New Zealand. The distribution of the 2006 CAUs in given in Figure 8.1A.

8.3.2 Bayesian model definition

The Bayesian hierarchical model described here was developed by Dr. Simon Spencer and Dr. Jonathan Marshall of Massey University. It has been described in detail in Spencer et al. (2011).

The number of cases in CAU *i* in week *t* by is denoted by Y_{it} and assume that Y_{it} ~ Poisson ($n_i\lambda_{it}$) where the offset n_i is the population in CAU *i* and $\lambda_{it}$is the risk associated with CAU *i* in week *t*. The log of the risk was decomposed into three components: a purely temporal component, R_t; a purely spatial component, U_i; and the spatio-temporal component W_{it}.

Equation 8.1

$$\text{Log}\,(\lambda_{it}) = R_t + U_i + W_{it}$$

The spatio-temporal component W_{it} is designed to capture short term localised periods of increased risk that are typical of outbreaks (Section 8.3.3).

8.3.3 Outbreak analysis

The model developed using Equation 8.1 was applied to each disease dataset to detect outbreaks clustered in time and space. In order to do this, Territorial Authorities (TAs) were used to group CAUs into regions (Figure 8.1B). This reduced the number of parameters that needed to be estimated in the models and the computation time. It also increased the identifiability of the spatio-temporal

parameters, as they were based on several observations rather than a single datum. Given equation 8.1, we set

Equation 8.2

$$W_{i,t} = \beta_{r(i)} X_{r(i),t}$$

Where r (i) is the index of the region containing CAU i, $X_{r,t}$ is the indicator for a presence or absence of an outbreak and β_r reflects the size of the increase in risk for outbreaks in region r. For detailed assessment of spatial and temporal patterns a predominantly urban TA (Auckland) and a predominantly rural TA (Clutha) were chosen (Figure 8.2).

8.4 Results

8.4.1 Spatial patterns of relative risk

Figure 8.3 shows the relative risks estimated by the spatial component of the model for giardiasis and cryptosporidiosis at the CAU level. The relative risk is interpreted as the risk of infection in each CAU as compared to the average risk across all units. Therefore, a value greater than 1.0 implies a higher than average risk, whereas a value less than 1.0 implies a lower than average risk.

In general, for the 12 year period analysed, the urban areas tended to have a higher risk of notification for giardiasis while rural areas had a higher notification risk for cryptosporidiosis. For cryptosporidiosis, in terms of areal extent, the South Island had larger areas with higher relative risk as compared to the North Island. For giardiasis, there was no apparent difference in extent of relative risk between the two islands.

In the urban Auckland region, the relative risk of giardiasis was spatially heterogeneous, with many of the high risk areas appearing along the coast (Figure 8.4A). In contrast, the relative risk of cryptosporidiosis notification in urban areas of Auckland was more uniform and was less than the average risk expected across all CAUs (Figure 8.4B).

In the rural Clutha District, the relative risk for giardiasis notifications was below the average estimated for all CAUs across the entire area (Figure 8.5A). Conversely, for cryptosporidiosis, the risk of notification was highest in the Clutha region as compared to the average expected risk (Figure 8.5B).

8.4.2 Temporal trend

Figure 8.6 shows the temporal trend of giardiasis and cryptosporidiosis notifications across the entire time period. For giardiasis, a decreasing trend for giardiasis till early 2000 was observed followed by a fairly consistent number of reported cases with seasonal fluctuations, but no distinct peaks. The trend for the average number of cryptosporidiosis cases remained fairly similar across the entire time period with clear dominant peaks in spring with two apparent peaks in early years.

8.4.3 Outbreak analysis

The posterior outbreak probabilities for the Auckland and Clutha Districts were analysed separately for cryptosporidiosis and giardiasis. For giardiasis, in Auckland, there were no clear patterns in the outbreak probabilities estimated (Figure 8.7A). The outbreak probability patterns in the neighbouring Manukau district has been highlighted to show the consistency of patterns across these regions (Figure 8.7B). For cryptosporidiosis, both the Auckland and the neighbouring Manukau District showed two distinct periods of increased outbreak probability, during the first half of 2001 and the first half of 2007 (Figure 8.7 C-D).

In the Clutha District for giardiasis there was no evident pattern in the estimated posterior outbreak probability (Figure 8.8 A). The outbreak probability patterns in the neighbouring Southland district has been highlighted to show the consistency of patterns across these regions (Figure 8.8B) In contrast, for cryptosporidiosis in both these districts, regular peaks mainly in spring were seen, particularly during the spring of 2000, 2001, 2002 (Figure 8.8 C-D).



Figure 8.1 Distribution of (A) 2006 Census Area Units (CAU) (B) grouping of CAUs into Territorial Authorities (TA) used for outbreak detection regions

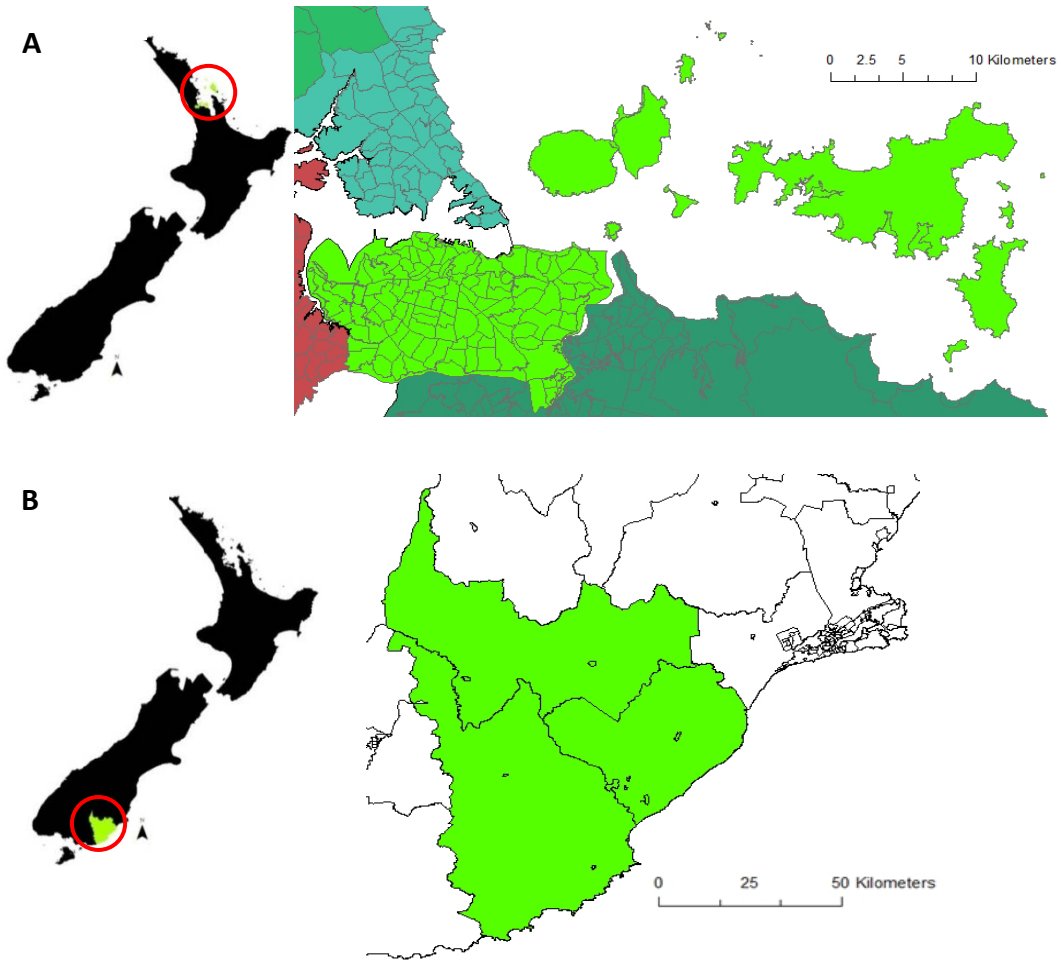


Figure 8.2 Regions selected for detailed descriptive analysis of patterns (A) Auckland City (urban) (B) Clutha District (rural)

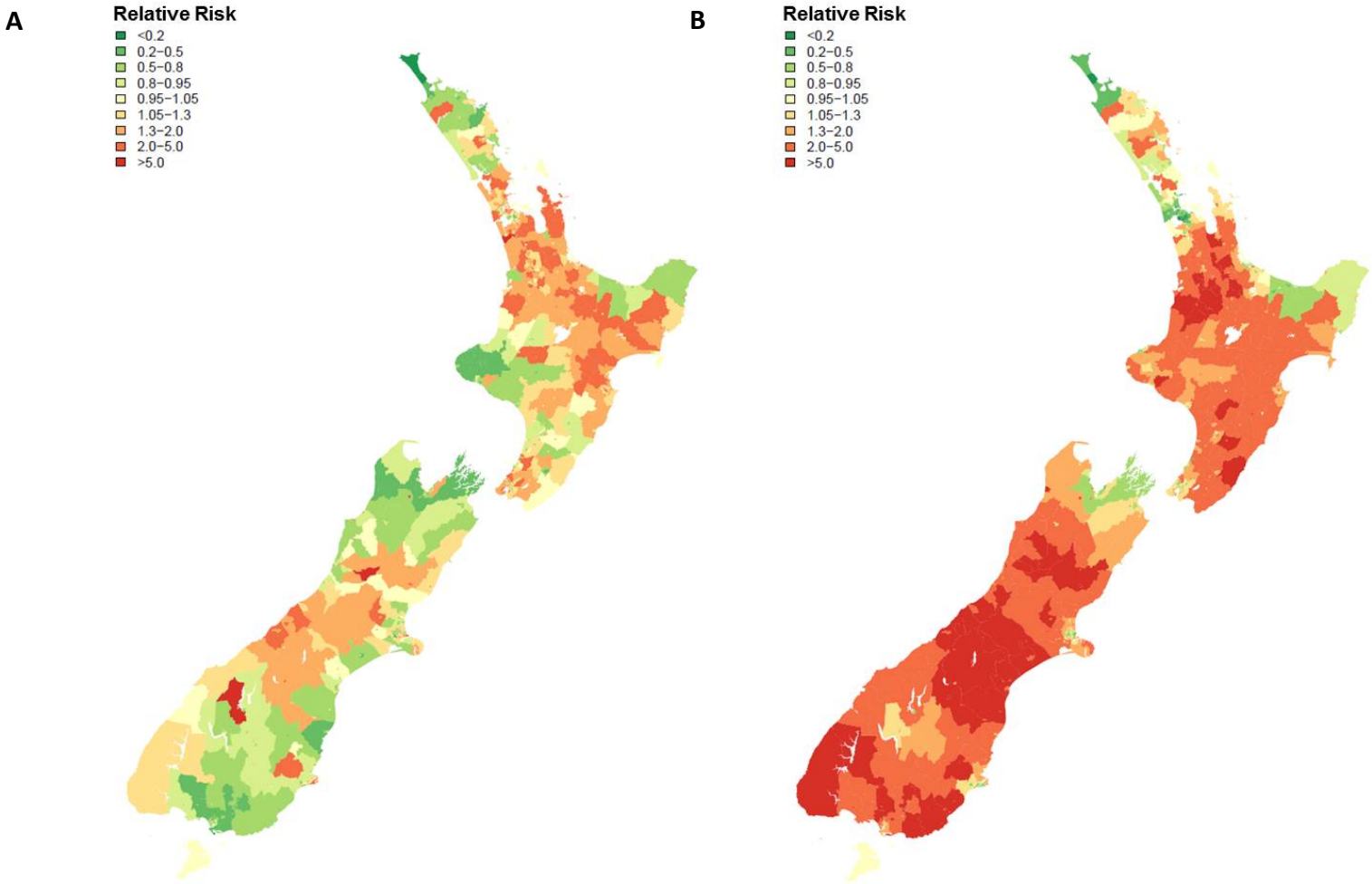


Figure 8.3 Spatial distribution of relative risk (1997-2008) for New Zealand at the CAU level (A) giardiasis (B) cryptosporidiosis

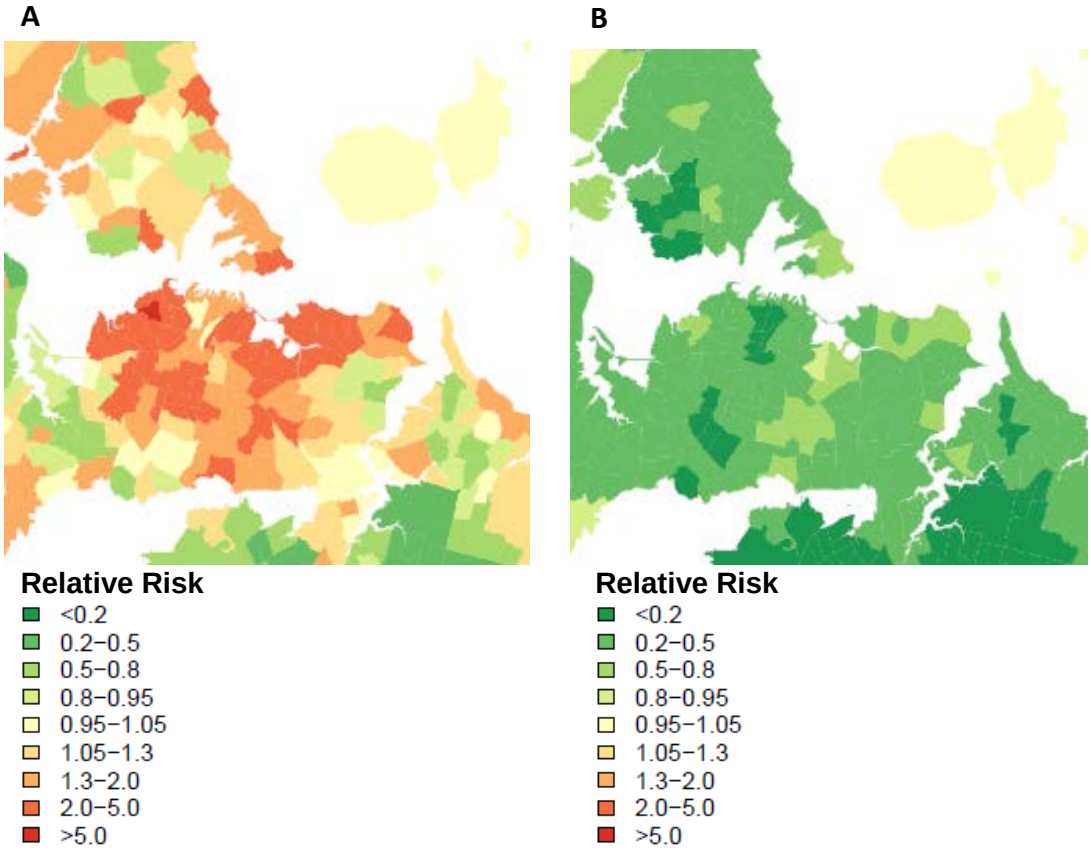


Figure 8.4 Auckland City: Spatial distribution of (A) Relative risk for giardiasis (B) Relative risk for cryptosporidiosis

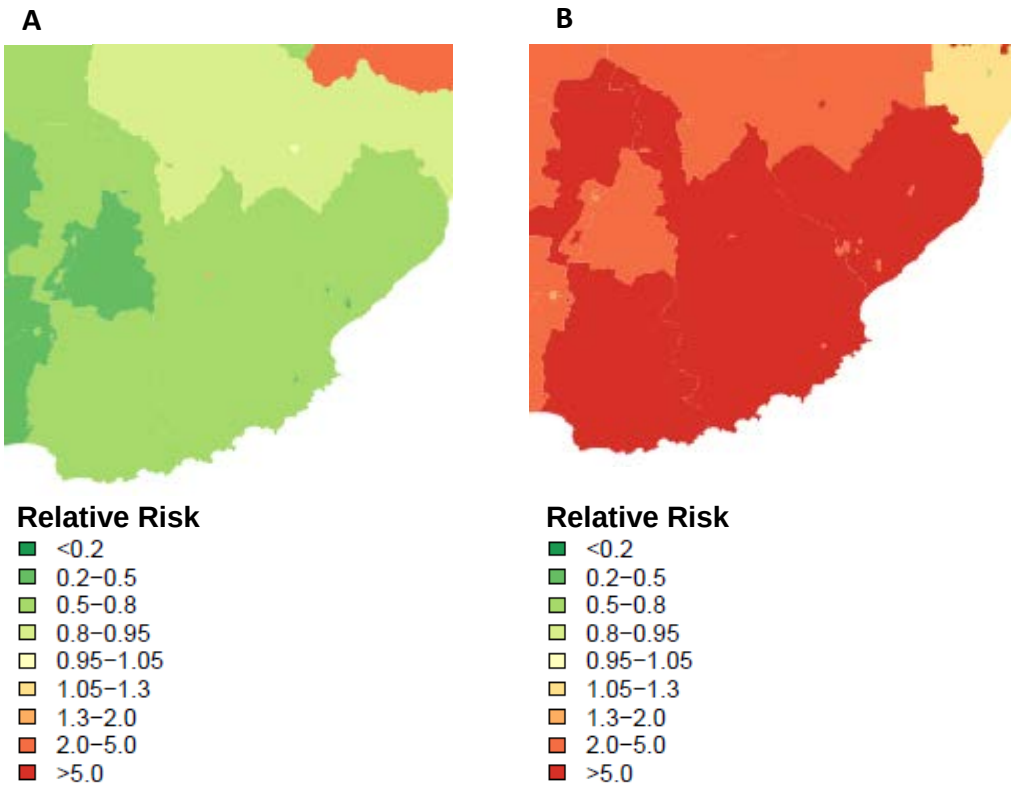


Figure 8.5 Clutha District: Spatial distribution of (A) Relative risk for giardiasis (B) Relative risk for cryptosporidiosis

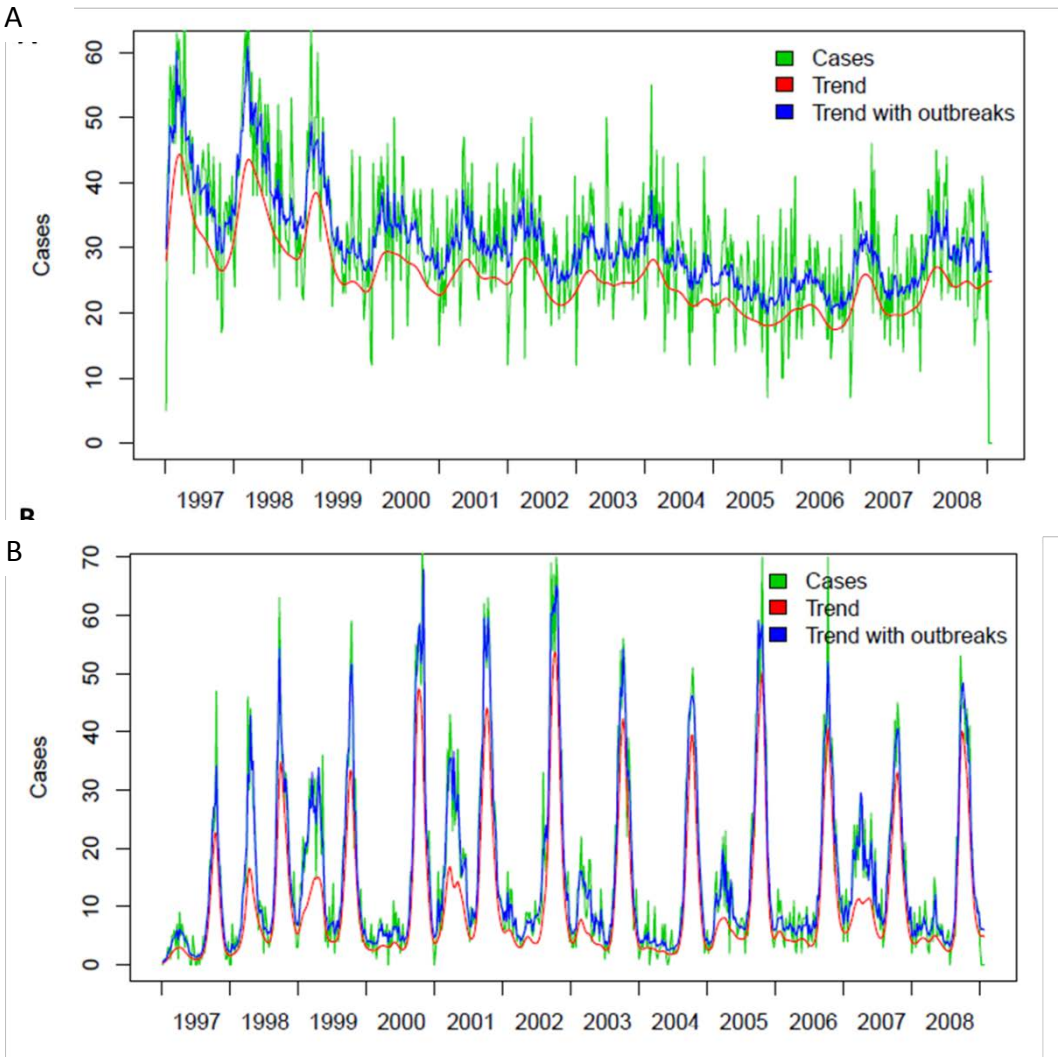


Figure 8.6 The observed cases (green), the temporal trend (red) and the temporal trend (1997-2008) with outbreaks (blue) (A) giardiasis (B) cryptosporidiosis

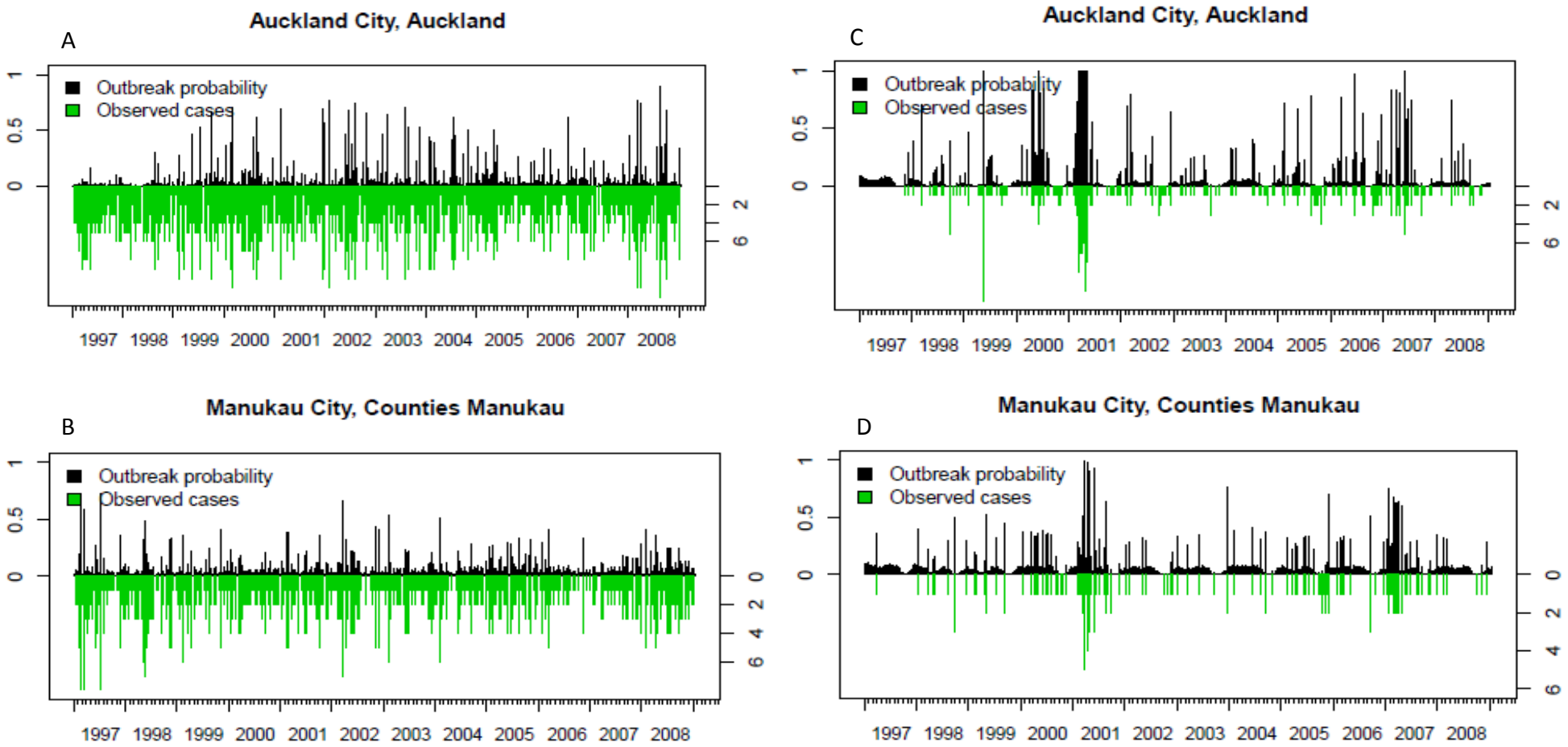


Figure 8.7 The posterior probability of a localised outbreak in Auckland and neighbouring Manukau City TAs (A-B) Giardiasis (C-D) Cryptosporidiosis. The y axis represents the probability (black) and the number of cases (green) and the x axis is month

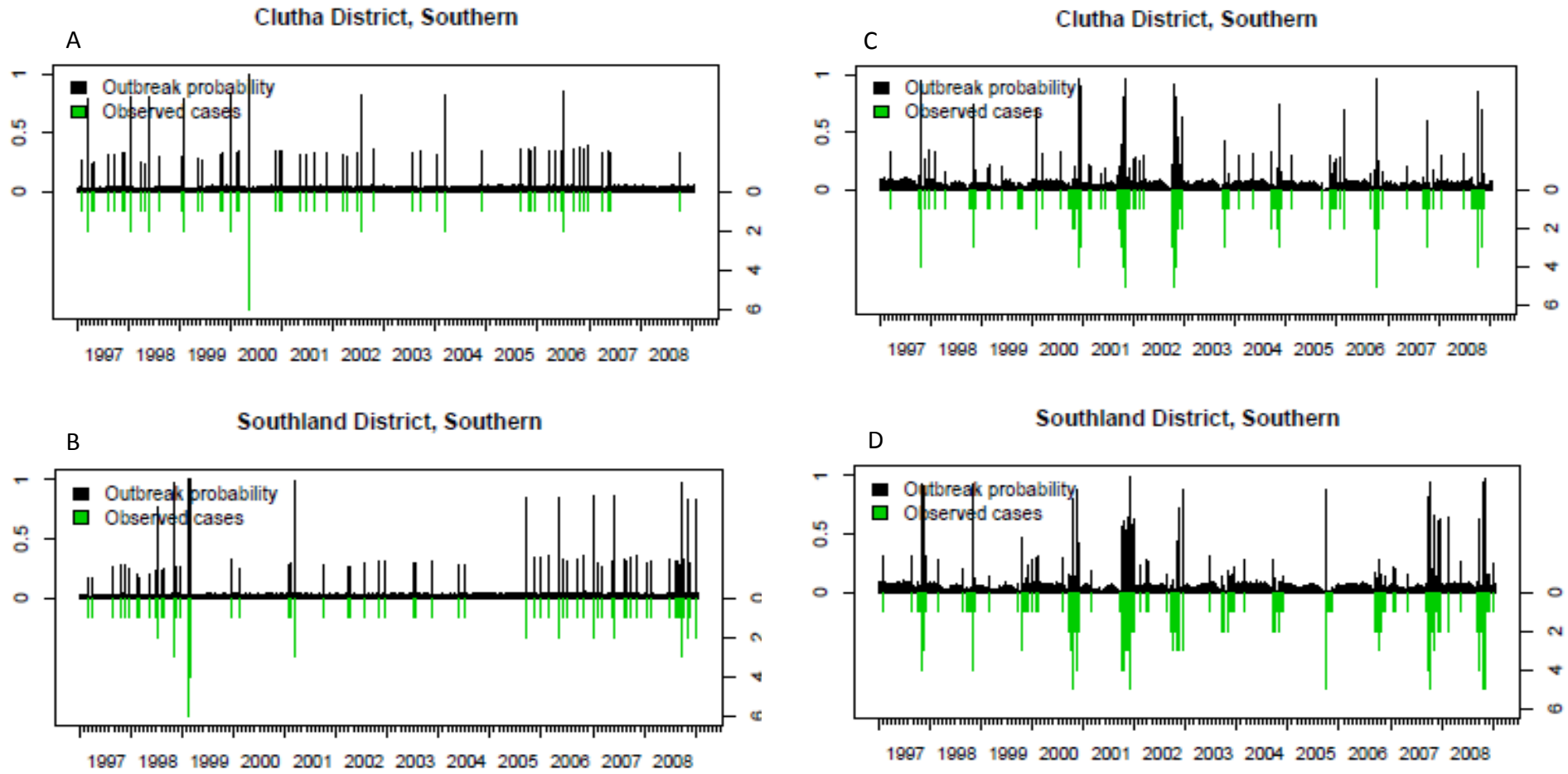


Figure 8.8 The posterior probability of a localised outbreak in Clutha and neighbouring Southland District City TAs (A-B) Giardiasis (C-D) Cryptosporidiosis. The y axis represents the probability (black) and the number of cases (green) and the x axis is month

8.5 Discussion

In this chapter, both cryptosporidiosis and giardiasis incidence showed distinct spatial variations in risk and temporal patterns in detected outbreaks. While giardiasis risk was higher in urban areas, results for cryptosporidiosis indicated a different epidemiology in rural areas which experienced higher overall rates and a dominant spring peak that was absent in urban populations.

8.5.1 Giardiasis

These results corroborate those in the previous chapter where generally higher rates of giardiasis were seen in urban areas. Moreover, the lack of a clear temporal pattern in outbreaks supports the hypothesis that infection sources are predominantly human and disease spread is primarily anthroponotic (Hoque, Hope et al. 2003, Hoque, Hope et al. 2004). This conclusion is also consistent with the observation that environmental factors such as weather play a minimal role in influencing disease patterns.

Anecdotal evidence citing food borne exposure to *Giardia* spp. has been reported worldwide (Smith, Cacciò et al. 2007). Food contaminated by infected handlers (Kusolsuk, Maipanich et al. 2011), contaminated fruit and vegetables (Mohammed Mahdy, Lim et al. 2008, Werner, Klaus et al. 2010) and shellfish growing in polluted waters (Graczyk, Graczyk et al. 2011) have been implicated as vehicles for pathogen transmission to humans. Higher giardiasis risk in urban areas could be related to retail food outlets and partially explain the patterns documented here. This suggests that food as a transmission pathway for giardiasis should be investigated further.

Giardiasis tends to be the least seasonal of the important enteric zoonotic diseases globally (Lal, Hales et al. 2012) (Chapter 4). In New Zealand, meteorological conditions such as temperature and rainfall do not appear to play an important role in transmission and maintenance of this enteric disease (Chapter 5 and 6). The small late summer peak noted in New Zealand (Hoque, Hope et al. 2004) is similar to that recorded in the United States (Naumova, Jagai et al. 2007) and

Canada (Odoi, Martin et al. 2003) and may be due to increased interaction with children over the holiday period (Greig, Michel et al. 2001) or increased contact with recreational water (Naumova, Jagai et al. 2007). Moreover, sequencing of *Giardia* isolates from young livestock have revealed the presence of host specific strains (Hunt, Ionas et al. 2000), suggesting limited zoonotic transmission. While sustained exposure to animal pathogen sources may result in the development of protective immunity and lower levels of symptomatic infection in rural areas, it seems unlikely, as this pattern is not repeated for cryptosporidiosis where rural rates are significantly higher. Errors and uncertainty in geocoding particularly for rural areas in New Zealand have been underlined as a limitation of notification data collected during the 1990s (Skelly, Black et al. 2002), though the quality of geocoding may have improved since then. This could potentially explain the high giardiasis risk in urban areas, although given the opposite patterns for cryptosporidiosis it seems unlikely that this bias drives the geographic patterns reported here. Thus, the relatively high incidence of giardiasis nationally coupled with the absence of a clear seasonal pattern and higher rates in urban areas implies a continuous endemic level of exposure mainly driven by population characteristics and behaviour rather than environmental conditions.

8.5.2 Cryptosporidiosis

In contrast to spatial patterns of giardiasis risk, the relative risk of cryptosporidiosis in urban areas was lower than average. This pattern is similar to that previously documented in New Zealand (Snel, Baker et al. 2009, Britton, Hales et al. 2010), and Scotland (Pollock, Ternent et al. 2009), supporting the premise that for cryptosporidiosis, agricultural sources of infection and environmental transmission pathways are dominant. However, it is important to note that *Cryptosporidium* spp. are easily transmitted by water (Fayer 2004) with evidence showing that, in New Zealand, quality of public drinking water supplies play an important role in disease spread (Duncanson, Russell et al. 2000, Britton, Hales et al. 2010). Numerous cryptosporidiosis outbreaks due to contamination of drinking water supplies have been reported (Karanis, Kourenti et al. 2007), with the largest outbreak ever recorded attributed to contamination of the town drinking water supply (Mac Kenzie, Hoxie et al. 1994). Thus, urban populations

with reticulated water supplies may be at increased risk from such spread. Indeed, the simultaneous outbreaks detected in the Auckland and Manukau Districts in the first half of 2001 and then again in 2007 suggest a common exposure that may be related to drinking water supplies and a detailed examination of these clusters may be worthwhile. Conversely, the lower than average risk in urban areas may also be due to the presence of routinely monitored public water supplies. In New Zealand, rural populations are largely characterized by private water supplies which tend to be less regulated and more prone to contamination (Simmons, Hope et al. 2001, Khan, Phillips et al. 2007). This could partially explain the high risk in rural areas and warrants further investigation.

The uniformly high risk patterns in the Clutha and Southland District, an area with high livestock densities, suggest that livestock may be a major determinant of cryptosporidiosis incidence. In addition, the clear recurrent spring peaks in outbreaks in the Clutha and Southland District imply a common environmental exposure. As pathogen shedding rates are maximum in young livestock (Coklin, Farber et al. 2010), and frequency of human contact with the animal reservoir is potentially highest at this time, there exist ample opportunities for zoonotic transmission. Furthermore, seasonal strain specific *Cryptosporidium* transmission cycles, implying zoonotic transmission in spring and anthroponotic transmission in autumn have been reported in New Zealand and the UK (Learmonth, Ionas et al. 2001, Chalmers, Smith et al. 2011, Zintl, Ezzaty-Mirashemi et al. 2011). In New Zealand, cryptosporidiosis outbreaks due to farm visits (Stefanogiannis, McLean et al. 2001) and among veterinary students (Grinberg, Pomroy et al. 2011) further support the premise that zoonotic transmission in rural areas is significant. Molecular subtyping may help retrospectively confirm outbreaks among archived specimens for cases that are suspected to be part of an outbreak. While seasonal patterns may also be due to the effect of ambient environmental conditions on pathogen survival (Li, Atwill et al. 2010) or spring peaks in rainfall facilitating spread (Naumova, Christodouleas et al. 2005), the patterns reported here and corroborated by other epidemiological and experimental data support the

hypothesis that livestock play an important role in cryptosporidiosis transmission in New Zealand.

The limitations of this analysis are presented in detail in Spencer et al (2011). In short, the outbreak detection regions in this chapter were the Territorial Authorities (TAs) which are spatially quite large (Figure 8.1B). As the outbreak indicators are defined as a collective increase in risk across the Census Area Units (CAUs) in a given TA, it is possible that highly localised outbreaks were masked by a larger number of sporadic cases occurring elsewhere in the TA. Conversely, when an outbreak is successfully identified, any sporadic cases occurring in the same region are automatically highlighted for further investigation. As stated by Spencer et al. (2011), the effect of these problems may be limited by choosing epidemiologically and biologically plausible regions.

In summary, the model described here presents the temporal probability of plausible outbreaks that may benefit from further investigation. Taken together with the spatial patterns of relative risk, these suggest regions and times of increased risk indicative of a common exposure or source of infection. For example, the increased relative risk of cryptosporidiosis in rural areas along with the distinct spring peaks in outbreak probability is suggestive of an association with spring agricultural activities such as calving and lambing. Conversely, for giardiasis the increased relative risk in urban areas together with no apparent pattern in suggested outbreaks suggests a population related, non-seasonal exposure.

CHAPTER 9 MULTIVARIATE ANALYSIS OF THE ENVIRONMENTAL AND SOCIAL DETERMINANTS OF CRYPTOSPORIDIOSIS AND GIARDIASIS IN NEW ZEALAND

9.1 Introduction

The interactions between local and large-scale environmental and social processes in structuring enteric disease patterns are under-recognised (Eisenberg, Trostle et al. 2012). An approach that considers these interdependencies is needed in order to understand the influence of landscape scale, long term processes like climate variability and land use change on disease risk.

So far, this thesis has provided ample evidence to suggest that the interactions between environmental and social factors could result in distinct, dominant pathogen sources and transmission pathways for enteric infections in New Zealand. While the preceding chapters highlighted the importance of considering spatial and temporal variations in disease patterns, they did not attempt to capture the relationships between environmental and social variables in influencing disease patterns across the spatial and temporal dimensions simultaneously.

In New Zealand, enteric protozoan disease in humans is a substantial economic concern (Moore, Black et al. 2010). In this chapter, a multivariate, retrospective analysis is used to evaluate the influence of climatic, agricultural land use and population characteristics on cryptosporidiosis and giardiasis risk across space and time in New Zealand.

9.2 Chapter aim

In this chapter, I modelled the historical relationship between meteorological variables (precipitation, temperature), agricultural land use (densities of dairy cows, poultry, deer, pigs, beef cattle) demographic (age, gender, ethnicity, index of socio-economic deprivation) ; drinking water quality variables and cryptosporidiosis and giardiasis incidence in New Zealand from 2000-2007 at the CAU level and a weekly time scale.

9.3 Methods

9.3.1 Disease data

Laboratory confirmed cases of cryptosporidiosis (n=8688) and giardiasis (n=16930) were extracted from the dataset for the time period 2000–2007 along with the following case information: report date, age, ethnicity prioritised, and CAU code of residence. To avoid "weekday effect" on notifications, cases were aggregated weekly where each week started on a Wednesday and ended on a Tuesday for every week in the eight year period.in this chapter, disease data were restricted to the period 2000-2007 to concur with data on livestock densities. This analysis was restricted to the period 2000-2007 as livestock density data 9Section 9.3.7) was only available from every alternate year starting 2000.

9.3.2 Population at risk

Population estimates based on CAU for each year from 1996-2007 were obtained through Statistics New Zealand. The population estimates are provided as at 30 June of each year and for each of the census years (1996, 2001, 2006). These data were linearly interpolated to produce population estimates across the study period. For 2000 - 2003 data was linearly interpolated from the 2001 Census; and the 2004 - 2007 data was linearly interpolated from the 2006 Census year. The total population as well as the population by age group was provided where population estimates at 30 June 2000 were based on 2001 CAU boundaries, while population estimates from 2001 onwards were based on 2006 CAU boundaries. Using a geographic concordance file, the 2001 CAU boundaries were matched to the corresponding 2006 CAUs. Based on previous research (Brock 2011), for the purposes of this analysis, cases were divided into age groups of 0-4; 5-64 and ≥65 years. Following this, the proportions of the total population in each CAU in each of the three categories were obtained by dividing the respective number by the total population of the CAU for each year (obtained from linear interpolation). Population density used as a covariate in the analysis was calculated by dividing the total population number in each CAU by the area in each CAU (obtained by calculating the area of 2006 CAU polygons in ArcGIS v10.1). All population variables were standardised using Equation 9.1.

9.3.3 Urban/Rural status

To create this variable, the 2006 CAU categorisation of urban/rural status was used (Statistics New Zealand 2012). Each CAU is categorised into one of the following categories: Main urban areas, Satellite urban areas, Independent urban areas, Rural areas with high urban influence, Rural areas with moderate urban influence, Rural areas with low urban influence, Highly rural/remote areas, Area outside urban/rural profile. As differing risk factors in main urban areas and rural areas was the main hypothesis underlying this analysis, only an urban/rural classification was required. Therefore, the categories 'Main urban areas', 'Satellite urban areas' and 'Independent urban areas' were classified as urban (Level 1) whereas the categories 'Rural areas with high urban influence', 'Rural areas with moderate urban influence', 'Rural areas with low urban influence' and 'Highly rural/remote areas' were classified as rural (Level 0).

9.3.4 New Zealand Deprivation Index

The NZDep Index of Deprivation for the census years 1996, 2001 and 2006 was used to categorise the CAU based on deprivation (Salmond and Crampton 2002). NZDep is constructed on a decile scale with deprivation level 1 representing socioeconomically affluent CAUs and level 10 representing the most deprived CAUs. NZDep2001 and NZDep2006 provide deprivation scores for each CAU in New Zealand. Again, 2001 Census values were assigned to the years 2000, 2001, 2002 and 2003 whereas 2006 Census calculations were used for the years 2004, 2005, 2006 and 2007. For this analysis, deprivation levels were grouped into tertiles, with levels 1-3 representing affluent CAUs (Level 1) (reference category), 4-7 representing medium (Level 2) and 8-10 representing the least affluent CAUs (Level 3).

9.3.5 Ethnicity estimates

Ethnicity estimates for the years 2001 and 2006 by CAU were provided by Statistics New Zealand and were based on 2006 CAU boundaries. For each major ethnic group, the proportion of the population number in each ethnic group to the total CAU population number of all ethnic groups in the CAU was calculated. Again the estimates for every year were calculated by linear interpolation of

census years. For 2000 - 2003 data was linearly interpolated from the 2001 Census; and the 2004 - 2007 data was linearly interpolated from the 2006 Census year. Ethnicity was based on Level 1 prioritised ethnicity which divides the population into European, Māori, Pacific, Asian and Other. These were then standardised using Equation 9.1.

9.3.6 Drinking water quality

Annual drinking water quality grading at the 5km x 5km grid was supplied by the ESR Water Programme for the years 1997-2007. ESR used both the zone code and protozoa compliance to construct a scoring system for drinking water quality in each 5km x 5km grid. Following Brock (2011), for the purposes of this study, a grid score of 0 denoted good drinking water quality (complied); a grid score of 1 denoted intermediate drinking water quality (inadequately monitored); a grid score of 2 represented poor drinking water quality (non-compliant and either not monitored or contained *E.coli*); and a grid score of 3 indicated the drinking water quality was unknown. The method of assigning drinking water from quality from the 5km x 5km grid to the CAU scale is detailed below (Section 9.3.9).

9.3.7 Livestock density

Numbers of dairy cattle, beef cattle, sheep, pigs, poultry and deer for each Meshblock in New Zealand were obtained from the Agribase^{TM} database for each alternate year from 2000-2008. Animal data for each farm were mapped to a Meshblock according to the location of the main farm gate or homestead. These data were then aggregated up to the corresponding 2006 CAUs. For this study, dairy cattle included milking cows, replacement heifers, breeding bulls and calves. Beef cattle included beef cows, bulls, heifers and calves; and sheep included ewes, rams and lambs. The total land area of the CAU (in km^2), calculated using ArcGIS v10.1 was used to determine the amount of land in each CAU and livestock densities were calculating by dividing the number of animals in each CAU by the total land area in each CAU. Data for the missing years were interpolated. These were then standardised using Equation 9.1.

9.3.8 Climate data

Climate data were provided by NIWA for the 8 year period 2000 – 2007. Data from approximately 150 climate stations were extracted from New Zealand's National Climate Database (CLIDB) and interpolated onto a regular ~5km grid (0.05° lat/long resolution), forming 11,491 Virtual Climate Station VCS) grid cells covering the entire country using a the thin-plate smoothing spline interpolation scheme (Tait, Henderson et al. 2006)As this data was created specifically for a collaborative project between ESR, Massey University and NIWA, generation of the retrospective and prospective climate data is detailed in Brock (2011). These data were then standardised using Equation 9.1 below.

Equation 9.1

$$Z_{kit} = \frac{W_{kit} - \bar{W}_k}{s.e.(W_k)}$$

where Z_{kit} is the standardized variable W_k, in the grid *i* during week *t*; $\bar{W}_k$ is the mean and $s.e.(W_k)$ is the standard error for the variable W_k over the study duration.

9.3.9 Data analysis

To assign grid point data to the corresponding CAUs, using ArcGIS V 10.1, first the centroid of each 5 km x 5km grid (11, 491) and each 2006 CAU (1927) was created. Following this, using the "near" spatial analysis in ArcGIS v10.1, for each CAU centroid the closest centroid of each grid was identified and the covariates of this grid point assigned to the CAU. For the purposes of this analysis, it was assumed that the covariates were distributed equally within a CAU.

The island CAUs and those classified as harbours, inlets and oceanic regions were excluded from the analysis as were CAUs with no resident populations. CAUs that did not have all of the exposures of interest (such as urban/rural status, Deprivation Index) assigned were also excluded. This resulted in a total of

1778/1927 (92 %) of valid CAUs (mainland populations with all the covariates of interest) being included in the final analysis.

The Knorr-Held Richardson model used to analyse space-time surveillance data on meningococcal disease incidence in France (Knorr-Held and Richardson 2003) was modified by Dr. Simon Spencer of Warwick University and Dr. Jonathan Marshall of Massey University and used to model the historical relationship between climatic, land use and social factors on cryptosporidiosis and giardiasis incidence (Equation 9.2). For longer term seasonality, with 52 weeks per year, the temporal random effect R_t should control for any seasonal variation and overall trend that the fixed effects don't account for. Here the outcome variable λ_{it} represents the rate of notified cases in CAU *i* during week *t*, and PAR_{it} represents the population at risk. The offset was set to the population at risk (PAR_{it}) in each CAU *i* during week *t*, to account for differing population sizes.

Equation 9.2

$$Log\ (\lambda_{it}) = \alpha + R_t + U_i + \hat{\beta}_1 Z_{1it} + ... + \hat{\beta}_k Z_{kit} + log\ (PAR_{it})$$

λ_{it} represents the rate of notified cases in CAU *i* during week *t*; α is the intercept (or fixed effect) representing the average per-person risk over New Zealand (assuming covariates at baseline); R_t represents the temporal component; U_i represents the spatial component; $\hat{\beta}_1$ …to $\hat{\beta}_k$ are the posterior coefficient estimates from the posterior distributions $\hat{\beta}_1 \ldots \hat{\beta}_k$; $Z_{1it}, ..., Z_{kit}$ are explanatory covariates, such as weather, demographic and environmental variables; and $\log(PAR_{it})$ is the offset of the population at risk in each CAU *i* during week *t*. To attain convergence, each model was run for 20,000 iterations sampling every 20th iteration after an initial burn-in of 5000 iterations.

Having adjusted for the effect of other covariates, the multiplicative effect of a one standard deviation change in each variable on the incidence risk (IR) of each protozoan disease was calculated using Equation 9.3.

Equation 9.3

$$\Delta\lambda_{it} = e^{\hat{\beta}_k}$$

where $\Delta\lambda_{it}$ represents the change in rate of a notified case of protozoan disease in grid *i* during week *t*; and $\hat{\beta}_k$ represents the posterior coefficient estimate of each covariate Z_{kit}.

9.4 Results

9.4.1 Giardiasis

Having adjusted for the effect of other covariates the variables significantly associated with an increased rate of notified giardiasis in CAU *i* in New Zealand were the standardized proportion of the population being less than four years old ($\hat{\beta}_1$= 0.146, p <0.001); and rurality($\hat{\beta}_2$= 0.251, p <0.001). Apparently protective factors (that is, those associated with a decreased rate of notified cases) included the standardized proportion identifying with Asian, Māori or Pacific Island ethnic groups ($\hat{\beta}_3$= -2.241, p <0.001; $\hat{\beta}_4$= -1.682, p <0.001; $\hat{\beta}_5$= -2.871, p <0.001 respectively) and the standardized proportion over 65 years old ($\hat{\beta}_6$= -0.048, p <0.01) and standardised dairy cattle density ($\hat{\beta}_7$= -0.034, p <0.01).

9.4.2 Cryptosporidiosis

Having adjusted for the effect of other covariates the meteorological and agricultural land use variables significantly associated with cryptosporidiosis cases were dairy cattle density ($\hat{\beta}_1$= 0.057, p <0.001; and rurality $\hat{\beta}_2$= 0.502, p <0.001, respectively). Average weekly temperature was negatively associated with rates of cryptosporidiosis ($\hat{\beta}_5$= -0.087, p <0.01). The population demographic variables significantly associated with cryptosporidiosis were the standardized proportion being less than four years old ($\hat{\beta}_1$= 0.154, p <0.001). Apparently protective factors included the standardized proportion identifying with Asian, Māori or Pacific Island ethnic groups ($\hat{\beta}_3$= -2.190, p <0.001; $\hat{\beta}_4$= -1.555, p <0.001; $\hat{\beta}_5$= -2.223, p <0.001 respectively) and the standardized proportion of the population over 65 years old ($\hat{\beta}_6$= -0.117, p <0.001).

The significant effects of covariates on the rate of notified cryptosporidiosis cases in CAU *i* during week *t* may be demonstrated by an example. For dairy cattle density in CAU *i*, the estimated coefficient is $\hat{\beta}_1 = 0.057$, which gives the magnitude of the multiplicative change in the rate of notified cases in grid *i* by $\Delta\lambda_{it} = e^{-0.057} = 1.058$. This indicates that for one standard deviation increase in the dairy cattle density, (an increase of 49/sq. km) assuming all other factors remain constant, the rate of notified cryptosporidiosis increases by a factor of 1.058, (95% CI 1.025-1.095).

An example of how this can be applied to the weekly IR of cryptosporidiosis in New Zealand can be illustrated with the use of CAU 607400 in the Clutha district. The average dairy cattle density in this CAU in 2006 was 0.317 cows/sq.km, the population at risk residing in this CAU was approximately 4140, and the average annual incidence of notified cryptosporidiosis was 0.038*52=2 cases. Based on model predictions, an increase in one standard deviation in dairy cattle density (that is, an increase from 0.31 /sq. km to 49.3/sq. km) would result in a change in the annual cryptosporidiosis IR by a factor of 1.058, resulting in an increase of 2.116 notified cases per year.

Table 9.1 Retrospective multivariate modelling for giardiasis for each independent variable (Z_i), its associated posterior coefficient estimate ($\hat{\beta}_k$), the expected change in the rate of notified case ($e^{\hat{\beta}_k}$) with the corresponding 95% credible interval, and level of significance. The baseline values are the proportion of the population aged between 4 and 65 years of age, the proportion of the population with European ethnicity (including New Zealand European), the most affluent CAUs, good drinking water quality and urban CAUs

Explanatory Variable (Z_i)	**Model coefficient ($\hat{\beta}_k$)**	**Incidence Risk ($e^{\hat{\beta}_k}$) (95% CI)**
Average Rainfall (mm)	0.034	1.033 (0.975, 1.096)
Average Temperature (°C)	-0.029	0.971 (0.917, 1.025)
Aged < 4 Years	0.146	1.156 (1.100, 1.222)***
Aged ≥ 65 Years	-0.048	0.938 (0.896, 0.987)**
Dairy Cattle Density‡	-0.034	0.960 (0.928, 0.992) **
Deer Density‡	0.012	1.102 (0.975, 1.049)
Poultry Density‡	-0.004	0.991 (0.960, 1.025)
Pig Density‡	0.018	1.018 (0.989, 1.045)
Beef Cattle Density‡	0.014	1.012 (0.972, 1.047)
Māori	-1.682	0.184 (0.112, 0.319)***
Pacific Islander	-2.733	0.063 (0.037, 0.118)***
Asian	-2.086	0.125 (0.065, 0.233)***
Middle Eastern/Latin American/African	1.065	3.180 (0.257, 27.635)
Intermediate Drinking Water Quality	-0.025	0.978 (0.916, 1.049)
Poor Drinking Water Quality	-0.073	0.929 (0.856, 1.013)
Unknown Drinking Water Quality	-0.023	0.980 (0.871, 1.091)
Rurality	0.251	1.295 (1.133, 1.450)***
Population Density	-0.018	0.990 (0.930, 1.039)
Socio-Economic Deprivation (Intermediate)	-0.079	0.930 (0.858, 1.001)
Socio-Economic Deprivation (Most Deprived)	-0.004	0.999 (0.878, 1.151)

*p<0.05
**p<0.01
***p<0.001
‡ Density is defined as the number of animals per square kilometre. It is standardised.

Table 9.2 Retrospective multivariate modelling for cryptosporidiosis for each independent variable (Z_i), its associated posterior coefficient estimate ($\hat{\beta}_k$), the expected change in the rate of notified case ($e^{\hat{\beta}_k}$) with the corresponding 95% credible interval, and level of significance. The baseline values are the proportion of the population aged between 4 and 65 years of age, the proportion of the population with European ethnicity (including New Zealand European), the most affluent CAUs, good drinking water quality and urban CAUs

Explanatory Variable (Z_i)	**Model coefficient ($\hat{\beta}_k$)**	**Incidence Risk ($e^{\hat{\beta}_k}$)**
Average Rainfall (mm)	0.036	1.033 (0.975, 1.111)
Average Temperature (°C)	-0.087	0.916 (0.865, 0.972)**
Aged < 4 Years	0.154	1.166 (1.103, 1.235)***
Aged ≥ 65 Years	-0.121	0.886 (0.838, 0.933)***
Dairy Cattle Density‡	0.057	1.058 (1.025, 1.095)***
Deer Density‡	-0.003	0.997 (0.962, 1.027)
Poultry Density‡	-0.005	0.995 (0.959, 1.031)
Pig Density‡	-0.032	0.968 (0.932, 1.002)
Beef Cattle Density‡	0.026	1.027 (0.974, 1.067)
Māori	-1.555	0.213 (0.114, 0.385)***
Pacific Islander	-2.223	0.107 (0.047, 0.254)***
Asian	-2.190	0.111 (0.050, 0.271)***
Middle Eastern/Latin American/African	-0.536	0.597 (0.054, 6.654)
Intermediate Drinking Water Quality	0.017	1.015 (0.948, 1.096)
Poor Drinking Water Quality	0.004	1.006 (0.917, 1.100)
Unknown Drinking Water Quality	-0.120	0.885 (0.769, 1.004)
Rurality	0.502	1.649 (1.483, 1.832)***
Population Density	-0.131	0.877 (0.822, 0.936)***
Socio-Economic Deprivation (Intermediate)	-0.053	0.948 (0.874, 1.031)
Socio-Economic Deprivation (Most Deprived)	-0.082	0.920 (0.785, 1.084)

* $p<0.05$
** $p<0.01$
*** $p<0.001$
‡ Density is defined as the number of animals per square kilometre. It is standardised.

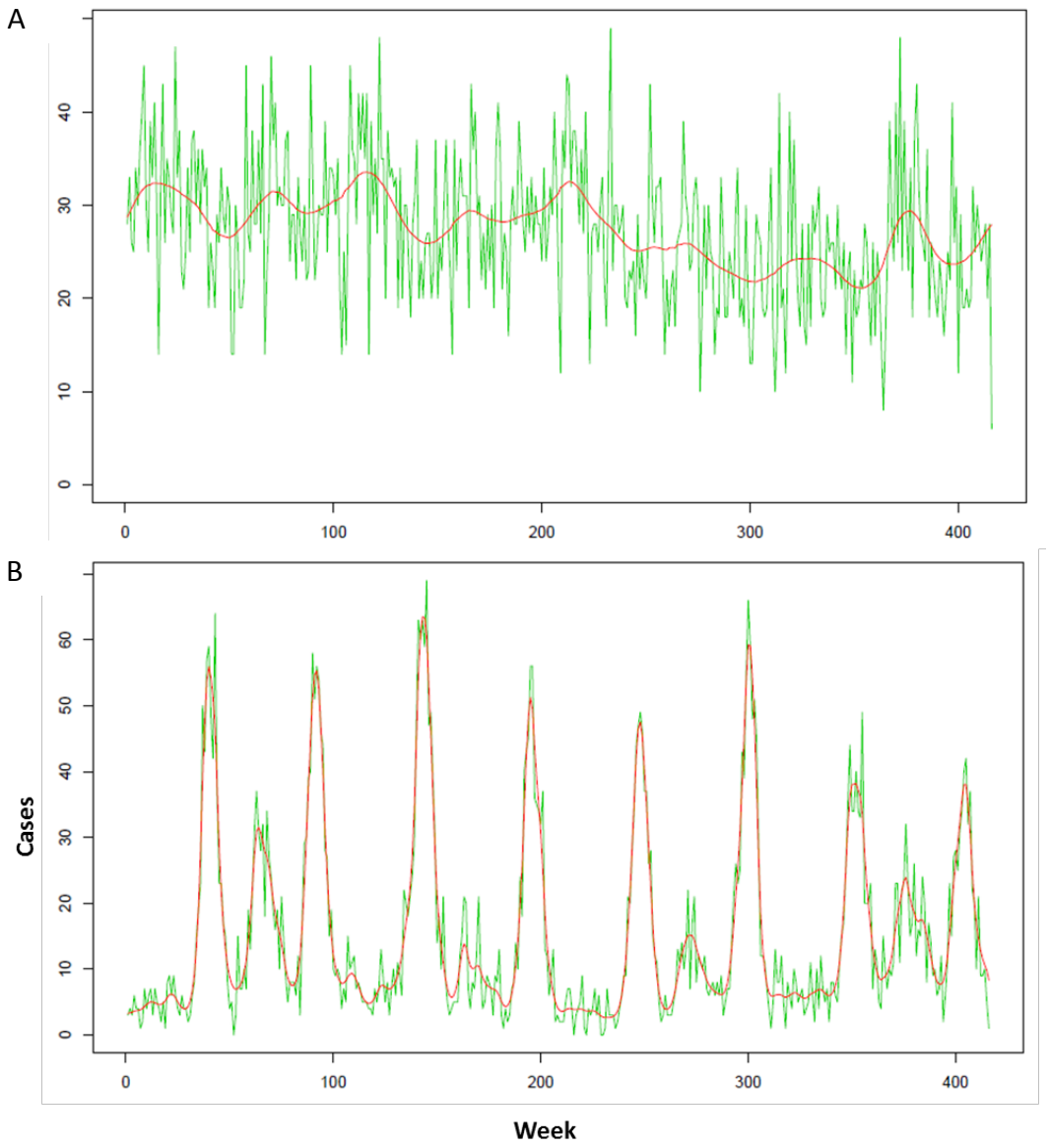


Figure 9.1 The weekly observed incidence (green) and the estimated weekly incidence (2000-2007) (red) (A) giardiasis (B) cryptosporidiosis

9.5 Discussion

This chapter presents the first attempt to compare retrospective models for the aquatic protozoan diseases cryptosporidiosis and giardiasis in relation to climatic, agricultural land use and social variables across space and time in New Zealand. For both diseases, identifying with the Asian, Māori, and Pacific Island ethnic

groups or being over 65 years appeared protective while being less than 4 years old and rural living were identified as risk factors. Cryptosporidiosis risk was positively associated with dairy cattle density and negatively associated with average weekly temperature and population density. Giardiasis risk was negatively associated with dairy cattle density.

Biases in case ascertainment may result in under representation of vulnerable groups in passive surveillance data (Wheeler, Sethi et al. 1999). A significant decrease in cryptosporidiosis and giardiasis risk associated with Asian, Māori, and Pacific Island ethnicities was seen here. This apparent protective effect is in keeping with results from Chapter 3 and previous studies in New Zealand (Snel, Baker et al. 2009, Britton, Hales et al. 2010) and is probably indicative of a significant bias in case ascertainment rather than a true effect of ethnicity. This is evident as opposite trends in giardiasis and cryptosporidiosis hospitalisations for these ethnic groups are seen, suggesting more severe outcomes for these populations (Chapter 3). This conclusion is further supported by a recent study showing that infectious diseases were the most common cause of hospital admissions in New Zealand, with age standardised risks for Māori and Pacific peoples markedly higher than any other ethnic group (Baker, Barnard et al. 2012). A community based survey of gastrointestinal illness in New Zealand also reported significantly higher rates for Māori participants (Adlam, Perera et al. 2010). Similar patterns with racial groups have emerged with enteric infections in the US (Chang, Groseclose et al. 2009). In indigenous communities in the Northwest Territories in Canada giardiasis risk was associated with health access and delivery systems factors (Pardhan-Ali, Wilson et al. 2013).

Similarly, increased access, and use of healthcare facilities by populations can also result in increased reporting of disease incidence. In Denmark, high-income and education were associated with increased risks of campylobacteriosis and salmonellosis (Simonsen, Frisch et al. 2008). Thus, the finding that the more socio-economically deprived CAUs were associated with disease risk (Table 9.1), although not significant, is also likely to be an artefact of passive surveillance data. Indeed, the highest giardiasis hospitalisation rate is seen in socio-

economically more deprived areas (Chapter3). Ethnic and socio-economic disparities tend to drive biases in health care access and utilisation by populations, limiting the extent to which notification data may be used to infer causal relationships with ethnic and socio-economic factors.

Giardia and *Cryptosporidium* spp. are the most common enteric parasites isolated from domestic animals (Hunter and Thompson 2005). However, a recent review suggests that compared to *Cryptosporidium*, data on the importance of zoonotic *Giardia* transmission is surprisingly scarce (Thompson, Palmer et al. 2008). In the US, a comparison of cryptosporidiosis and giardiasis rates in the elderly showed increasing rates of cryptosporidiosis with increasing cattle density, while for giardiasis this trend was not apparent (Jagai, Griffiths et al. 2010). The finding that dairy cattle density was significantly negatively related to giardiasis risk (Table 9.1) is interesting and deserves further investigation. To my knowledge, to date there has been no published longitudinal study conducted in New Zealand genotyping *Giardia* isolates from animal hosts and humans to determine the importance of zoonotic transmission. Given the public health significance of giardiasis in New Zealand (Snel, Baker et al. 2009), clarifying the zoonotic potential of *Giardia* from livestock would be useful.

As most private well users live in rural areas, it is possible that the association of giardiasis with rurality is in part reflecting this difference. Significantly higher rates of cryptosporidiosis and giardiasis in populations living in land parcels in Canada serviced by private wells compared to areas with municipal ground water system has been reported (Uhlmann, Galanis et al. 2009). Moreover, rural populations having livestock contact were more likely to have an untreated private well as their drinking water source (David, Ravel et al. 2013). In one of the few studies evaluating giardiasis incidence rates in relation to environmental and population factors, being under 4 years old and poor quality drinking water were identified as significant risk factors for giardiasis in rural Québec (Kabore, Levallois et al. 2010). Alternatively, as suggested by Britton et al. (2010), areas with the best drinking water quality may correspond with populations that have better access to health services, resulting in higher notification rates.

While the modelling approach used here accounted for spatial and temporal correlation in the data, it did not account for possible interactions between variables. As seen in Chapter 6, the association of disease incidence with environmental variable may be nonlinear and temporally lagged. However, in this analysis lagged environmental and disease variables (at time *t-1*) were not included. Assigning grid point data for climate to a Census Area Unit may result in misclassification, which possibly underestimates the effects of temperature and rainfall (Peng and Bell 2010), as they do not account for individual-level exposure (Bell 2006). In this study, weekly temperature and rainfall for CAUs that were small (in urban areas) are less likely to suffer from misclassification bias compared to rural CAUs which are large. Future studies at a finer spatial resolution would be useful to examine the influence of climatic variables on disease incidence particularly in rural areas.

The association of giardiasis with rurality was unexpected. Results from previous chapters suggest that the dominant drivers in urban and rural areas for both these diseases are likely to be different. However, this analysis did not analyse urban and rural areas separately, making the results hard to interpret. It is likely that for giardiasis, population related factors may drive infection risk in urban areas. Once confounding by livestock densities were allowed for, giardiasis incidence showed an apparent positive association with rurality. This may be a statistical artefact as the analyses included all covariates, regardless of statistical significance. The correlations between rurality and livestock densities make interpretation of these relationships complex. For example, results indicate that increased giardiasis risk in rural areas would be attenuated in rural areas with high cattle density. This is an interesting result that deserves further exploration.

Multivariate analyses for cryptosporidiosis were in keeping with results from previous chapters. A significant negative association with population density and a significant positive association with rurality and dairy cow density suggest that in New Zealand, dairying intensification may influence disease patterns.

Genotyping of human and animal isolates in New Zealand, the UK and Australia suggest that sporadic cryptosporidiosis in rural areas is primarily driven by zoonotic transmission (Learmonth, Ionas et al. 2001, Ng, Eastwood et al. 2008, Chalmers, Smith et al. 2011). The dominant mechanisms and transmission pathways driving spatial and temporal variations in enteric, protozoan disease risk in New Zealand appear to be quite distinct.

SECTION III: KEY FINDINGS

1. Detection of space-time clusters of cryptosporidiosis and giardiasis in New Zealand using SaTScan identifies locations and times that did not follow the observed distribution of disease incidence rates. While giardiasis clusters occurred in predominantly urban areas, cryptosporidiosis clusters occurred in primarily agricultural, livestock dominated areas. Recurrent giardiasis clusters in the upper half of the South Island were more likely to occur in the autumn-winter period. For cryptosporidiosis, all recurrent clusters in the southern half of the South Island in the Southland region occurred in spring (October-December).

2. Purely spatial patterns in relative risk for giardiasis showed higher than expected risk in urban areas. In addition, temporal analyses revealed no apparent seasonal patterns in outbreak probability in either urban or rural areas. In contrast, spatial relative risk patterns for cryptosporidiosis showed higher than expected risk in rural areas. Moreover, while there were no clear seasonal patterns in outbreak probability in urban areas, rural areas showed a distinct spring peak in outbreak probability, over and above background temporal patterns.

3. Multivariate analyses revealed that for both cryptosporidiosis and giardiasis, identifying with Asian, Māori, Pacific ethnic groups or being over 65 years was apparently protective, while being under 4 years old and rural residence was significantly positively associated with infection risk. Giardiasis risk was negatively associated with dairy cattle density, and positively associated with rurality, but these conflicting findings may have been the result of model overfitting. Cryptosporidiosis risk was significantly positively associated with dairy cattle density and negatively associated with population density and average weekly temperature.

CHAPTER 10 GENERAL DISCUSSION, STUDY IMPLICATIONS AND RECOMMENDATIONS

The central aim of this thesis is to understand how global environmental changes, specifically climatic variability and agricultural intensification, may influence zoonoses incidence in humans. Historically high rates of enteric zoonoses in humans, recent trends in livestock intensification and a considerable influence of regional climate on local weather patterns made New Zealand an ideal location to investigate these relationships.

In New Zealand, regional climate and livestock production influence enteric disease incidence patterns. A description of case characteristics demonstrates that these patterns are pathogen specific, and are strongly modulated by human population characteristics (Section I). Using the Gini co-efficient and a novel seasonality index, I show that seasonality in enteric zoonoses is ubiquitous, albeit with regional variations. In New Zealand, time series models establish that enteric disease incidence is related to regional climate and indicators of climatic extremes (Section II). Multivariate space-time analyses are used to advance our understanding of the relationships between environmental and social factors and disease incidence. Overall, children less than four years old and those living in rural, livestock dominated areas have increased protozoan disease risk (Section III).

I discuss the findings of this thesis in the context of existing knowledge on the role of climate variability and agricultural intensification as determinants of enteric zoonotic disease patterns. Following this, I consider the implications of a changing climate and increasing agricultural intensification for population health, globally, and in New Zealand. Finally, I translate this understanding into recommendations for future research and policy directions.

10.1 Climate variability and enteric zoonotic diseases

10.1.1 Seasonality

Seasonality is a key attribute of enteric zoonotic disease incidence globally, with distinct, pathogen specific seasonal patterns (Chapter 4). Here, I develop an easily interpretable index for use by public health agencies to measure the timing and

magnitude of seasonal variation. I show consistent summer peaks across geographic regions for campylobacteriosis and salmonellosis. Cryptosporidiosis demonstrates distinct regional variations in seasonality with spring peaks in predominantly agricultural countries such as New Zealand, UK and Canada and summer peaks in the US and the rest of Europe. Giardiasis displays minimum seasonality.

The dominant summer peak in salmonellosis across geographic regions indicates that environmental factors may be an important factor driving disease patterns. This conclusion is supported by the association of disease incidence with warmer, wetter weather (Chapter 5) and an estimated 15% increase in salmonellosis predicted for every 1°C rise in temperature (Britton, Hales et al. 2010). Bacterial pathogens such as *Salmonella* are sensitive to environmental conditions (Winfield and Groisman 2003). In New Zealand, warmer summer temperatures are also associated with outdoor activities such as barbequing and recreational water contact, known risk factors for sporadic *Salmonella* infections (Domingues, Pires et al. 2012, Ziehm, Dreesman et al. 2012). This suggests that salmonellosis patterns are likely to be driven by a combination of enhanced multiplication and increased opportunities for exposure. A description of disease seasonality reveals temporal periods of increased risk and identification of possible risk factors. Establishing trends in seasonality also allows changes in patterns to be monitored, which is useful to detect responses of environmentally sensitive diseases such as salmonellosis to future climate change (Bennett, Dear et al. 2013).

Seasonal patterns in cryptosporidiosis show a bi-modal peak with spring peaks in agricultural countries and summer highs in others (Chapter 4). In the current study, recurrent, highly plausible cryptosporidiosis clusters with distinct spring peaks in Southland, a region of intensified dairy farming are detected (Chapters 7, 8). Synchronised agricultural practices such as calving may be a risk factor for human enteric infections at this time. New born calves are a significant reservoir of enteric zoonotic pathogens (Atwill, Johnson et al. 1999). While direct animal contact is a presumed risk factor (Hale, Scallan et al. 2012), contact with

contaminated rural or farming environments may be an equally important exposure (O'Brien, Adak et al. 2001, Crump, Sulka et al. 2002). Minimising human contact with livestock when they are in this “hyperinfectious” state or increased protection measures in these agricultural settings could help prevent seasonal outbreaks in humans (Codeco and Coelho 2006).

Using a summary measure to capture temporal variations across different sources may help identify source specific, seasonal triggers for disease clusters. In New Zealand, human campylobacteriosis attributed to poultry are seasonal with summer peaks, while cases attributed to livestock are seasonal with spring peaks (Jonathan Marshall, personal communication). Multi-locus sequence typing (MLST) of human isolates in Scotland found that while campylobacteriosis in rural children in spring was mainly due to ruminant and wild bird strains, adults showed a prolonged summer peak linked with chicken strains (Strachan, Rotariu et al. 2013). Although strain specific information was not available for this study, this approach is potentially useful to establish source specific, seasonal patterns.

10.1.2 Regional climate

As the first study to examine the potential role of inter-annual climate variability on enteric disease incidence (Chapter 5), I provide an insight into an aspect of infectious disease epidemiology primarily driven by research on vector- borne diseases (Poveda, Rojas et al. 2001, Shaman and Lipsitch 2013).

Salmonellosis is positively associated with the Southern Oscillation Index (SOI) (that is La Niña phase with generally warmer, wetter conditions) (Chapter 5) with increased risk at a high rate of runoff (Chapter 6). These findings are biologically plausible, as the SOI influences local weather patterns that might affect *Salmonella* ecology, known to be sensitive to dehydration. The detection of *Salmonella* in surface water exclusively after rainfall events also suggests the possibility of non-point pollution sources such as agriculture (Gaertner, Garres et al. 2009) and supports the runoff-disease relationships found here.

Cryptosporidiosis is inversely related to the SOI (that is, El Niño phase with typically cooler, drier conditions) (Chapter 5), with increased disease risk at a low rate of runoff (Chapter 6) and an inverse association of risk with average weekly temperature (Chapter 9). *Cryptosporidium* oocysts are largely regarded as environmentally robust (Dumètre, Aubert et al. 2012). This suggests that the El Niño Southern Oscillation, through its effect on local weather may be influencing environmental transmission of the pathogen. Using field studies along with modelling approaches to investigate the role of rainfall extremes in cryptosporidiosis transmission in New Zealand is needed.

Alternatively, the effect of ENSO on local weather may influence human behaviour patterns which drive infection risk. Thus, forecasts of enteric disease risk may need to account for regional climatic and social factors. Although these analyses did not account for non-climatic factors, the results present the interesting possibility that prediction of enteric disease incidence with climatic extremes in New Zealand is possible.

10.2 Agricultural intensification and enteric zoonotic diseases

Salmonellosis incidence in rural populations showed a dominant spring peak with overall higher notification rate in rural areas (Chapter 3), suggesting that agricultural land use affects disease burden. This premise is supported by evidence showing a spring peak in *S.* Brandenburg cases in humans in 2002-2003 in the South Island following a seasonal epidemic of the same strain in sheep (Baker, Thornley et al. 2007). During the same time, black backed gulls in the South Island were found to carry *S.* Brandenburg asymptomatically, implicating them in pathogen transmission between farms (Clark, Fenwick et al. 1999). Wild birds have been linked to epidemics of other strains (*S.* Typhimurium DT160) in humans in New Zealand (Alley, Connolly et al. 2002), indicating a potentially understudied mode of spread in rural areas.

Land use associated with livestock production is likely to influence cryptosporidiosis incidence patterns in New Zealand. There was a clear dose-

response relationship between rurality and cryptosporidiosis (Chapter 3), increased relative risk in rural areas (Chapter 8), with plausible cryptosporidiosis outbreaks detected in spring in livestock dominated regions (Chapter 8). These results were further supported by multivariate spatio-temporal analyses showing a significant positive association of disease incidence with dairy cattle density and rural living and a significant negative relationship with population density (Chapter 9). The consistency of these results with other studies in New Zealand (Snel, Baker et al. 2009, Brock 2011, Thorburn 2011) and elsewhere (Pollock, Ternent et al. 2009, Jagai, Griffiths et al. 2010), conducted across different spatial scales and using varying methodologies suggest that the cryptosporidiosis–livestock association is likely to be causal.

Proximity of humans to livestock could result in reverse zoonotic transmission of infectious pathogens. In New Zealand, a recent molecular study in Canterbury dairy calves found a high prevalence of the predominantly human associated *C. hominis* strain of *Cryptosporidium* (Abeywardena, Jex et al. 2012). This suggests that livestock could be a future reservoir of human infection with *C. hominis*, presenting a threat to both animal and human health.

Insect vectors are competent vehicles for transmission of enteric protozoan parasites (Graczyk, Knight et al. 2005). Laboratory experiments have found that Filth flies (*Family*: Calliphoridae) facilitate the mechanical transport of *Cryptosporidium* oocysts, with a positive relationship between number of oocysts being transported and those deposited (Graczyk, Fayer et al. 2000). In Botswana, diarrhoeal disease incidence peaked in the dry season, with authors postulating that these were ideal conditions for mechanical transmission of diarrhoeal pathogens by fly vectors (Friedrich 2013). Given the association of cryptosporidiosis with drier conditions, the public health risk from such alternate transmission pathways has not been adequately explored in New Zealand. This needs to be evaluated given the recent reconsideration to introduce exotic species of dung beetles to remove cow pats (New Scientist 2011).

Land use patterns can drive changes in ecological processes that influence the amount of the pathogen in the environment (hereafter referred to as 'pathogen load'), alter the distribution of infective and vulnerable hosts, and modify transmission pathways (Patz, Olson et al. 2008). In this thesis, livestock densities and rural living are used as surrogates for local ecological change driven by agricultural land use. Intensive farming systems rely on genetic selection of stock and management practices such as high animal densities. Low genetic diversity and high animal numbers create optimal opportunities for pathogens to amplify and evolve into more pathogenic strains (Jones, Grace et al. 2013). Results indicate that livestock production, in particular dairying intensification, is likely to impact human infection risk. Investigating and quantifying the mechanisms and pathways by which such environmental alteration affect public health in New Zealand is clearly needed.

10.3 Exception or preconception? Campylobacteriosis and Giardiasis

The distinct summer peak in campylobacteriosis common across most geographic regions studied was suggestive of a positive association with temperature (Chapter 4). This finding was not borne out by subsequent analyses as this association was not statistically significant in analyses that included the Southern Oscillation Index (SOI). Also, models without climatic variables (temperature, rainfall, SOI) performed better at forecasting disease incidence (Chapter 5). A multi- country analysis of *Campylobacter* infection rates with temperature reported a weak association both at the short term (weather) and longer term (seasonal) time scales (Kovats, Edwards et al. 2005). Previous analyses in New Zealand reveal that temperature is not a significant predictor of campylobacteriosis incidence (Brock 2011, Spencer, Marshall et al. 2011). These findings may reflect a feature of *Campylobacter* physiology, which, unlike *Salmonella*, does not multiply at temperatures below 30°C (Park 2002). Interestingly, the association of campylobacteriosis risk with a high rate of runoff and at a lag of 5-6 weeks (Chapter 6) and the increase in disease risk with an increase in absolute humidity

(Brock 2011) suggest that the rainfall-campylobacteriosis association merits further attention.

Poultry remains the dominant source of *Campylobacter* infections in New Zealand (Mullner, Shadbolt et al. 2010). While agricultural land use may contribute an important zoonotic source of *Campylobacter* spp., examining the impacts of projected climate change on foodborne transmission of *Campylobacter* may provide larger health benefits.

For giardiasis, the majority of results allude to the importance of infection sources that are predominantly human, and that host behaviour rather than environmental factors are likely to drive infection patterns. The lack of a clear temporal pattern in outbreaks and the negligible association of disease incidence with climatic factors (Chapters 5, 6 and 9) further support this conclusion. Urban areas are more likely to have higher background rates of infection and atypical disease clusters (Chapter 7, 8).

Unexpectedly, in Chapter 9, rural living was identified as an important risk factor for giardiasis, while dairy cattle density was apparently protective. There is evidence to suggest potential zoonotic transmission of *Giardia* from livestock in the North Island (Learmonth, Ionas et al. 2003) and the South Island (Winkworth, Matthaei et al. 2008), although the actual extent of transmission to humans is still not clear. Evaluating the public health risks of *Giardia* from environmental sources has previously been suggested (Winkworth 2010). Such a risk assessment could provide important insights into the epidemiology of *Giardia* in rural New Zealand.

The positive association of giardiasis incidence with rurality, once livestock densities were accounted for, may reflect an aspect of the rural environment not captured by this study. High animal densities can facilitate pathogen movement across species' barriers (Cutler, Fooks et al. 2010), indicating that domestic companion animals such as dogs and cats may act as an intermediary host for

transmission of enteric pathogens from livestock to humans (Cleaveland, Laurenson et al. 2001). Contact with contaminated environments and surfaces have also been implicated in enteric pathogen transmission (Cummings, Warnick et al. 2012) and disease outbreaks (Crump, Sulka et al. 2002). An interesting hypothesis worthy of further investigation is the role of asymptomatic carriers. A study in India showed that children carrying viruses asymptomatically were an important infection source as their behaviour was not limited by disease manifestations (Gladstone, Iturriza-Gomara et al. 2008). In this context, sustained exposure to enteric pathogens from livestock could confer short term immunity to disease (Swift and Hunter 2004). However, these persons may still carry low levels of the pathogen, and as they are not restricted by illness, they may inadvertently spread disease in the rural community. These results also highlight the observational nature of this study, where inter relationships between independent and response variables make disentangling their influences complex. Nonetheless, the apparent association of giardiasis and rurality which is weakened in areas with high cattle density is interesting and deserves further examination.

Reticulated public drinking water supplies have previously been found to be protective against *Giardia* and *Cryptosporidium* infections in New Zealand (Hoque, Hope et al. 1999, Britton, Hales et al. 2010). In contrast to earlier studies, I found that drinking water quality had no significant effect on either cryptosporidiosis or giardiasis risk. This result may have been due to misclassification of drinking water quality at the CAU level. It is also possible that the giardiasis rurality association may be partly driven by quality of private rural water supplies. Rural populations are more likely to harvest rainwater, a drinking water source susceptible to enteric pathogen contamination (Simmons, Hope et al. 2001). However, drinking water quality may play a greater role in disease outbreaks than in sporadic disease. Peaks in cryptosporidiosis incidence in adjoining urban areas were seen (Chapter 8). This finding suggests a common source of infection and deserves further research. The largest cryptosporidiosis outbreak ever recorded in New Zealand was attributed to contamination of reticulated town water supply (Mac Kenzie, Hoxie et al. 1994). This highlights a

study limitation, as it is likely that sporadic and outbreak cases have different sources and evaluating risk factors separately may have been more informative.

10.4 Study strengths and limitations

Uncertainty in the accuracy of data sources affect observational analyses such as those performed here. The main limitation of this study is the use of passive disease surveillance data, known to suffer from significant case under ascertainment (Arshad, Wilkins et al. 2007). Evidence from the UK, for example suggests that only one in ten cases of campylobacteriosis in the community are ever diagnosed and recorded in national notification datasets (Tam, Rodrigues et al. 2012). Combining data from multiple sources, I identify some of the biases that affect public health surveillance systems. In particular, notifications which are dependent on access to medical care and use of diagnostics services appear to under-represent Māori and Pacific peoples and deprived populations (Chapter 3). When using and interpreting these data, such biases need to be considered. This bias is also highlighted in Chapter 9, where, identifying with Māori, Pacific or Asian ethnicity and living in less affluent areas is associated with an apparent decreased risk of disease.

In this study, the weather variables, the population census and drinking water quality data covering 2000- 2007, for 11,491 5km x 5km grid points across New Zealand, was averaged up to the Census Area Unit (CAU) scale. Aggregating will result in the loss of resolution, but as the disease data were only available at the CAU scale, this was the only practical option. However, the fine scale grid used in a previous study (Brock 2011) also presents the possible drawback of pseudo-replication, as multiple grid points were assigned the same covariates based on their spatial location, which can artificially increase sample size.

Public health grading of water supplies is largely restricted to urban areas, and a considerable proportion of rural populations have private drinking water supplies not monitored by this national grading system. Private rural water supplies are likely to have different qualities, an aspect not addressed by the grading data.

Finally, as demographic data were obtained by interpolating data between censuses, temporal variations in demographic variables were assumed constant between censuses.

While this study has strong implications for the role of climatic and agricultural change on enteric disease risk in New Zealand, its scope does not extend to quantifying the importance of the different pathogen sources and transmission pathways. By integrating different data sources intended for unrelated purposes, this thesis identifies public health problems that may be exacerbated by future environmental change. This approach provides a resource efficient, but data intensive method for public health authorities to prioritise future research needs and areas for intervention.

10.5 Think Global: Implications of environmental change for health

The current rate of human driven environmental change is unprecedented and may overwhelm the capacity of natural systems to adapt (Millennium Ecosystem Assessment 2005, Brook, Ellis et al. 2013). An increase in zoonoses emergence and resurgence is one of the consequences of rapid environmental modification (Jones, Grace et al. 2013); therefore, it is important to understand the impacts of climate change on infectious diseases (Wilson, Slaney et al. 2011). Some researchers conclude that the potentially reversible impacts of land-use change make it a bigger issue than climate change (Slaney, Derraik et al. 2010). Through the conceptualisation presented in Chapter 1 and subsequent analyses, I show that to separate these environmental influences with regards to their health impacts is complex. Climatic and agricultural land use variables and social and demographic factors interact in multiple ways and across spatial and temporal scales to influence disease outcomes.

Without a multidisciplinary approach, our ability to assess the impacts of future anthropogenic environmental change on health is limited. Findings from this thesis emphasise the challenge that arises from translating this understanding into

analyses of disease drivers. Results highlight why deterministic cause-effect models may oversimplify relationships between specific risk factors and outcomes. The conceptual framework used in Chapter 1 may help facilitate integration across sectors and disciplines to improve human health in the face of global environmental change.

10.6 Act Local: Environmental change and health in New Zealand

New Zealand is expected to experience a rise in average temperature and increasing variability in rainfall extremes (Hennessy, Fitzharris et al. 2007). Trends in dairy cattle production and recent economic incentives suggest a further expansion of the dairy farming sector (Livestock Improvement Corporation 2012).

In the present study, cryptosporidiosis incidence is associated with cooler, drier conditions and a low rate of runoff, with rural residence and dairy cattle density identified as a significant predictors of disease risk. Climate change projections based on Global Circulation Models indicate that the South Islands east coast could get drier (Ministry for Environment 2008, Reisinger, Mullan et al. 2010). Intensification of dairy farming in the South Island is projected to continue (Livestock Improvement Corporation 2012). Increased overland runoff of *Cryptosporidium* spp. from pastures in Otago following prolonged drought has been shown (Caruso 2002). This potential increase in pathogen reservoir combined with decreased rainfall could result in an amplified risk to populations in these areas.

Campylobacteriosis risk is highest at a high rate of runoff and a lag of 5-6 weeks. Molecular typing of *Campylobacter* strains from the Manawatu region in the North Island showed that during peak flow, recreational surface water samples were dominated by ruminant strains associated with human disease (McBride, Ball et al. 2011). Using the same multivariate space-time models used in Chapter 9, Brock (2011) found that absolute humidity, dairy and beef cattle density were significant predictors of campylobacteriosis risk. Although seasonally dependant, higher than average rainfall is projected for this region (Reisinger, Mullan et al.

2010). Therefore, although the majority of New Zealand's population now reside in urban areas, rural populations in dairy farming regions may experience an increased enteric disease burden as a result of future agricultural intensification and increased variability in rainfall extremes. Reduced access to health care providers and access to diagnostic services is common in rural areas. Future policy decisions will need to more closely match health needs in rural areas (Parkes, Morrison et al. 2010).

Urban populations may be at increased risk from zoonotic pathogens due to their lack of exposure. In the UK, increased immunity as measured by the seroprevalence of antibodies to zoonotic *E. coli* O157 is attributed to recent contact with beef cattle, having a private water supply and contact with a child less than 5 years old (Quilliam, Chalmers et al. 2012). In New Zealand, 2006 National Census figures suggest that rural populations are the most mobile, with an influx of transient, urban people (Statistics New Zealand 2012). Intensifying livestock production will increase the enteric zoonotic pathogen reservoir. In conjunction with an inflow of urban, largely unexposed commuters, zoonotic disease risk in rural areas may increase further. Raising awareness of rural exposures and institutional support of local community initiatives to improve health will be crucial to minimise risk from zoonotic pathogens (Parkes, Morrison et al. 2010).

Even for an industrialised nation like New Zealand, projected climate change and agricultural intensification will impact human health. The consequences of environmental change for zoonotic disease need to be addressed as they will have a disproportionate effect on vulnerable populations.

10.7 Study recommendations for research and policy

10.7.1 Population specific vulnerability

In New Zealand, disease risk projections for children will be a key aspect of environmental change focussed interventions. Historically, pre-schoolers are especially vulnerable to enteric protozoan diseases (Chapter 9). The projection of

infectious disease burden in children under different scenarios of climate change is an important knowledge gap (Xu, Sheffield et al. 2012). The historically disproportionate disease burden in children found here suggests that projected climate change could affect enteric disease risk in children (Zhang 2007). At risk populations need to be identified to develop specific adaptation measures to reduce their vulnerability to climatic extremes.

10.7.2 Climate change adaptation

Climate change adaptation options proposed for pasture based dairying systems in New Zealand include increased stocking rates to deal with increased potential pasture production as a result of projected warmer temperatures and carbon dioxide fertilisation, and a heavier reliance on irrigation to deal with projected variability in rainfall extremes (Lee, Clark et al. 2013). Increased abstraction of water for irrigation could result in groundwater sources of drinking water in rural areas being contaminated. This could exacerbate the health risks faced by rural populations, which historically have higher zoonotic disease rates. While a proposed increase in livestock densities may help deal with the impacts of climate change on agriculture; as shown by this thesis, this has public health implications that need to be considered. Combining climate scenario based and hydrological modelling with field experiments to determine environmental pathogen load and transmission potential provides an opportunity for assessment of regional climate change adaptation measures on health.

10.7.3 Flood risk management

Catchment scale processes like hydrology can influence pathogen transmission. The nonlinear and lagged relationships of disease incidence with runoff rate found in this thesis are novel (Chapter 6) and support this premise. An extension of this analysis at the catchment scale to identify patterns of development or land use and hydrological parameters that might enhance, or conversely mitigate flood/drought related disease risk may be useful. This would inform landscape scale climate change adaptation options for the health sector. In the Netherlands, flood defence strategies did not anticipate increasing societal vulnerability in flood plain areas

(Klijn, de Bruijn et al. 2012). This omission could lead to severe health effects for vulnerable populations in catchments prone to weather extremes.

Agricultural intensification can cause increased runoff generation in floodplains (Wheater and Evans 2009). This is partly due to stream channelization, removal of natural vegetation and an increasingly monotonous landscape; features typically associated with increased flood risk (Jackson, Wheater et al. 2008). Although a provisional result, this study found a positive relationship between runoff rate and enteric disease risk. The presence of riparian buffers can reduce *Giardia* runoff from farmland (Winkworth, Matthaei et al. 2008). Farm management practices may benefit human health and catchment scale flood risk management strategies.

10.7.4 Disaster preparedness

Building outbreak indicators into disease surveillance systems could help predict and manage future outbreaks. Climatic extremes can synchronize infectious disease outbreaks over large spatial scales (Curriero, Patz et al. 2001) exerting increasing pressure on public health services. For example, distinct cholera epidemics concurrent with precipitation extremes were seen in several African nations hit by floods simultaneously (De Magny, Guégan et al. 2007). This study found significant associations between disease incidence and indicators of regional climatic extremes (Chapter 5), with plausible outbreaks identified using a reliable method (Chapter 8) (Mullner, Pleydell et al. 2013). Although effective outbreak response would depend on timely notification of illness, developing policies allowing climate based indicators to be integrated into disease surveillance would be useful. This refinement could help forecast periods of increased risk, thereby assisting efforts to reduce the intensity of outbreaks should they occur (IFRC 2013).

10.7.5 One Health

To my knowledge, there is no central authority whose responsibility it is to address environmental change associated health risks in New Zealand. “One Health” is a collaborative effort across the fields of human and veterinary medicine and environmental science to achieve improved human, animal and environmental health (One Health Initiative 2008). The core principle underlying

this concept is increased communication between discipline specific experts at local, regional and international scales. This cross disciplinary approach is especially relevant to zoonoses prevention, which depends on interrupting the disease transmission cycle shown in Figure 1.1. The most effective interventions may not necessarily emerge from the health sector as human-to-human transmission is not the primary mode of spread (Zinsstag, Roth et al. 2005). New Zealand presents some past successes in using a multi-disciplinary approach to reduce the health risk from zoonotic pathogens. These include the recent substantial reduction in human campylobacteriosis (Sears, Baker et al. 2011), and the eradication of the southern saltmarsh mosquito *Ochlerotatus camptorhynchus*, a vector of Ross River Virus in Australia (Wilson, Lush et al. 2011) hydatid disease and brucellosis among others (Davidson 2002).

10.8 Overall conclusion

Results from this study support the need to establish an environment conducive to cross disciplinary health research, an essential prerequisite to achieving “One Health”. Viewing human health in disciplinary isolation constrains our understanding of a complex system that is socially and ecologically connected. Such a perception limits our capacity to evaluate the impacts of future anthropogenic environmental change on health. In New Zealand, regional climate variability and agricultural intensification influence enteric zoonotic disease patterns. Importantly, environmental change associated disease risk is moderated by proximal population characteristics. Rural populations and children less than four years old bear a disproportionate burden of enteric disease. There is extensive scope to use modelling approaches, epidemiological methods and field experiments to develop research across sectors and establish policies that benefit New Zealand’s economy, environment and health in the long term. The tools used here can be applied to understand the implications of global change for health, and to optimise available resources to reduce the impacts of environmental change on health in New Zealand, and elsewhere.

Appendix 1 Attributes of 72 studies selected for review

Study Citation	Location, Years of Study	Study Design, Sample Size	Temporal Scale	Age Range (Yrs)	Peak season noted by the authors											
					J	F	M	A	M	J	J	A	S	O	N	D
(A) CAMPYLOBACTERIOSIS																
USA																
Hopkins and Olmsted 1985	Colorado, 1981-1982	Surveillance, 1185	Monthly	0-≥60								+	+			
Blaser et al. 1982	Denver, 1978-1980	Surveillance, 124	Monthly	0->60							+	+				
Altekruse et al. 1999	US, 1996	Surveillance (FoodNet)[a]	Monthly	0-≥60						+	+	+				
CANADA																
Thompson et al. 1986	Ontario, 1978-1985	Surveillance, 412	Monthly	0->60						+	+	+	+			
Michaud et al. 2004	Quebec, 2000-2001	Prospective Matched Case-Control, 158 (cases), 314 (controls)	Monthly	0->60							+	+	+			
Allard et al. 2010	Montreal, 1990-2006	Surveillance[a]	Weekly	None[b]												
UNITED KINGDOM																
Kendall and Tanner 1982	UK, 1979-1981	Surveillance, 518	Monthly	0->60						+	+	+				
Bradshaw et al. 1980	Chelmsford, 1977-1978	Surveillance, 109	Monthly	0->60						+	+	+	+			
Skirrow 1987	England, 1983-1984	Surveillance, 1873	Monthly	0->60					+	+						
Sopwith et al. 2003	NW England, 1997-1999	Surveillance, 3939	Monthly	0->60					+	+						
Jones et al. 1990	Lancaster, 1988-1989	Surveillance[a]	Monthly						+	+						

Study Citation	Location, Years of Study	Study Design, Sample Size	Temporal Scale	Age Range (Yrs)	Peak season noted by the authors											
					J	F	M	A	M	J	J	A	S	O	N	D
Sibbald and Sharp 1985	Scotland, 1978-1982	Surveillance, 7808	Monthly	0->60					+	+						
EUROPE																
Jepsen et al. 2009	Funen, Denmark, 1995-2004	Surveillance, 2984		None[b]												
Lassen and Kapperud 1984	Norway, 1980-1982	Surveillance, 249	Monthly	0->60							+	+				
Denis et al. 2009	Brittany, France, 2003-2004	Surveillance, 177	Monthly	0->60							+	+	+			
Samonis et al. 1997	Crete, Greece, 1992-1994	Surveillance, 169	Monthly	0->15							+	+				+
Studahl and Anderrson 2000	Älvsborg, Sweden,1995	Retrospective Matched Case-Control, 101 (cases), 198 (controls)	Monthly	0->60								+	+	+		
Nakari et al. 2010	Finland, 1996-2001	Surveillance, 5650	Monthly	0->60						+	+	+	+			
Karelampi et al. 2007	Helsinki, Finland, 1996, 2002,2003	Surveillance, 307	Monthly	19->60							+	+	+			
Liesenfield et al. 1993	Germany, 1989-1991	Surveillance, 98	Quarterly,	0->60				+	+	+						
Cabrita et al. 1992	Portugal, 1984-1989	Surveillance, 150	Monthly	0->19	+	+										
OCEANIA																
Brieseman et al. 1985	Christchurch, New Zealand, 1981-1983	Surveillance, 517	Monthly	0->60	+	+									+	+
			(B) SALMONELLOSIS													
USA																
Arshad et al. 2007	Michigan, 1995-2001	Surveillance, 6797	Monthly	0-≥60						+	+					
Oloya et al. 2007	Dakota, 2000-2005	Surveillance, 286	Monthly	None[b]						+	+	+				

Study Citation	Location, Years of Study	Study Design, Sample Size	Temporal Scale	Age Range (Yrs)	Peak season noted by the authors											
					J	F	M	A	M	J	J	A	S	O	N	D
Altekruse et al. 1999	US, 1996	Surveillance (FoodNet)[a]	Monthly	0-≥60						+	+	+				
Cherubin et al. 1996	New York, 1965-1966	Surveillance, 2200	Monthly	0->60							+	+	+			
Aserkoff et al. 1970	US, 1963-1967	Surveillance, 20,000	Monthly	0->60							+	+	+	+		
Younus et al. 2006	Michigan, 1995-2001	Surveillance, 1296	Monthly	0->60					+	+	+					
CANADA																
Ravel et al. 2010	Ontario2005-2008	Surveillance (C-EnterNet), 216	Monthly	0-≥60						+	+					
UNITED KINGDOM																
Banatvala et al. 1999	North East Thames, 1993	Surveillance, 1760	Monthly	0->60						+	+	+				
Sharp and Heyman 1976	Scotland, 1967-1974	Surveillance, 194	Monthly	0->60								+	+	+		
Skirrow 1987	England, 1983-1984	Surveillance, 1149	Monthly	0->60							+	+				
EUROPE																
Leisenfield et al. 1993	Germany, 1989-1991	Surveillance, 264	Monthly	0->60							+	+	+			
Samonis et al. 1997	Crete, Greece, 1992-1994	Surveillance, 491	Monthly	0-≥15						+	+	+				
Cabrita et al. 1992	Portugal, 1984-1989	Surveillance, 416	Monthly	0-≥19							+	+	+			
Collard et al. 2008	Belgium, 1970-2005	Surveillance[a]	Monthly								+	+	+			
OCEANIA																
D'Souza et al. 2004	Australia, 1991-2001	Surveillance[a]	Monthly	None[b]	+	+	+									
ASIA																
Cho et al. 2006	Republic of Korea, 2003	Surveillance, 376	Monthly	0->60						+	+	+	+			

Study Citation	Location, Years of Study	Study Design, Sample Size	Temporal Scale	Age Range (Yrs)	Peak season noted by the authors										
					J	F	M	A	M	J	J	A	S	O	N	D
Cho et al. 2008	Republic of Korea, 2004-2006	Surveillance, 957	Monthly	0->60							+	+	+			
Toyofuku 2008	Japan, 1998-2004	Surveillance[a]	Monthly	None[b]							+	+	+			
(C) CRYPTOSPORIDIOSIS																
USA																
Naumova et al. 2000	Massachusetts, 1993-1996	Surveillance, 230	Daily	0->60								+	+	+		
Dietz et al. 2000a	7 States, 1997-1998	Surveillance (FoodNet), 1023	Monthly	0->60							+	+	+	+		
Dietz et al. 2000b	47 States, 1995-1998	Surveillance, 11612	Monthly	0->60							+	+	+	+		
Roy et al. 2004	7 States, 1999-2001	Retrospective Matched Case-Control, 282 (cases) 490 (controls)	Monthly	0->60						+	+	+	+			
Amin 2002	48 States, 2000	Surveillance, 121	Monthly	0->60			+							+		
CANADA																
Pintar et al. 2009	Ontario, 2005-2007	Case Control,36 (cases) 803 (controls)	Monthly	0≥60							+	+	+			
Majowicz et al. 2001	Ontario, 1996-1997	Surveillance, 451	Quarterly	0≥60								+	+	+		
Laupland and Church 2005	Calgary, 1999-2002	Surveillance, 173	Monthly	0->60	no seasonality noted											
Mann et al. 1986	Manitoba, 1983-1984	Surveillance, 39	Monthly	0->60								+	+			
UNITED KINGDOM																
Callaghan et al. 2009	West Ireland, 2004-2007	Surveillance, 569	Monthly	None[b]			+	+	+							

Study Citation	Location, Years of Study	Study Design, Sample Size	Temporal Scale	Age Range (Yrs)	Peak season noted by the authors											
					J	F	M	A	M	J	J	A	S	O	N	D
Garvey and McKeown 2009	Ireland, 2004-2006	Surveillance, 1363	Monthly	0->60				+	+	+						
Zintl et al. 2009	Ireland, 2000-2007	Surveillance, 199	Monthly	0->60			+	+	+							
Sopwith et al. 2005	North West England, 1996-2000	Surveillance, 3711	Weekly	0≥45				+	+	+						
Chalmers et al. 2009	England and Wales, 2000-2003	Surveillance, 7829	Monthly	0->60								+	+	+		
Pollock et al. 2009	Scotland, 2005-2007	Surveillance, 560	Monthly	0->60								+	+	+		
EUROPE																
Derouin et al. 2010	France, 2006-2009	Surveillance (Anofel), 407	Monthly	0->60								+	+	+		
Wielinga et al. 2008	Netherlands, 2003-2005	Surveillance, 91	Monthly	0->60									+	+		
OCEANIA																
Snel et al. 2009	New Zealand, 1997-2006	Surveillance, 8212	Monthly	0->60									+	+	+	
		(D) GIARDIASIS														
USA																
Dennis et al. 1993	New Hampshire, 1984	Retrospective Case-Control, 273 (cases), 375 (controls)	Monthly	0≥55							+	+	+	+		
Birkhead and Vogt 1989	Vermont, 1983-1986	Surveillance, 1211	Monthly	0->60							+	+	+	+	+	
Naumova et al. 2000	Massachusetts, 1993-1996	Surveillance, 4508	Monthly	0->60							+	+	+	+	+	
Wright et al. 1977	Colorado, 1972-1973	Retrospective Matched Case-Control, 256 (cases), 256 (controls)	Monthly	0≥60							+					

Study Citation	Location, Years of Study	Study Design, Sample Size	Temporal Scale	Age Range (Yrs)	Peak season noted by the authors										
					J	F	M	A	M	J	J	A	S	O	N	D
Addiss et al. 1992	Wisconsin, 1981-1988	Surveillance, 9836	Monthly	0->60								+	+	+		
Navin et al. 1985	Nevada, 1982-1983	Retrospective Matched Case-Control, 45 (cases), 45 (controls)	Bi-weekly	0->60										+	+	
CANADA																
Laupland and Church 2005	Calgary, 1999-2002	Surveillance, 552	Monthly	0->60								+	+	+	+	
Odoi et al. 2003	Ontario, 1990-1998	Surveillance, 17031	Monthly	0≥60							+	+	+			
Greig et al. 2001	Ontario, 1990-1998	Surveillance, 25289	Monthly	0≥60								+	+	+		
UNITED KINGDOM																
Flanagan 1992	Scotland, 1983-1989	Surveillance[a]	Monthly	0->60							+	+	+			
Breathnach et al. 2010	South West London, 1999-2005	Surveillance, 819	Monthly	0->60										+	+	+
Gray et al. 1994	Avon and Somerset, 1992-1993	Matched Case- Control, 74 (cases), 108 (controls)	Monthly	0->60								+	+	+	+	
OCEANIA																
Kettlewell et al. 1998	Tasmania, 1995-1997	Surveillance, 456	Monthly	0->60	no seasonality noted											
Snel et al. 2009	New Zealand , 1997-2006	Surveillance, 16471	Monthly	0->60			+	+	+							
Hoque et al. 2002	Auckland, New Zealand, 1996-2000	Surveillance, 2510	Monthly	0->60		+	+									

[a] Total sample size not provided in the article

[b] Age range of study population not provided in the article

Appendix 2 Giardiasis space-time clusters identified by SaTScan

Giardiasis clusters identified in 1997-2000

Cluster	Start date	End date	*P*-value	Observed	Expected
1	14/07/1997	27/07/1997	1.24E-10	12	0.24
2	13/11/2000	24/12/2000	1.43E-06	14	0.88
3	19/04/1999	25/04/1999	3.53E-06	7	0.077
4	1/12/1997	7/12/1997	7.74E-06	6	0.042
5	15/02/1999	7/03/1999	8.38E-06	9	0.24
6	3/03/1997	9/03/1997	1.07E-05	7	0.09
7	28/12/1998	3/01/1999	2.41E-05	5	0.02
8	25/01/1999	14/02/1999	0.00013	14	1.26
9	23/10/2000	29/10/2000	0.000533	5	0.037
10	8/12/1997	14/12/1997	0.000619	5	0.038
11	15/12/1997	21/12/1997	0.000826	5	0.04
12	13/01/1997	9/02/1997	0.000997	10	0.59
13	27/03/2000	7/05/2000	0.00101	11	0.78
14	12/04/1999	2/05/1999	0.00125	6	0.099
15	2/03/1998	8/03/1998	0.00247	6	0.11
16	27/09/1999	3/10/1999	0.00444	4	0.019
17	7/06/1999	13/06/1999	0.00632	4	0.021
18	22/12/1997	28/12/1997	0.00641	5	0.062
19	17/11/1997	23/11/1997	0.00989	6	0.14
20	31/01/2000	12/03/2000	0.017	12	1.29
21	9/03/1998	22/03/1998	0.022	9	0.6
22	15/06/1998	28/06/1998	0.026	6	0.17
23	15/11/1999	28/11/1999	0.026	4	0.03
24	3/01/2000	9/01/2000	0.033	3	0.0067
25	14/02/2000	5/03/2000	0.04	6	0.18
26	2/10/2000	8/10/2000	0.04	4	0.034
27	25/05/1998	14/06/1998	0.042	7	0.32
28	18/08/1997	31/08/1997	0.042	5	0.094
29	26/06/2000	9/07/2000	0.047	5	0.095
30	31/08/1998	6/09/1998	0.049	4	0.036
31	15/09/1997	28/09/1997	0.061	4	0.037
32	6/01/1997	12/01/1997	0.067	4	0.039
33	19/07/1999	29/08/1999	0.086	18	3.67
34	27/09/1999	10/10/1999	0.093	7	0.35
35	20/04/1998	3/05/1998	0.118	5	0.11
36	16/10/2000	12/11/2000	0.148	7	0.38
37	15/02/1999	4/04/1999	0.162	7	0.38
38	10/02/1997	6/04/1997	0.175	18	3.83

Cluster	Start date	End date	*P*-value	Observed	Expected
39	1/05/2000	7/05/2000	0.177	7	0.39
40	17/08/1998	30/08/1998	0.261	7	0.41
41	19/05/1997	29/06/1997	0.285	14	2.4
42	22/03/1999	11/04/1999	0.311	5	0.14
43	17/08/1998	23/08/1998	0.326	4	0.059
44	5/10/1998	15/11/1998	0.331	5	0.14
45	19/10/1998	8/11/1998	0.345	5	0.15
46	14/12/1998	27/12/1998	0.345	4	0.061
47	17/05/1999	30/05/1999	0.366	10	1.15
48	10/08/1998	16/08/1998	0.391	4	0.063
49	13/01/1997	2/03/1997	0.391	17	3.7
50	15/09/1997	21/09/1997	0.396	5	0.15
51	5/06/2000	25/06/2000	0.448	8	0.67
52	30/06/1997	6/07/1997	0.451	6	0.29
53	18/12/2000	31/12/2000	0.481	4	0.068
54	9/08/1999	22/08/1999	0.506	4	0.069
55	18/08/1997	7/09/1997	0.543	5	0.17
56	14/06/1999	11/07/1999	0.562	5	0.17
57	12/01/1998	25/01/1998	0.57	4	0.072
58	13/04/1998	19/04/1998	0.57	4	0.072
59	22/06/1998	28/06/1998	0.57	4	0.072
60	16/10/2000	12/11/2000	0.578	5	0.17
61	19/05/1997	6/07/1997	0.583	6	0.31
62	15/09/1997	9/11/1997	0.601	8	0.72
63	15/03/1999	21/03/1999	0.608	3	0.02
64	7/04/1997	4/05/1997	0.611	6	0.32
65	4/08/1997	10/08/1997	0.65	3	0.021
66	17/07/2000	13/08/2000	0.669	5	0.18
67	12/01/1998	1/02/1998	0.676	5	0.18
68	2/03/1998	8/03/1998	0.699	3	0.022
69	24/08/1998	11/10/1998	0.715	9	1.01
70	22/09/1997	28/09/1997	0.73	3	0.023
71	21/02/2000	16/04/2000	0.731	5	0.19
72	13/04/1998	7/06/1998	0.756	8	0.77
73	11/01/1999	7/02/1999	0.776	7	0.54
74	9/03/1998	15/03/1998	0.814	3	0.025
75	6/01/1997	26/01/1997	0.824	6	0.36
76	10/07/2000	23/07/2000	0.846	4	0.09
77	6/12/1999	19/12/1999	0.907	3	0.028
78	14/04/1997	8/06/1997	0.913	5	0.21
79	10/05/1999	13/06/1999	0.94	5	0.22
80	25/10/1999	21/11/1999	0.951	13	2.55
81	15/02/1999	21/02/1999	0.966	4	0.11

Cluster	Start date	End date	*P*-value	Observed	Expected
82	29/03/1999	16/05/1999	0.966	14	2.99
83	27/10/1997	9/11/1997	0.967	3	0.033
84	6/03/2000	12/03/2000	0.973	5	0.24
85	27/07/1998	2/08/1998	0.975	3	0.034
86	9/08/1999	5/09/1999	0.979	5	0.24
87	13/10/1997	26/10/1997	0.985	6	0.42
88	27/03/2000	2/04/2000	0.987	3	0.035
89	28/09/1998	25/10/1998	0.99	4	0.12
90	28/07/1997	3/08/1997	0.99	5	0.25
91	31/03/1997	4/05/1997	0.992	10	1.54
92	8/03/1999	14/03/1999	0.994	3	0.037
93	29/06/1998	19/07/1998	0.994	6	0.43
94	6/01/1997	2/02/1997	0.995	8	0.93
95	20/07/1998	9/08/1998	0.995	3	0.039
96	28/06/1999	4/07/1999	0.995	4	0.12
97	14/02/2000	19/03/2000	0.999	5	0.27
98	6/01/1997	12/01/1997	0.999	3	0.042
99	1/09/1997	14/09/1997	0.999	4	0.13
100	7/04/1997	4/05/1997	0.999	4	0.13
101	6/09/1999	12/09/1999	0.999	6	0.47

Giardiasis clusters identified in 2001-2004

Cluster	Start date	End date	*P*-value	Observed	Expected
1	17/08/2002	6/09/2002	1.57E-08	11	0.3
2	1/12/2001	14/12/2001	1.45E-06	11	0.45
3	6/07/2002	26/07/2002	6.69E-06	10	0.38
4	9/08/2003	15/08/2003	1.23E-05	6	0.051
5	13/10/2001	7/12/2001	9.64E-05	13	1.06
6	21/09/2002	27/09/2002	0.000162	4	0.0096
7	3/01/2004	9/01/2004	0.000454	5	0.04
8	12/05/2001	1/06/2001	0.000463	8	0.28
9	13/03/2004	19/03/2004	0.000522	5	0.042
10	25/10/2003	7/11/2003	0.00123	5	0.049
11	6/11/2004	12/11/2004	0.00282	5	0.058
12	2/08/2003	19/09/2003	0.00449	19	3.44
13	21/07/2001	31/08/2001	0.00461	14	1.75
14	27/03/2004	2/04/2004	0.00666	4	0.024
15	6/03/2004	30/04/2004	0.00676	23	5.17
16	16/02/2002	22/02/2002	0.022	4	0.031
17	14/12/2002	20/12/2002	0.024	4	0.032
18	16/03/2002	29/03/2002	0.025	5	0.087
19	4/12/2004	17/12/2004	0.037	5	0.096
20	5/05/2001	8/06/2001	0.038	7	0.33
21	20/04/2002	10/05/2002	0.052	12	1.49
22	15/06/2002	21/06/2002	0.079	4	0.042
23	6/12/2003	12/12/2003	0.082	4	0.043
24	29/09/2001	5/10/2001	0.095	4	0.044
25	4/08/2001	10/08/2001	0.102	4	0.045
26	31/07/2004	6/08/2004	0.124	4	0.048
27	10/03/2001	16/03/2001	0.129	3	0.012
28	16/06/2001	6/07/2001	0.136	6	0.24
29	23/02/2002	1/03/2002	0.14	5	0.13
30	3/04/2004	23/04/2004	0.184	5	0.13
31	22/11/2003	28/11/2003	0.184	4	0.055
32	9/06/2001	22/06/2001	0.198	5	0.14
33	27/03/2004	30/04/2004	0.219	6	0.26
34	27/03/2004	16/04/2004	0.302	5	0.15
35	29/11/2003	12/12/2003	0.303	6	0.28
36	9/03/2002	29/03/2002	0.34	4	0.065
37	28/09/2002	18/10/2002	0.36	4	0.067
38	14/04/2001	8/06/2001	0.382	21	5.6
39	12/07/2003	1/08/2003	0.407	5	0.16
40	12/06/2004	2/07/2004	0.437	6	0.3
41	4/08/2001	10/08/2001	0.473	4	0.073

Cluster	Start date	End date	*P*-value	Observed	Expected
42	25/05/2002	12/07/2002	0.521	11	1.58
43	22/05/2004	28/05/2004	0.597	4	0.079
44	20/01/2001	2/02/2001	0.61	3	0.022
45	9/11/2002	22/11/2002	0.658	3	0.023
46	24/08/2002	20/09/2002	0.693	5	0.19
47	10/02/2001	6/04/2001	0.702	12	2
48	4/09/2004	1/10/2004	0.746	5	0.2
49	23/10/2004	10/12/2004	0.76	10	1.35
50	3/05/2003	16/05/2003	0.763	4	0.088
51	14/08/2004	27/08/2004	0.775	3	0.026
52	30/11/2002	20/12/2002	0.79	5	0.2
53	18/08/2001	31/08/2001	0.812	9	1.08
54	19/06/2004	13/08/2004	0.819	7	0.57
55	24/05/2003	30/05/2003	0.86	4	0.095
56	4/05/2002	21/06/2002	0.892	7	0.59
57	24/07/2004	30/07/2004	0.892	3	0.029
58	20/11/2004	26/11/2004	0.905	4	0.099
59	15/12/2001	28/12/2001	0.919	3	0.03
60	29/03/2003	4/04/2003	0.928	3	0.03
61	1/12/2001	7/12/2001	0.939	3	0.031
62	17/04/2004	23/04/2004	0.941	3	0.031
63	18/09/2004	1/10/2004	0.952	3	0.032
64	9/08/2003	29/08/2003	0.955	4	0.11
65	14/02/2004	5/03/2004	0.96	5	0.23
66	27/11/2004	3/12/2004	0.962	3	0.033
67	31/05/2003	6/06/2003	0.963	3	0.033
68	9/08/2003	12/09/2003	0.971	4	0.11
69	2/03/2002	22/03/2002	0.981	6	0.42
70	28/12/2002	3/01/2003	0.986	2	0.0043
71	2/11/2002	8/11/2002	0.986	3	0.037
72	27/12/2003	2/01/2004	0.986	3	0.037
73	12/10/2002	18/10/2002	0.988	3	0.037
74	16/02/2002	1/03/2002	0.99	3	0.038
75	6/01/2001	26/01/2001	0.993	4	0.12
76	24/01/2004	6/02/2004	0.993	5	0.26
77	10/08/2002	4/10/2002	0.994	6	0.44
78	19/05/2001	15/06/2001	0.994	5	0.26
79	6/01/2001	19/01/2001	0.994	3	0.04
80	21/07/2001	3/08/2001	0.995	6	0.46
81	1/02/2003	14/03/2003	0.996	4	0.13
82	1/09/2001	14/09/2001	0.996	4	0.13
83	27/04/2002	10/05/2002	0.998	3	0.044
84	11/12/2004	17/12/2004	0.999	3	0.046

Giardiasis clusters identified in 2005-2008

Cluster	Start date	End date	*P*-value	Observed	Expected
1	19/04/2007	13/06/2007	1E-17	40	3.25
2	3/07/2008	9/07/2008	4.16E-13	12	0.18
3	1/05/2008	11/06/2008	9.98E-13	26	2.49
4	7/08/2008	13/08/2008	1.18E-10	16	0.79
5	27/11/2008	10/12/2008	1.97E-10	12	0.3
6	10/07/2008	20/08/2008	2.9E-10	32	5.05
7	22/05/2008	28/05/2008	1.13E-09	10	0.17
8	18/10/2007	31/10/2007	5.37E-09	8	0.075
9	26/06/2008	9/07/2008	9.61E-09	10	0.21
10	14/08/2008	20/08/2008	5.51E-07	10	0.31
11	18/09/2008	24/09/2008	5.84E-07	18	1.82
12	22/05/2008	25/06/2008	8.04E-07	30	5.88
13	9/10/2008	15/10/2008	1.45E-06	10	0.34
14	15/05/2008	21/05/2008	5.42E-06	6	0.048
15	22/05/2008	28/05/2008	5.92E-06	10	0.39
16	18/09/2008	8/10/2008	9.74E-06	10	0.41
17	30/10/2008	19/11/2008	9.95E-06	10	0.41
18	4/08/2005	24/08/2005	0.00001	9	0.29
19	1/03/2007	4/04/2007	0.00001	11	0.57
20	10/04/2008	16/04/2008	0.00001	8	0.19
21	20/03/2008	9/04/2008	0.00002	20	2.86
22	28/02/2008	16/04/2008	0.00002	22	3.55
23	8/05/2008	21/05/2008	0.00003	8	0.2
24	20/11/2008	3/12/2008	0.00003	8	0.21
25	21/02/2008	26/03/2008	0.00005	52	18.12
26	3/07/2008	16/07/2008	0.00005	10	0.47
27	5/06/2008	11/06/2008	0.00009	6	0.074
28	7/08/2008	3/09/2008	0.00009	14	1.32
29	12/06/2008	2/07/2008	0.00018	10	0.54
30	21/08/2008	3/09/2008	0.000455	8	0.29
31	3/02/2005	2/03/2005	0.000653	7	0.19
32	11/09/2008	24/09/2008	0.000842	6	0.11
33	4/12/2008	10/12/2008	0.000881	8	0.31
34	20/03/2008	14/05/2008	0.002	18	2.92
35	4/09/2008	10/09/2008	0.002	6	0.12
36	4/10/2007	17/10/2007	0.002	5	0.059
37	6/11/2008	17/12/2008	0.003	18	3.01
38	30/08/2007	10/10/2007	0.003	9	0.52
39	1/12/2005	14/12/2005	0.003	6	0.13
40	20/03/2008	16/04/2008	0.004	14	1.74
41	6/07/2006	30/08/2006	0.004	10	0.73

Cluster	Start date	End date	*P*-value	Observed	Expected
42	11/12/2008	31/12/2008	0.007	14	1.83
43	19/06/2008	2/07/2008	0.008	8	0.41
44	14/02/2008	5/03/2008	0.009	8	0.41
45	27/07/2006	2/08/2006	0.009	4	0.026
46	3/03/2005	30/03/2005	0.011	7	0.27
47	23/08/2007	5/09/2007	0.010	5	0.079
48	22/03/2007	18/04/2007	0.010	8	0.43
49	25/12/2008	31/12/2008	0.010	4	0.029
50	3/07/2008	9/07/2008	0.012	6	0.16
51	31/08/2006	6/09/2006	0.016	5	0.085
52	24/04/2008	21/05/2008	0.016	8	0.45
53	10/04/2008	21/05/2008	0.019	10	0.87
54	10/03/2005	27/04/2005	0.020	8	0.47
55	29/05/2008	11/06/2008	0.024	6	0.18
56	22/09/2005	5/10/2005	0.024	4	0.034
57	20/11/2008	3/12/2008	0.024	6	0.19
58	17/01/2008	30/01/2008	0.027	6	0.19
59	3/01/2008	9/01/2008	0.029	4	0.036
60	7/08/2008	17/09/2008	0.030	10	0.91
61	24/01/2008	13/02/2008	0.030	6	0.19
62	13/12/2007	9/01/2008	0.053	6	0.2
63	29/05/2008	4/06/2008	0.054	4	0.04
64	24/07/2008	20/08/2008	0.055	6	0.21
65	20/03/2008	26/03/2008	0.059	4	0.041
66	16/06/2005	13/07/2005	0.059	6	0.21
67	27/12/2007	2/01/2008	0.060	3	0.0094
68	30/10/2008	26/11/2008	0.067	6	0.21
69	27/11/2008	17/12/2008	0.093	8	0.55
70	29/06/2006	5/07/2006	0.121	3	0.012
71	5/01/2006	8/02/2006	0.148	7	0.4
72	16/03/2006	19/04/2006	0.165	5	0.13
73	27/03/2008	16/04/2008	0.234	6	0.26
74	6/03/2008	9/04/2008	0.234	10	1.12
75	8/05/2008	21/05/2008	0.306	6	0.28
76	1/02/2007	28/03/2007	0.318	7	0.45
77	24/07/2008	30/07/2008	0.332	4	0.064
78	14/07/2005	27/07/2005	0.380	3	0.018
79	18/09/2008	15/10/2008	0.392	8	0.68
80	2/08/2007	19/09/2007	0.422	14	2.58
81	6/12/2007	16/01/2008	0.445	7	0.48
82	20/03/2008	26/03/2008	0.462	4	0.072
83	27/07/2006	9/08/2006	0.482	4	0.073
84	11/12/2008	17/12/2008	0.486	4	0.073

Cluster	Start date	End date	*P*-value	Observed	Expected
85	2/10/2008	15/10/2008	0.490	6	0.31
86	12/06/2008	18/06/2008	0.512	4	0.075
87	24/11/2005	30/11/2005	0.523	3	0.021
88	14/04/2005	18/05/2005	0.621	4	0.08
89	24/04/2008	30/04/2008	0.659	4	0.082
90	1/05/2008	7/05/2008	0.701	4	0.085
91	27/03/2008	2/04/2008	0.794	4	0.091
92	10/07/2008	23/07/2008	0.872	6	0.38
93	16/10/2008	12/11/2008	0.890	4	0.098
94	10/01/2008	30/01/2008	0.890	4	0.098
95	4/12/2008	17/12/2008	0.919	4	0.1
96	17/07/2008	30/07/2008	0.942	8	0.86
97	29/06/2006	2/08/2006	0.972	5	0.24
98	23/03/2006	12/04/2006	0.983	3	0.036
99	1/11/2007	14/11/2007	0.986	3	0.036
100	6/12/2007	30/01/2008	0.999	13	2.77

Appendix 3 Cryptosporidiosis space-time clusters identified by SaTScan

Cryptosporidiosis clusters identified in 1997-2000

Cluster	Start date	End date	*P*-value	Observed	Expected
1	16/03/1998	10/05/1998	1.00E-17	136	28.79
2	15/03/1999	25/04/1999	1.00E-17	65	6
3	23/10/2000	29/10/2000	1.00E-17	23	0.68
4	10/05/1999	16/05/1999	3.04E-14	18	0.79
5	16/08/1999	26/09/1999	2.23E-09	41	9.42
6	11/01/1999	7/03/1999	1.53E-08	27	4.27
7	19/10/1998	15/11/1998	1.25E-07	24	3.6
8	16/02/1998	29/03/1998	1.01E-06	17	1.76
9	11/05/1998	5/07/1998	6.59E-06	14	1.2
10	31/08/1998	18/10/1998	1.44E-05	36	9.75
11	7/06/1999	13/06/1999	3.05E-05	4	0.009
12	25/10/1999	31/10/1999	3.69E-05	5	0.034
13	16/06/1997	29/06/1997	0.000146	4	0.013
14	27/11/2000	10/12/2000	0.000162	9	0.44
15	27/09/1999	24/10/1999	0.000391	31	8.42
16	29/09/1997	19/10/1997	0.00162	14	1.79
17	23/11/1998	20/12/1998	0.00675	11	1.12
18	18/10/1999	24/10/1999	0.021	6	0.21
19	25/09/2000	22/10/2000	0.034	9	0.78
20	8/11/1999	19/12/1999	0.039	10	1.04
21	24/11/1997	30/11/1997	0.186	3	0.019
22	25/05/1998	7/06/1998	0.26	4	0.078
23	3/08/1998	23/08/1998	0.331	3	0.023
24	30/03/1998	26/04/1998	0.664	10	1.46
25	27/11/2000	17/12/2000	0.92	4	0.13
26	13/09/1999	17/10/1999	0.998	11	2.22
27	25/08/1997	14/09/1997	0.998	4	0.17

Cryptosporidiosis clusters identified in 2001-2004

Cluster	Start date	End date	*P*-value	Observed	Expected
1	10/03/2001	4/05/2001	1.00E-17	91	22.38
2	17/03/2001	27/04/2001	7.25E-13	44	8.43
3	8/02/2003	4/04/2003	4.58E-12	50	11.38
4	6/10/2001	30/11/2001	0.00228	27	6.91
5	27/10/2001	9/11/2001	0.00621	7	0.28
6	4/08/2001	28/09/2001	0.012	37	12.73
7	7/09/2002	11/10/2002	0.012	20	4.25
8	26/04/2003	2/05/2003	0.047	4	0.045
9	14/02/2004	20/02/2004	0.136	3	0.016
10	27/10/2001	30/11/2001	0.176	8	0.66
11	4/10/2003	28/11/2003	0.325	18	4.35
12	11/05/2002	5/07/2002	0.355	17	3.93
13	17/02/2001	23/02/2001	0.505	4	0.087
14	25/09/2004	19/11/2004	0.532	22	6.52
15	23/08/2003	17/10/2003	0.706	19	5.21
16	6/04/2002	24/05/2002	0.986	4	0.14
17	16/10/2004	22/10/2004	0.996	4	0.14
18	30/11/2002	27/12/2002	0.998	3	0.05
19	20/04/2002	17/05/2002	0.998	5	0.3

Cryptosporidiosis clusters identified in 2005-2008

Cluster	Start date	End date	*P*-value	Observed	Expected
1	8/06/2006	14/06/2006	1.00E-17	24	1.24
2	15/02/2007	4/04/2007	1.01E-06	24	3.73
3	21/08/2008	17/09/2008	4.86E-05	26	5.3
4	16/06/2005	10/08/2005	0.000524	9	0.45
5	10/03/2005	6/04/2005	0.00243	12	1.19
6	1/03/2007	4/04/2007	0.00352	8	0.39
7	16/11/2006	10/01/2007	0.013	20	4.1
8	17/04/2008	11/06/2008	0.013	16	2.62
9	16/10/2008	3/12/2008	0.014	14	2
10	10/02/2005	6/04/2005	0.026	11	1.19
11	28/02/2008	16/04/2008	0.027	7	0.33
12	3/04/2008	28/05/2008	0.032	8	0.51
13	28/02/2008	19/03/2008	0.033	4	0.04
14	15/11/2007	5/12/2007	0.041	6	0.21
15	21/09/2006	27/09/2006	0.055	4	0.047
16	16/08/2007	22/08/2007	0.078	5	0.13
17	21/09/2006	1/11/2006	0.13	16	3.2
18	13/11/2008	19/11/2008	0.191	3	0.017
19	9/08/2007	26/09/2007	0.296	14	2.63
20	18/10/2007	21/11/2007	0.311	11	1.57
21	19/04/2007	6/06/2007	0.552	23	7.06
22	25/09/2008	1/10/2008	0.565	5	0.2
23	17/03/2005	23/03/2005	0.758	5	0.23
24	13/01/2005	19/01/2005	0.808	2	0.0037
25	3/08/2006	20/09/2006	0.855	13	2.63
26	13/09/2007	19/09/2007	0.912	3	0.037
27	2/10/2008	19/11/2008	0.954	10	1.59
28	6/10/2005	19/10/2005	0.981	8	0.98
29	9/10/2008	5/11/2008	0.988	9	1.31
30	5/10/2006	11/10/2006	0.994	3	0.047

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