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Spatial epidemiological approaches to monitor and measure the risk of human leptospirosis

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Abstract

Leptospirosis, a life-threatening yet neglected disease caused by Gram negative spirochete *Leptospira*, is a zoonotic disease of global public health importance. In China, at least 2.5 million cases have been reported since the 1950s. Although there has been a decline in incidence since the 2000s, leptospirosis remains a major public health issue. The incidence of leptospirosis has remained at a low level in the past few years; this provides opportunities to eliminate the transmission. However, effective control and elimination strategies in China are hindered by considerable knowledge gaps regarding the epidemiology, burden, and the geographical distribution of leptospirosis in the country. There is a need to develop spatial explicit tools to help analyse the spatiotemporal heterogeneity of leptospirosis incidence to provide a necessary evidence base to better inform planning and implementation of targeted leptospirosis surveillance and control strategies.

The overall objectives of the program of research are to (1) review and critically evaluate the spatial analytical tools used in leptospirosis studies (Chapter 4); (2) quantify and map the spatial trends of the burden of leptospirosis in China (Chapter 5); (3) explore the geographical pattern and hotspots of leptospirosis incidence, and its socioecological characteristics (Chapter 6); (4) quantify the role of environmental and socioeconomic factors on the spatial variation of leptospirosis incidence and to produce spatially-explicit predictive maps of incidence of leptospirosis (Chapter 7); and 5) assess the association of weather, environmental indicators and leptospirosis incidence to develop localised temporal prediction models (Chapter 8).

A total of 115 peer-reviewed published articles were reviewed and critically evaluated; gaps in knowledge and future directions of the use of spatial techniques in the field of human and animal leptospirosis were discussed (Chapter 4). In Chapter 5, I analysed 8158 notified human leptospirosis cases reported during 2005–2016 to estimate geographical variation in the leptospirosis burden. I found that approximately 10,313 disability-adjusted life-years (DALY) were lost due to *Leptospira* infection during 2005–2015. Those most affected by leptospirosis were males, young populations, and farmers. Of the total DALYs, 30% was from premature death among those aged under 20 years. The spatial analyses in Chapter 6 revealed that the high-risk counties for leptospirosis were clustered and were mainly in the southwest and southern region of China along the Yangtze River and Pearl River. High-risk counties were significantly different in terms of

their demographical, environmental, and socioeconomic profiles compared with low-risk counties. The study in Chapter 7 further revealed that the environmental and socioeconomic effects significantly differed between the Upper Yangtze River Basin and the Pearl River Basin, confirming that leptospirosis transmission is highly geographic specific. After accounts for environmental and socioeconomic factors, the Bayesian spatial conditional autoregressive models indicated that the highest leptospirosis incidence was identified throughout the western and southern part of the Upper Yangtze River Basin and in the midstream and lower reaches of the Pearl River Basin (Chapter 7). For timely intervention, the evidence from the study of high-risk counties—Yilong County and Mengla County (Chapter 8)—demonstrated that variability of rainfall and satellite-based physical environmental parameters, including vegetation (indicated by normalized difference vegetation) and flooding (indicated by modified normalized difference water index), can be used as predictors of leptospirosis outbreaks. However, the response and lag effects of such indicators are significantly varied between locations.

This thesis demonstrates that spatial epidemiological tools have benefited the understanding of the epidemiology of leptospirosis in China and they can be further used to support intervention programs to eliminate transmission of leptospirosis in the residual hotspots. This thesis lays a foundation for further development of an integrated spatial-temporal decision support system for leptospirosis control to support health authorities in planning and implementing effective and timely spatially targeted public health interventions in the identified residual high-risk regions.

Declaration by author

This thesis *is composed of my original work, and contains* no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly authored works that I have included in my thesis.

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Publications included in this thesis

The thesis comprises of five research chapters which include four published papers and one paper submitted for publication.

1. **Dhewantara, P.W.,** Lau, C.L., Allan, K.J., Hu, W., Zhang W., Mamun, A.A. and Soares Magalhães, R.J. 2019. Spatial epidemiological approaches to inform leptospirosis surveillance and control: A systematic review and critical appraisal of methods. *Zoonoses and Public Health*. 66, 185– 206. https://doi.org/10.1111/zph.12549. Incorporated as **Chapter 4**.

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1. **Dhewantara, P.W**., Ipa, M. and Widawati, M. 2019. Individual and contextual factors predicting self-reported malaria among adults in eastern Indonesia: findings from Indonesian community-based survey. *Malaria Journal*. 18(1), 118. https://doi.org/10.1186/s12936-019-2758-2
2. Astuti, E.P., **Dhewantara, P.W.,** Prasetyowati, H., Ipa, M., Herawati, C. and Hendrayana, K. 2019. Paediatric dengue infection in Cirebon, Indonesia: a temporal and spatial analysis of notified dengue incidence to inform surveillance. *Parasites & Vectors*. 12(1), 186. https://doi.org/10.1186/s13071-019-3446-3
3. Xu, Z., Bambrick, H., Yakob, L., Devine, G., Frentiu, F.D., Marina, R., **Dhewantara, P.W**., Nusa, R., Sasmono, R.T. and Hu, W. 2019. Using dengue epidemics and local weather in Bali, Indonesia to predict imported dengue in Australia. *Environmental Research*. 175:213-220. https://doi.org/10.1016/j.envres.2019.05.021
4. **Dhewantara, P.W**., Marina, R., Puspita, T., Ariati, Y., Purwanto, E., Hananto, M., Hu, W. and Soares Magalhães, R.J. 2019. Spatial and temporal variation of dengue incidence in the island of Bali, Indonesia: an ecological study. *Travel Medicine and Infectious Disease*. 101437. https://doi.org/10.1016/j.tmaid.2019.06.008

Conference abstracts

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2. **Dhewantara, P.W.**, Mamun, A.A., Zhang, W.Y., Guo, D., Hu, W., Costa, F., Ko, A.I. and Soares Magalhães, R.J. 2017. The changing epidemiology and burden of human leptospirosis in China. The 10th International Leptospirosis Society Conference 2017, Palmerston North, New Zealand, November 27th - December 1st, 2017 (Oral presentation).

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4. **Dhewantara, P.W.,** Hu, W., Zhang, W., Yin, W.W., Ding, F., Mamun, A.A. and Soares Magalhães, R.J. 2019. Leptospirosis, climate and satellite-based environmental factors: a temporal modelling. 2019 International Society for Disease Surveillance Annual Conference, San Diego, California, United States of America, January 29th – February 1st, 2019. Available online at https://ojphi.org/ojs/index.php/ojphi/article/view/9879/7986
5. **Dhewantara, P.W.,** Mamun, A.A., Zhang, W.Y., Guo, D., Hu, W., Yin, W.W., Ding, F. and Soares Magalhães, R.J. Geographical distribution of human leptospirosis incidence in the Upper Yangtze and Pearl River Basin, China: tools to support surveillance and focused intervention. The 68th American Society of Tropical Medicine and Hygiene (ASTMH) Annual Meeting in National Harbor, Maryland, United States of America, November 20-24, 2019 (Poster presentation). Available online at https://www.abstractsonline.com/pp8/#!/7935/presentation/4383

Contributions by others to the thesis

None

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List of Abbreviations

AIC: Akaike’s information criterion
BIC: Bayesian information criterion
CAAT: cross agglutination absorption test
CAR: conditional autoregressive
CCF: cross-correlation function
CDC: Center for Disease Control and Prevention
CFR: case fatality-rate
CI: confidence interval
CIDARS: China Infectious Disease Automated-alert and Response System
CISDCP: China Information System for Disease Control and Prevention
CrI: credible interval
CSF: cerebrospinal fluid
DALY: disability-adjusted life-year
DEM: digital elevation model
DIC: deviance information criteria
DW: disability weight
ELISA: Enzyme-linked immunosorbent assay
ENSO: El Niño-Southern Oscillation
EWS: early warning system
GDP: gross domestic product
GIS: geographical information system
GLM: generalized linear model
GLEAN: Global Leptospirosis Environmental Action Network
GR: geographical reconnaissance
GRUMP: Global rural-urban mapping project
IDO: indolamine 2,3-dioxygenase
IgM: Immunoglobulin M
IHA: indirect hemagglutination assay
IQR: interquartile range
IR: incidence rate
IRR; incidence rate ratio
LERG: Leptospirosis Research Group

LFA: lateral flow assay

LISA: local indicators of spatial association

LST: land surface temperature

MAT: microscopic agglutination test

MNDWI: modified normalized difference water index

MODIS: moderate-resolution imaging spectroradiometer

MR: mortality rate

NDVI: Normalized Difference Vegetation Index

NDWI: Normalized Difference Water Index

NHFPC: National Health and Family Planning Commission

NIDRIS: Notifiable Infectious Diseases Reporting Information System

PCR: polymerase chain reaction

PPE: personel protective equipment

PRB: Pearl River Basin

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RESDC: Resources and Environmental Sciences, Chinese Academy of Sciences

RFLP: restriction fragment length polymorphism

RH: relative humidity

RS: remote sensing

SAF: seasonal factor

SAR: simultaneous autoregression

SARS: severe acute respiratory syndrome

SDSS: spatial decision support system

SMR: standardized morbidity ratio

STL: seasonal-trend decomposition analysis based on Loess

STDSS: spatial temporal decision support system

USGS: United States Geological Survey

UYRB: Upper Yangtze River Basin

VIF: variance inflation factor

WASH: water, sanitation and hygiene

WHO: World Health Organization

YLD: years-lived with disability

YLL: years of life-lost

ZIP: zero-inflated Poisson

Chapter 1 Introduction

1.1 Background

Leptospirosis is a widespread emerging zoonosis caused by spirochetes belonging to the genus *Leptospira* (Faine et al., 1999; Bharti et al., 2003; Pappas et al., 2008). Each year, there have been at least one million human cases of leptospirosis infection resulting in approximately 58,900 deaths worldwide. Recent disease burden estimates indicate that approximately 2.9 million disability-adjusted life-years (DALYs) were lost per year with the highest burden found in low-income developing countries, especially affecting communities in tropical and subtropical regions (Costa et al., 2015; Torgerson et al., 2015). However, there are concerns that current burden estimates are possibly an underestimate due to diagnostic and surveillance constraints and lack of disease awareness (WHO, 2003; Bharti et al., 2003). In 2009 the World Health Organization formed the Leptospirosis Burden Epidemiology Reference Group (LERG) with the aim of carrying out more research and formulating policies to reduce the burden of leptospirosis (WHO, 2010).

Leptospiral infection in human occurs due to direct exposure of injured skin or mucous membranes to infected animal tissues or urine, or by indirect contact with mud or water containing pathogenic *Leptospira* spp. (Levett, 2001). There are 13 pathogenic species, eleven “intermediate” species which occasionally cause mild clinical manifestations, and eleven saprophytes which are free-living environmental micro-organisms not known to cause disease (Xu et al., 2016b; Casanovas-Massana et al., 2020). More than 250 pathogenic serovars and 40 genomospecies have been identified worldwide (Haake and Levett, 2015; Vincent et al., 2019; Casanovas-Massana et al., 2020). Various carrier animals, including companion animals, livestock and wild mammals, have been identified as potential reservoirs of infection. In rural settings, agricultural animals, such as pigs, cattle, sheep and goats, are known to carry *Leptospira* serovars but rodents are also known to be an important carrier (Adler and de la Pena Moctezuma, 2010). In urban areas, rodents are the main reservoir for carrying and shedding pathogenic *Leptospira* into the environment (Vinetz et al., 1996; de Faria et al., 2008; Santos et al., 2017; Blasdell et al., 2019; Briskin et al., 2019). Different epidemiological settings might lead to variation on the mode of transmission, distribution, and the clinical expression and severity of illness (Ko et al., 1999; Ashford et al., 2000; Bharadwaj et al., 2002; Cosson et al., 2014).

Traditionally, leptospirosis has been an occupational-hazard commonly affecting farmers, abattoir workers, veterinarians, miners, and soldiers (Terry et al., 2000; Lacerda et al., 2008; Parveen et al., 2016; Burns et al., 2016). Nowadays, leptospirosis is commonly reported after flooding due to severe weather events; it especially affects poor urban communities in tropical and subtropical regions where access to basic services, such as safe water and sanitation, adequate drainage systems, and housing and waste management, is deficient (Ko et al., 1999; Barcellos and Sabroza, 2001; Bharadwaj et al., 2002). Recently, leptospirosis has generated travel-related concerns as a considerable number of cases have been reported among travellers returning from endemic countries after engaging in outdoor recreational activities (e.g., triathlon and water-sports) (Sejvar et al., 2003, Ricaldi and Vinetz, 2006; Brockmann et al., 2010, de Vries et al., 2018; Schönfeld et al., 2019).

Leptospirosis transmission involves the interaction of climate, environmental, and sociodemographical factors which makes disease-control interventions challenging. Leptospirosis incidence is known to follow a seasonal pattern and it is closely linked with variation in weather conditions (Desvars et al., 2011; Coelho and Massad, 2012; Chadsuthi et al., 2012; Weinberger et al., 2014; Joshi et al., 2017; Matsushita et al., 2018; Deshmukh et al., 2019). Climate change is presumed to intensify severe weather events and flooding which could escalate leptospirosis outbreaks, especially in tropical and subtropical countries (Lau et al., 2010). Moreover, uncontrolled urbanisation, resulting from population growth and economic development, has boosted significant environmental changes and widened the economic gap, making leptospirosis control more challenging. It is expected that by 2050, 68% of the global population will reside in urban areas; moreover, the urban population living in slums is estimated to increase, especially in developing countries (UN-DESA, 2019; UN-HABITAT, 2016). Together extreme weather events, population growth, and urbanisation under low level sanitation conditions are thought to be critical drivers for the (re)emergence of leptospirosis and the shift in its geographical and temporal distribution (Lau et al., 2010). The dynamic relationships between leptospirosis incidence and weather, anthropogenic environments and animal husbandry systems (including rodent ecology and control) remain unclear. Such lack of evidence limits the effectiveness of public health interventions for leptospirosis control and elimination.

The effectiveness of leptospirosis prevention strategies depends on understanding its distribution and local risk factors (Haake and Levett, 2015). For instance, in rural areas where *Leptospira* infection is mainly associated with agricultural practices, in addition to promoting protective measures among farmers, improving farm biosecurity measures and livestock vaccination are the most important components of an integrated strategy (i.e. a One Health approach) for reducing the risk of human leptospirosis (Ellis, 2015; Pimenta et al., 2019). In contrast, in urban settings, especially in flood-prone areas and urban slums, strategies should focus on improving local community environmental and socioeconomic conditions to reduce rodent infestations and leptospiral exposure by providing drainage systems, housing, and access to safe water hygiene and sanitation (WASH) (Lau and Jagals, 2012; Hagan et al., 2016). Hence, better understanding of the local epidemiology and transmission mechanisms will allow policy makers to define appropriate preventive and control programs that are tailored to the local epidemiological characteristics.

In many developing countries, surveillance systems are often inadequate in detecting and reporting leptospirosis cases, and this hampers leptospirosis control (Sejvar et al., 2005; Costa et al., 2012), especially in remote and resource-limited areas. Developing countries greatly depend on passive case finding rather than conducting active surveillance or epidemiological surveys as it is much more cost-efficient. However, such passive surveillance notification data could still provide important information which can improve our understanding about the epidemiology and disease distribution. For example, routine surveillance data gathered using geographic information system (GIS) technology could be utilised to generate operational maps and spatiotemporal forecasting models to guide decision-makers in planning and implementing interventions locally. Despite the public health importance of leptospirosis, so far, such approaches are not embedded in existing surveillance systems (WHO, 2011; Goarant, 2016), making resource allocation for leptospirosis diagnosis and disease control inefficient. Developing a simple and low-cost prediction tool for helping decision-makers and local health workers is therefore a priority (WHO, 2011).

Motivated by the complexity of leptospirosis epidemiology, gaps in knowledge, and challenges to controlling the disease, the Global Leptospirosis Environmental Action Network (GLEAN) was launched in 2010 with the aim of strengthening multi-disciplinary and inter-sectoral collaboration to establish contemporary, cost-effective, feasible, and sustainable solutions to control leptospirosis—especially in high-risk populations (Durski et

al., 2014). To pursue its mission, a plan of action was designed under four key elements, namely predict, prevent, detect, and intervene. Understanding the key drivers of transmission and developing predictive models, risk maps, and outbreak detection tools are some of the actions that should be followed up by the GLEAN members. The development of such tools to support surveillance and control of leptospirosis will improve local and regional preparedness for a leptospirosis outbreak (WHO, 2011).

Recent progress in statistical analysis, GIS and remote-sensing (RS) processing provide opportunities to produce reliable tools that could be used to support and strengthen health systems (Tatem, 2014; Lindström et al., 2015). A variety of approaches have been used to support health officials in designing and applying disease control strategies. Of which, spatial epidemiological tools, such as mapping and spatial-temporal risk modelling, are now widely recognised as one of the effective tools that allow for the identification of high-risk areas and the prediction of risks. This approach can provide a scientific basis or evidence that can effectively guide public health agencies in distributing and improving resources for disease control and prevention at specific areas (Rezaeian et al., 2007). Spatial epidemiology is a specialist branch of epidemiology that aims understand geographical disease patterns and factors that influence the distribution of disease—including demographic, environmental, behavioural, socioeconomic, genetic, and infectious risk factors (Elliott and Wartenberg, 2004). This approach has been widely used to understand the epidemiology of diseases, including vector-borne diseases (Bi et al., 2013; Houngbedji et al., 2016; Eisen and Lozano-Fuentes, 2009; Fan et al., 2014; Dhewantara et al., 2015), waterborne diseases—such as schistosomiasis (Soares Magalhães and Clements, 2011; Hodges et al., 2012; Soares Magalhães et al., 2014; Lai et al., 2015; Wang et al., 2016), cholera (Gatto et al., 2012), cryptosporidiasis and giardiasis (Burnet et al., 2014)—and rodent-borne diseases, including scrub typhus (Wu et al., 2016), hemorrhagic fever with renal syndrome (Wu et al., 2011), Lassa fever (Fichet-Calvet and Rogers, 2009), and plague (Qian et al., 2014).

In China, leptospirosis is of public health importance. Because it was commonly spread at harvest time, leptospirosis was known in the ancient Chinese language as ‘rice-harvest jaundice’ and it was believed to be caused by a ghost or bad spirit (Faine, 1999). Leptospirosis was first reported in 1934 and it has been a mandatory notifiable disease since 1955. Cases of leptospirosis have been reported in more than 80% of the total provinces (34 provinces) and since 1955, there have been more than 2.5 million cases and

20,000 deaths (Zhang et al., 2012; Shi et al., 2000). *Leptospira interrogans* serovars have been responsible for most human infections in China. So far, 76 serovars belonging to 18 serogroups of pathogenic *Leptospira* have been identified from a wide range of animals in China (Hu et al., 2014; Han et al., 2018; Zhang et al., 2019; Ma et al. 2020). Among these animals, rats *Apodemus agrarius* is known as the most important *Leptospira* host among other animal reservoirs, such as pigs, cattle, and dogs (Shi et al., 2000; Zhang et al., 2012; Liu et al., 2016, Zhang et al., 2019). Different animals can harbour one specific or multiple serogroups, for instance, Icterohaemorrhagie is predominantly found in rodents, Canicola in dogs, Hardjo, Pomona, and Grippothyphosa is found in cattle, Pomona, Kennewicki, Tarrasovi, or Bratislava is found in pigs (Levett, 2001; Ellis, 2015; Zhang et al., 2019). In fact, a recent study by Zhang et al (2019) have demonstrated the genetic diversity across China, which suggested the animal reservoirs responsible for human leptospirosis in a region. The diversity and variation of *Leptospira* spp and animal hosts abundance and its relationships could be geographically varied depending on the climate and environmental conditions, which in turn may influence the variation in the relative risk of leptospirosis transmission.

The incidence of leptospirosis in China has been dramatically decreasing since the 1990s, reaching a relatively low annual incidence rate of 0.70 per 100,000 people (Zhang et al., 2012; Hu et al., 2014). Despite the reported reduction in leptospirosis incidence, local outbreaks still occur in parts of the country (Li et al., 2013; Fan et al., 2014; Wang et al., 2014; Wu et al., 2015; Xu et al., 2016a; Tang et al., 2017). This low-level leptospirosis incidence has been viewed by China's health authority as the best opportunity for eliminating leptospirosis in China. To maintain this momentum and to achieve the elimination goal, there is a need for evidence on the burden and the geographical distribution of the residual high-risk areas for leptospirosis across China and key factors associated with the transmission on a regional and local scale.

China has the third largest surface area in the world with diverse weather and landscape, the largest human population, and some of the largest livestock populations (UN-DESA, 2019). China has favorable conditions for *Leptospira* transmission both climatologically and ecologically (Zhao et al., 2016). Differences in weather and landscape ecological conditions, circulating serovars, animal hosts and human socioeconomic conditions across the country are suggested as influencing the geographical distribution of human leptospirosis incidence in China (Zhang et al., 2012). However, the distribution of residual

leptospirosis hotspots and the role of such determinants in the heterogeneity of leptospirosis risk, both at regional and local levels, remain inconclusive. Knowing the residual distribution and the heterogeneity in the epidemiology and risks would allow for better identification of intervention priorities for each area at-risk, as well as guiding health authorities in allocating the resources and determining where improved interventions should be implemented (Herbreteau et al., 2007; Hamm et al., 2015).

One approach to understanding and exploring the geographical and temporal distribution of leptospirosis, the profile of high-risk areas for leptospirosis, and the effects of environmental and socioeconomic factors in the spatial heterogeneity of leptospirosis risk is by performing an ecological study. The aim of my research is not to determine the causal relationship between socioecological factors and leptospirosis transmission. Instead, it is designed to utilise available leptospirosis notification data, available environmental and sociodemographic data, and spatial analytical approaches to generate an evidence base for informed decision-making for policy makers in planning and implementing efficient spatially targeted interventions to help control and eliminate leptospirosis transmission in China.

1.2 Hypothesis and research aim

This program of research aimed to answer the primary research question "*How did the incidence and burden of leptospirosis in China vary geographically and temporally and what environmental and socioeconomic factors have influenced the spatiotemporal distribution nationally and locally?"*

This Thesis set out to assess the general research hypothesis that the distribution of and risk factors for notified leptospirosis incidence and burden is spatially and temporally heterogeneous across China and that this phenomenon is due to the heterogeneity in local environmental and socioeconomic factors throughout China.

The overall aim of my research was to apply spatial and temporal analytical techniques to uncover the epidemiology and disease ecology of leptospirosis at the national and local level in China. These insights can assist local health authorities in the design and implementation of effective and timely leptospirosis control programs to pursue the disease-elimination goal.

1.3 Objectives

To meet the aim of this research, I defined ten specific research objectives:

a. Identify and critically evaluate the use of spatial analytical tools for leptospirosis control to develop a general framework on the application of spatial epidemiological tools for leptospirosis (Presented in Chapter 4)
b. Estimate burden of disease in terms of disability-adjusted life-years (DALY) at province-level across China (Presented in Chapter 5)
c. Map the geographical distribution of the incidence and burden in terms of DALY at a sub-national level across China (Presented Chapter 5)
d. Determine spatial and temporal patterns of incidence of leptospirosis at county-level across China (Presented in Chapter 6)
e. Identify spatial clusters (high-risk and low-risk counties as well as outliers) across China (Presented in Chapter 6)
f. Determine and compare demographical, environmental, and socioeconomic characteristics among the identified high-risk counties relative to low-risk counties for leptospirosis in China (Presented in Chapter 6);
g. Quantify the role of the climatic, physical environment and socioeconomic risk factors in the spatial heterogeneity of leptospirosis incidence in high-risk regions in China (Presented in Chapter 7)
h. Develop predictive incidence maps for leptospirosis, accounting for the environmental and socioeconomic risk factors to identify counties at highest risk of leptospirosis (Presented in Chapter 7).
i. Assess the short-term association between climate variability and remotely-sensed physical environmental factors—including precipitation, humidity, temperature, vegetation, and flooding—and leptospirosis incidence in high-risk counties to develop temporal prediction models (Presented in Chapter 8).

1.4 Significance of research

The research detailed in this thesis provides essential evidence on the recent estimates of the geographical variation in the burden of leptospirosis in terms of DALYs. It allows the identification of areas and population at the highest burden for leptospirosis in China. By using spatial analytical tools, my research extended novel evidence in that it provides fine hotspot maps and key demographical, environmental, and socioeconomic characteristics within residual hotspots. Additionally, using state-of-the-art spatial modelling techniques, I

have successfully developed the first smoothed leptospirosis incidence maps that take into account various climatic, environmental and socioeconomic factors, spatial dependency in the data, and uncertainty. These maps can help in the identification of areas where interventions and resources are most needed, and where surveillance and case management need to be improved. Finally, to deliver effective public health interventions promptly, I developed risk forecasting models to provide actionable information for prevention and preparedness for leptospirosis epidemics at a local level. The program of research presented in this thesis demonstrates the value of GIS/RS and spatial analytical tools. It lays an essential foundation for the development of a spatial decision support system (SDSS) and an early warning system to inform decision-makers in planning and implementing geographic-specific interventions programs for leptospirosis with potential application for other zoonotic diseases.

1.5 Structure of the thesis

The thesis incorporates nine chapters (Figure 1-1). In the first chapter, I provide an introductory chapter, which explains the motivation, significance and objectives of the research. It is then followed by a general literature review in Chapter 2 and the description of the general methods (Chapter 3) used in each research chapter. In Chapter 4, I present a systematic review of spatial epidemiological tools applied to leptospirosis. This is followed by research chapters which look at the small-scale historical trend in disease burden in China (Chapter 5), identifying the high-risk areas and profiling their environmental and socioeconomic conditions (Chapter 6), quantifying the role of ecological and socioeconomic factors to develop a spatially explicit predictive map for the incidence of leptospirosis in high-risk regions in China (Chapter 7). Finally, assessing the short-term association of climate variability and remote-sensed environmental indicators on the incidence of leptospirosis (Chapter 8) to lay a foundation for the early warning system. The thesis ends with a general discussion and conclusions (Chapter 9) that highlight key research findings, implications for public health intervention, general limitations, as well as the recommendation for future studies.

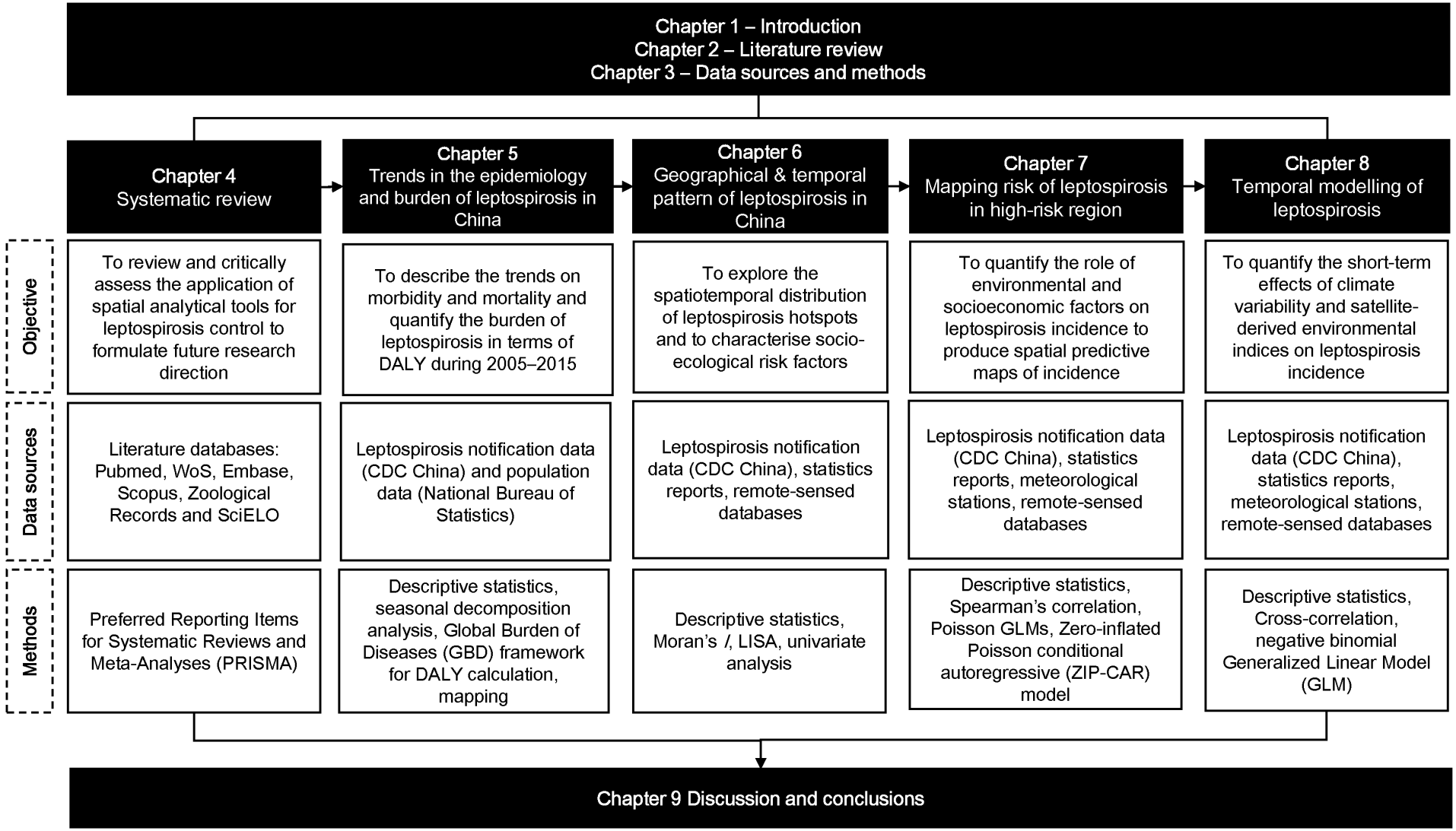

Figure 1-1 Organization of the thesis

Chapter 2 General literature review

2.1 Context

The literature review outlined in this chapter describes the brief discovery of *Leptospira* and leptospirosis, its biology and classification, transmission mechanism, factors driving the transmission of leptospirosis, morbidity and burden of leptospirosis, clinical manifestations and diagnosis, and current approaches to prevent and control the transmission. In addition, the literature review explains the significance of spatial analytical approaches to support disease control and how such approaches have been used in the previous leptospirosis studies. This literature review presents gaps in knowledge in the existing literature that provided the rationale for my program of research presented in this thesis.

2.2 History, biology and classification of *Leptospira*

2.2.1 History

The first evidence of jaundice was identified in Mesopotamia mythology, where a jaundice epidemic was described as when the river brought yellow plants (Sigerist, 1951). Yet, the specific description of the disease was recognised before Hippocrates discovered it. A hundred years later, based on the records provided by Hippocrates, Galen, and Avicenna, modern scientific communities attempted to define jaundice and the causative agent of disease clearly. In 1812, Larrey provided a clear description of the *fièvre jaune,* which became known as Weil's disease among Napoleon's armies at Heliopolis in 1800 (Faine, 1999). Before that, however, Dr. Wittman's record had also provided information about the characteristics of Weil's symptoms and climate conditions when the epidemic occurred, which he observed in the Ottoman camp during his mission with the Turkish Army and the British Militar (Wittman, 1803). During the nineteenth century, a considerable number of Weil's infections were reported over Western Europe among troops. In 1886, Adolf Weil published his historic report *Ueber eine eigentümliche, mit Milztumor, Icterus und Nephritis einhergehende akute Infektionskrankheit* (Concerning a characteristic infectious disease, accompanied bysplenomegaly, jaundice and nephritis) (Weil, 1886). The causative agent of Weil's disease was not discovered until in 1907 Stimson demonstrated the identification of *Spirochaete interrogans* in the kidney tissue of a patient who reportedly died due to yellow fever (Stimson, 1907). About three years later, during the period 1910 to 1920, German and Japanese scientists—such as Huebener, Reiter, and Inada—discovered the

cause of Weil's disease (Hubbert and Reiter, 1915, 1916; Inada et al., 1916). The role of rodents as *Leptospira* carriers and different serovars was also discovered by Inada's team (Ido et al., 1917,1918).

2.2.2 *Leptospira*: Biology and Classification

Leptospira has helically shaped with hooked ends, 0.1 µm long in diameter and 6-20 µm in length, highly motile, Gram-negative, obligate aerobic with optimum growth occuring at a temperature of 28–30°C and in the pH range 7.2–7.6 (Faine et al., 1999) (Figure 2-1). They grow in media, enriched with vitamins B2 and B12, long-chain fatty acids, and ammonium salts, where the long-chain fatty acids are used as the carbon source and are metabolised by β-oxidation (Haake, 2000). In natural conditions, it can survive in rivers, mud, swamps, and alkaline soils (Elder et al., 1986). However, acidity (pH), temperature, and the occurrence of inhibitory compounds can affect its survival rate in the environment. In favorable environmental conditions, leptospires can survive for months, even years (Chang et al., 1948; Smith and Self, 1955; Andre-Fontaine et al., 2015).

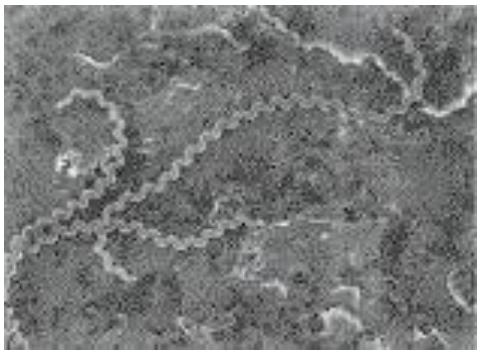

Figure 2-1 Image of *Leptospira interrogans* serovar copenhageni under scanning electron microscope. Reprinted from Bharti et al. (2003) with permission from Elsevier Ltd. ©2003

Leptospira is a genus of bacteria belonging to the family Leptospiraceae and phylum of Spirochaetes. Based on its phylogenetic, this genus is classified into three groups: saprophytic, intermediate, and pathogenic species (Picardeau et al., 2008; Ko et al., 2009; Picardeau, 2017). To date, 35 *Leptospira* species have been identified. Eleven species are considered as saprophytic—a free-living bacteria and harmless for humans, including *L. biflexa, L. brenneri, L. harrisiae, L. idonii, L. levettii, L. macculloughii, L. meyeri, L. terpstrae, L. vanthielii, L. wolbachii,* and *L. yanagawae*. Eleven species are known in the intermediate group, which means that the species intermittently cause human and animal

infection, including *L. broomii, L. fainei, L. haakeii, L. hartskeerlii, L. inadai, L. licerasiae, L. perolatii, L. neocaledonica, L. saintgironsiae, L. venezuelensis,* and *L. wolffii.* Lastly, 13 species are known to be pathogenic, including *L. adleri, L. alexanderi, L. alstonii, L. barantonii, L. borgpetersenii, L. ellisii, L. interrogans, L. kirschneri, L. kmetyi, L. mayottensis, L. noguchii, L. santarosai* and *L. weilii* (Feine et al., 1999, Petersen et al., 2001; Matthias et al., 2008; Vincent et al., 2019). Recently, a study revealed two novel species belong to the pathogenic group: *L. yasudae* sp. nov. and *L. stimsonii* sp. nov (Casanovas-Massana et al., 2020). Of which, *L. interrogans* is known to be the significant causative agent for the incidence of severe leptospirosis (Tubiana et al., 2013). This pathogenic group is classified into more than 250 serovars belonging to 24 serogroups (Cerqueira and Picardeau, 2009; Hartskeerl and Smythe, 2015).

2.3 Transmission, epidemiology and burden of Leptospirosis

2.3.1 Transmission

Leptospirosis is a worldwide emerging zoonotic disease. Transmission occurs involving the interaction between pathogenic *Leptospira*, animal hosts, and the environment (Figure 2-2). A broad range of animals have been identified that can host *Leptospira,* including domestic/companion animals (e.g., dogs, cats, horses), livestock (e.g., cattle, pigs, sheep) and wild animals (e.g., possums, bats) (Eymann et al., 2007; Tulsiani et al., 2011; Ellis, 2015; Han et al., 2018, Zhao et al., 2019). However, among these, rats and other rodents are known as the most important source for human infection. In China, *Leptospira interrogans* serovars have been responsible for most human infections and *Apodemus agrarius* is the most important animal host among other animals, such as pigs, cattle and dogs (Shi et al. 2000; Zhang et al. 2012; Liu Y. et al. 2016). So far, 76 serovars belonging to 18 serogroups of pathogenic *Leptospira* have been identified from a wide range of animals in China (Hu et al., 2014; Han et al., 2018; Zhang et al., 2019; Ma et al. 2020). Different animals can harbour one specific or multiple serogroups, for instance, Icterohaemorrhagie is predominantly found in rodents, Canicola in dogs, Hardjo, Pomona, and Grippothyphosa is found in cattle; Pomona, Kennewicki, Tarrasovi, or Bratislava is found in pigs (Levett, 2001; Ellis, 2015; Zhang et al., 2019). In rural areas, livestock animals may also act as a reservoir for *Leptospira* spp (Agampodi et al., 2011, 2015). While in urban settings, rats and other rodents have been reported as the major source for many human infections (Ko et al., 1999; Hagan et al., 2016). From the literature review, it

is evident that the mode of transmission could vary geographically as it greatly depends on the ecology, diversity of animal reservoirs, and the predominant serovars.

Infected hosts carry leptospires on their renal tubules and shed the bacteria to the environment via urine or faeces excretion. These animals become asymptomatic carriers and can shed *Leptospira*-contaminated urine into the environment over a long period. The free-living *Leptospires* enter the human body through abrated or open skin wounds and through mucous membranes, causing broad clinical signs and complications within days. The clinical presentation of the infection is discussed in the next section. Human infection could be due to incidental exposure to the contaminated soil or water, or by direct contact with urine or tissues of infected animals (Milner et al., 1980; Plank et al., 2000; McLean et al., 2014). Human-to-human transmission has been rarely reported (Levett, 2001). As water is an important medium facilitating the animal-to-human transmission, leptospirosis is, hence, considered as one of the zoonotic water-associated diseases as well (Moe, 2004).

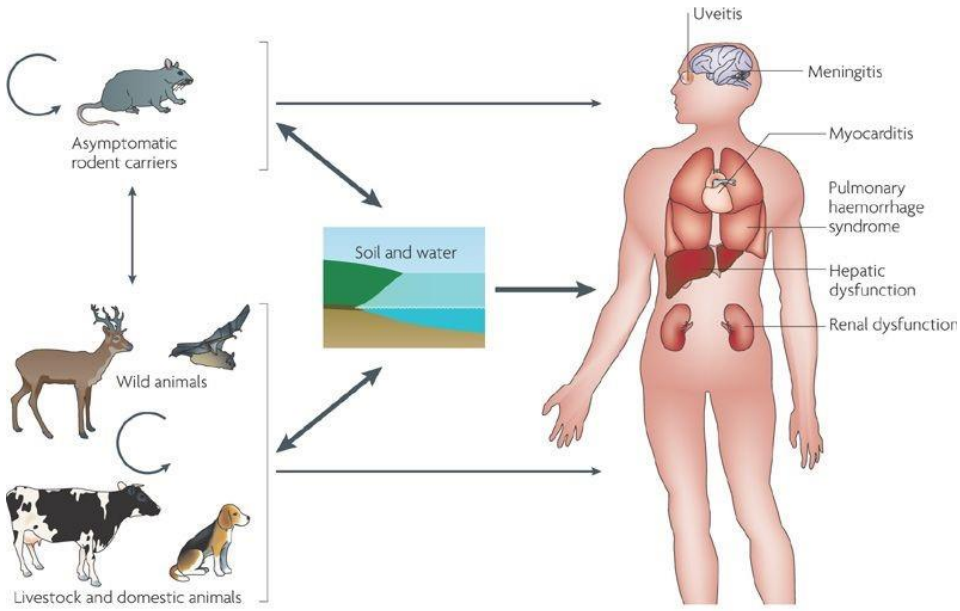

Figure 2-2 Leptospirosis transmission. Reprinted from Ko et al. (2009) with permission from Nature ©2009

2.3.2 Epidemiology

Leptospira infection is likely to affect young adults between the age of 20 and 49 years (Costa et al., 2015). However, studies have also reported that school-age children (aged

under 20 years) are at the highest risk of acquiring severe leptospirosis (Weil's disease) (Zhang et al., 2012; Cassadou et al., 2016; Hem et al., 2016; Lokida et al., 2016; Narayanan et al., 2016; Tan et al., 2016). About 80% of the total burden of leptospirosis is likely to affect males (Torgerson et al., 2015). Traditionally, leptospirosis has been associated with occupational hazards, affecting farmers (Lacerda et al., 2008; Yupiana et al., 2019; Mgode et al., 2019), soldiers (Mccrumb et al., 1957; Johnston et al., 1983; Burns et al., 2016), miners (Parveen et al., 2016), and abattoir workers (Terry et al., 2000). But, leptospirosis infection can also be acquired by people in non-specific occupational groups.

Globalisation and tourism have shifted the mode of leptospiral exposure. Leptospirosis is now also considered an important travel-related risk (Ricaldi and Vinetz, 2006; Pappas et al., 2008; Bandara et al., 2014; Brockmann et al., 2010, de Vries et al., 2018; Schönfeld et al., 2019). Leptospirosis has been linked with outdoor sport and leisure activities. In the past two decades, a considerable number of leptospirosis cases have been reported among international travellers who returned from endemic countries where they participated in eco-adventure activities, such as triathlon, canyoning, canoeing, whitewater rafting, and kayaking (Sejvar et al., 2003, Hochedez et al., 2012; Gundacker et al., 2017).

Leptospirosis is generally found in rural and urban areas that are tropical or subtropical. The epidemiology and driver of leptospirosis may be different in both settings. In rural areas, leptospirosis is often associated with small-scale subsistence agricultural activities (Bharti et al., 2003; Garcia-Ramirez et al., 2015). Farmers are, therefore, likely to have a greater risk of being exposed to the contaminated environment or infected animals (rats and livestock) during harvesting or milking. In contrast, in cities, leptospirosis is likely to occur due to incidental exposure to a contaminated environment following severe weather-related events, such as typhoons and flooding (Amilasan et al., 2012; Lin et al., 2012; Smith et al., 2013; Mendoza et al., 2013; Lin et al., 2015; Mohd Radi et al., 2018; Togami et al., 2018). Urban leptospirosis disproportionately affects impoverished urban dwellers living in flood-prone areas and in poor living conditions where essential services—such as safe drinking water, sanitation, environmental hygiene, waste management and access to health services—are lacking (Ko et al., 1999; Bacallao et al., 2014; McBride et al., 2005; Felzemburgh et al., 2014). In developing countries, urbanisation and flooding play a significant role in the (re)emergence of leptospirosis in urban areas (Lau et al., 2010).

The occurrence of leptospirosis is influenced by climate, environment, and poverty (Hotez et al., 2008, 2015; Tan et al., 2014). Studies have reported that leptospirosis incidence is

seasonal and is likely driven by climate, especially in tropical countries (Desvars et al., 2011; Coelho and Massad, 2012; Chadsuthi et al., 2012; Weinberger et al., 2014; Joshi et al., 2017; Matsushita et al., 2018; Deshmukh et al., 2019). In tropical regions, most outbreaks occur during the rainy season resulting from high exposure to the abundant contaminated environment (water or soil) due to high rodent populations. In contrast, in temperate climates, leptospirosis is more likely linked with occupational and recreational activities (e.g., contact with infected livestock, contact with contaminated water/soil) (Desai et al., 2009; Garvey et al., 2014).

The risk of leptospirosis is expected to be higher in the future. Climate change is presumed to intensify severe weather events and flooding that could escalate frequent outbreaks, especially in tropical and subtropical countries (Lau et al., 2010). Research by Sanchez-Montez et al. (2015) and Zhao et al. (2016) suggests that climate is one of the factors favouring the emergence of the geographical distribution of leptospirosis.

In a developing country where topography, climate, biodiversity, and demographic and socioeconomic condition are highly complex, such as China, the epidemiology and geographical distribution of leptospirosis is likely to be heterogeneous (Shi et al., 1995), making general interventions inefficient. Thus, it is crucial to understand local epidemiology to better inform planning and implementation of targeted interventions that suit local conditions.

2.3.3 Risk factors

Based on the literature review, risk factors for leptospirosis are categorised into individual or behavioural, climatic, animal exposure, physical environmental and socioeconomic risks.

Individual-level risks

At the individual level, leptospirosis infection is mainly related to behaviours. Infection could be due to (i) occupational exposure, such as farming, mining, slaughtering, soldiering, animal farming and veterinary medicine (Mccrumb et al., 1957; Johnston et al., 1983; Terry et al., 2000; Lacerda et al., 2008; Burns et al., 2016; Parveen et al., 2016; Yupiana et al., 2019; Mgode et al., 2019); (ii) recreational exposures (e.g., triathlon, swimming, canyoning, canoeing, whitewater rafting, kayaking, fishing, hunting) (Sejvar et al., 2003, Hochedez et al., 2012; Agampodi et al. 2014; Gundacker et al., 2017); or (iii) poor sanitation and hygiene practices (e.g., drinking or swallowing river water, walking

barefoot, bathing in the river, cooking using flood water, not using protective wear) (Murhekar et al., 1998; Leal-Castellanos et al., 2003; Bhardwaj et al., 2008; Agampodi et al., 2015; Neela et al., 2019). Demographically, leptospirosis risk is higher among adults and males as they are most likely to engage in such high-risk occupations and recreational activities. However, several studies have also reported leptospirosis incidence in children (Mohan et al., 2009; Adesiyun et al., 2011; Narayanan et al., 2016; Mišić-Majerus et al., 2017).

Climatic

The association of meteorological factors on leptospirosis occurence has been numerously studied at different geographical settings, either in rural or urban areas (Chadsuthi et al., 2012; Coelho and Massad, 2012; Desvars et al., 2011; Ghizzo Filho et al., 2018; Gutiérrez and Martínez-Vega, 2018; Matsushita et al., 2018; Pappachan et al., 2004; Robertson et al., 2012; Soares et al., 2010; Suwanpakdee et al., 2015; Weinberger et al., 2014; Zhao et al., 2016; Baquero and Machado, 2018). Weather factors, such as rainfall, temperature, and relative humidity, are known important climatic factors associated with leptospirosis incidence (Mohan et al., 2009; Socolovschi et al., 2011; Batchelor et al., 2012; Benacer et al., 2016; Sumi et al., 2016). However, the effects of weather on the spatial distribution of leptospirosis risk is varied in each location. In Thailand, Chadsuthi et al. (2012) demonstrated that rainfall and temperature might vary in effect across different regions within the country, suggesting the need for specific interventions and further exploration at a local scale. Studies have shown significant association between rainfall and spatial distribution of leptospirosis risk (Mayfield et al., 2018; Baquero and Machado, 2018). In Mexico, Sanchez-Montes et al. (2015) demonstrated that temperature was more likely to be associated with the geographical variation of leptospirosis cases than rainfall/precipitation. In contrast, in Brazil, Baquero and Machado (2018) found that temperature was a preventive factor for leptospirosis.

Abundant precipitation, optimum temperature and humid conditions provide plentiful food resources or vegetation and suitable conditions for rodents to breed (Previtali et al., 2009, Perez et al., 2011) and in turn increases the abundance of rodents (Mills and Childs, 1998) and the likelihood of exposure to a leptospiral contaminated environment. In Cambodia, Ivanova et al. (2012) found that the prevalence of *Leptospira* in rodents caught in paddy fields, inundated areas, and forests was higher during the rainy season. In Brazil, Casanovas-Massana et al. (2018) demonstrated that the abundance of *Leptospira* DNA in surface waters was 47% higher during the wet season than during the dry season.

Environmental risks

Leptospirosis is strongly associated with environmental health. Leptospirosis outbreaks are known to be strongly associated with flooding after severe weather events (Leal-Castellanos et al., 2003; Amilasan et al., 2012; Smith et al., 2013; Suwanpakde et al., 2015; Tang et al., 2017; Wang et al., 2014; Matshushita et al., 2018; Widiyanti et al., 2019). Living in flood-prone areas or in densely populated settlement areas, which have poor sanitation, a poor sewage system and improper garbage disposal, favours rodent infestation, and are the most important environmental risk factors associated with leptospirosis (Ko et al., 1999; Bhardwaj et al., 2008; Reis et al., 2008; Lau et al., 2016, Mwachui et al., 2015; Barcellos et al., 2001, Gracie et al., 2014; Hagan et al., 2016, Falzemburgh et al., 2014; Blasdell et al., 2019; Briskin et al., 2019).

Disease incidence results from dynamic interactions between humans, vectors or reservoirs, and pathogens which are influenced by landscape composition and configuration (Lambin et al., 2010). Vegetation cover, surface temperature, and altitude are landscape features that may influence the magnitude of disease transmission; while spatial proximity of habitats of hosts, reservoirs, and pathogens affects the degree of disease risks. Previous studies have shown that leptospirosis is associated with land use and land cover (LULC) (Rood et al., 2017; Gracie et al., 2014; Lau et al., 2012a), elevation (Hagan et al., 2016; Lau et al., 2016), proximity to waterbodies or flooding (Della Rossa et al., 2016; Lau et al., 2016; Soares et al., 2010; Briskin et al., 2019), and vegetation (Della Rossa et al., 2016; Hagan et al., 2016).

The risk of leptospirosis is associated with LULC. Rood et al. (2017) demonstrated that leptospirosis incidence was associated with areas characterised by a low proportion of built-up areas and a high coverage of grassland. In Thailand, Della Rossa et al. (2016) demonstrated that infected rodents were most likely to be found in fragmented habitats with dense forest cover located on sloping ground areas. Likewise, in American Samoa, Lau et al. (2012a) found that living in areas surrounded by vegetated land was correlated with leptospirosis seropositivity.

Risk of human leptospirosis was higher in an area situated near a river or paddy fields that are prone to flooding (Soares et al., 2010; Robertson et al., 2012; Della Rossa et al., 2016; Lau et al., 2016). A recent study by Briskin et al. (2019) demonstrated that the risk of infection was reduced as the distance to the canal increased. Living at lower elevation was

associated with *Leptospira* seropositivity or risk of infection (Lau et al., 2012a; Hagan et al., 2016).

The risk however could be heterogenous geographically and temporally (Gracie et al., 2014; Suwanpakde et al., 2015; Hagan et al., 2016). The spatial risk of infection variesgreatly depending on the local microenvironmental conditions. Suwanpakde et al. (2015) demonstrated that flooding was not directly associated with leptospirosis but different drivers such as agriculture practices have influenced the geographical and temporal pattern of the incidence across regions in Thailand. A study conducted by Hagan et al. (2016) demonstrated that, in the slum community (local level), households living in the lowest altitude areas, surrounded by more vegetation and minimal access to waste collection, were at higher risk of leptospiral infection. Whereas Gracie et al. (2014) found that at regional level leptospirosis incidence was associated with the number of people residing in urban slums while at a local level the risk was determined by the proportion of the area likely to flood.

Animal exposure

Rats and other rodents are the important risk factors associated with leptospirosis, both in rural and urban areas. However, in rural areas, where subsistence farming is common, leptospirosis risk is also associated with exposure to livestock animals, such as cattle, pigs, goats, and sheep (Leal-Castellanos et al., 2003; Salmon-Mulanovich et al., 2019; Brockmann et al., 2016; Lau et al., 2012b; Allan et al., 2018; Shresta et al., 2018). Moreover, the risk is likely to be higher when livestock are raised in a traditional or subsistence farming system with lack of pasture grazing management and poor biosecurity measures (Schoonman and Swai, 2010). Whereas in urban slums, the presence of rats and other rodents is the primary risk associated with leptospirosis (Sarkar et al., 2002; Reis et al., 2008; Costa et al. 2015b; Vitale et al., 2018).

Socioeconomic risks

Unchecked urbanisation and poverty are believed to be the key driver for the emergence of leptospirosis (Ko et al., 1999; Lau et al., 2010). Rapid urbanisation has led to severe urban poverty as seen in the uncontrolled growth of urban slums. Poverty generates circumstances that favour the spread of infectious diseases and prevents communities from obtaining adequate access to basic services, such as sanitation, safe water, education, and health services (World Health Organization, 2012; Hotez et al. 2008, 2015).

Prior studies have demonstrated that socioeconomic status (SES) was associated with leptospirosis risk (Reis et al., 2008, Bacallao et al., 2014). Several indicators explaining SES have been used, including proportion of population living in extreme poverty (Bacallao et al., 2014), gross domestic product (GDP) (Zhao et al., 2016), poverty rate (proportion of population under the poverty line) (Lau et al., 2016; Mayfield et al., 2018b), Gini index and illiteracy rates (Schneider et al., 2015). Bacallao et al. (2014) demonstrated that areas with a large proportion of people living in extreme poverty were at highest risk of acquiring leptospirosis. However, Schneider et al. (2015) found no association between Gini index (as indicator describing inequality income per capita by municipality) and number of leptospirosis cases. Poor urban and peri-urban communities and rural communities are found to have a higher risk of leptospirosis. This was partly because of inadequate access to health education, healthcare, and proper housing and basic sanitation that was unfavourable to rat infestations.

In China, the relationship between these socioeconomic indicators and the burden of leptospirosis remains poorly understood. Enormous economic development has sent more than 600 million people out of extreme poverty during 1981–2010; the poverty rate fell from 84% in 1980 to 10% in 2013 (UN-HABITAT, 2016). The extent to which the socioeconomic changes during the past decades in China has contributed to the shift in the epidemiology and burden of leptospirosis has not been adequately analysed.

2.3.4 Incidence and Burden

Worldwide, it has been estimated that there have been 1.03 million cases of leptospirosis, causing approximately 60,000 deaths each year, with 73% of global incidence estimates taking place in poor-resource countries (Costa et al., 2015). Asia has been estimated to be the region with the highest annual incidence (5.5–55.5/100,000 population) and mortality (0.29–2.96/100,000 population) rates. However, available incidence and mortality estimates are believed to be inaccurate since disease surveillance and laboratory diagnostic capacity in many countries are inadequate, especially in developing countries (Bharti et al., 2003). Tropical countries are more likely to have higher incidence than temperate countries as there is a more favourable environment for *Leptospira* to survive longer. In particular, most of the tropical countries are developing countries with high-risk conditions owing to their diverse potential animal reservoirs and a greater population at risk owing to a limited health system (WHO, 2011).

Leptospirosis was responsible for a significant health burden globally. It has been estimated that approximately 2.90 million DALYs (95% uncertainty interval [UI] 1.25–4.54 million DALYs) were lost per year globally because of leptospirosis (Torgerson et al., 2015). This put the burden of leptospirosis (41.8 DALYs per 100,000 population) relatively equal with the burden of lymphatic filariasis (40 DALYs per 100,000 population) and schistosomiasis (48 DALYs per 100,000 population). Leptospirosis is most likely affecting males (2.3 million DALYs or 80% of total DALYs) more than females. Among age groups, adults aged 20–49 years are the group most affected (1.5 million or 52% of total DALYs). The biggest contribution to the DALY is the number of years of life lost due to premature mortality (YLLs), which accounts for 2.80 million YLLs (95% UIs: 1.16–4.46 million). However, these burden estimates were based on the incidence and mortality data reported by Costa et al. (2015) who obtained the data from passive surveillance, which is prone to uncertainty and underestimation.

The seminal study by Torgerson and colleagues (2015) provided the first global country-level map of the burden of leptospirosis. Distribution of the burden of leptospirosis is varies geographically, with the highest burden estimates identified in low-income countries along the equator, particularly South-East Asia countries. Among the Asian countries, it has been estimated that China has the second largest burden estimate (301,688 DALYs, 95% UI: 119,388–525,491 or 22.05 DALYs per 100,000 population, 95 UI: 8.82–38.81) after India (684,369 DALYs, 95% UI: 290,213–1,217,287 or 56.35 DALY per 100,000 population, 95% UI: 23.90–100.23). This burden estimate, however, may be irrelevant since the morbidity and mortality of leptospirosis in China has been gradually declining for the past 20 years (Zhang et al., 2012) and, since 1997, the incidence of leptospirosis has declined to less than 1 per 100,000 (Zhang et al., 2012; Hu et al., 2014). However, the researchers assumed that the burden was homogenously distributed within China. Since leptospirosis epidemiology is quite complex—greatly depending on the local climate, environment, and socio-demographic conditions—the geographical distribution of the burden is most likely to vary even within a country. Mapping the most recent burden estimates, particularly at finer spatial resolution, is essential so that policymakers are better informed when planning and implementing region-specific public health interventions.

Despite this reduction, local outbreaks still occur in parts of the country (Li et al., 2013; Fan et al., 2014; Wang et al., 2014; Wu et al., 2015; Xu et al., 2016a; Tang et al., 2017), indicating that the transmission of leptospirosis are still exist. This low-level transmission

has been viewed by China's health authorities as an opportunity for eliminating leptospirosis in the country. To achieve this operational goal, clear evidence about which demographic groups are at highest risk of leptospirosis, the location of residual high-risk areas for leptospirosis, as well as information on local drivers of infection (e.g., demographical, climatic, environmental and socioeconomic) are required.

2.4 Clinical manifestations and diagnosis

2.4.1 Clinical features

Generally, the incubation period for leptospirosis takes 5–14 days, with ranges between 2 and 30 days (Faine et al., 1999) (Figure 2-3). Most people may probably not seek immediate medical attention since, in its early phase (known as acute 'leptospiraemic' phase), leptospiral infection commonly presents as undifferentiated, mild flu-like symptoms. Fever, chills, headache, abdominal pain, nausea, conjunctival suffusion, vomiting, skin rash, muscle tenderness, myalgia, prostration, cough, jaundice, anorexia, diarrhea, hemoptysis are common symptoms during this acute stage. After the initial week of illness, leptospirosis could resolve suddenly but it could also lead to a severe, icteric presentation known as Weil's disease. This severe form generally evolves among approximately 5–15% of patients, with case fatality rates around 10–50% (McBride et al., 2015). Weil's disease could lead to severe complications, such as acute renal failure, pulmonary haemorrhage syndromes, myocarditis, cardiac involvement, and Guillain-Barré syndrome (Haake et al., 2015; Dev et al., 2019; Herath et al., 2019). Host susceptibility factors, the concentration of *Leptospira,* and the virulence of the strain influence the amelioration of illness (Ko et al., 2009).

Symptoms of leptospirosis could resemble symptoms of other diseases, such as dengue, malaria, scrub typhus, hantavirus, pneumonia, and acute undifferentiated fever (AUF) (Levett, 2001; Gasem et al., 2009, 2016; Lokida et al., 2016). As a result, physicians often misdiagnose leptospirosis due to it exhibiting broad and non-specific clinical manifestations. Moreover, in the absence of adequate disease awareness and diagnostic laboratory capacity, leptospirosis is difficult to recognise, and accurate diagnosis becomes challenging, particularly in developing countries.

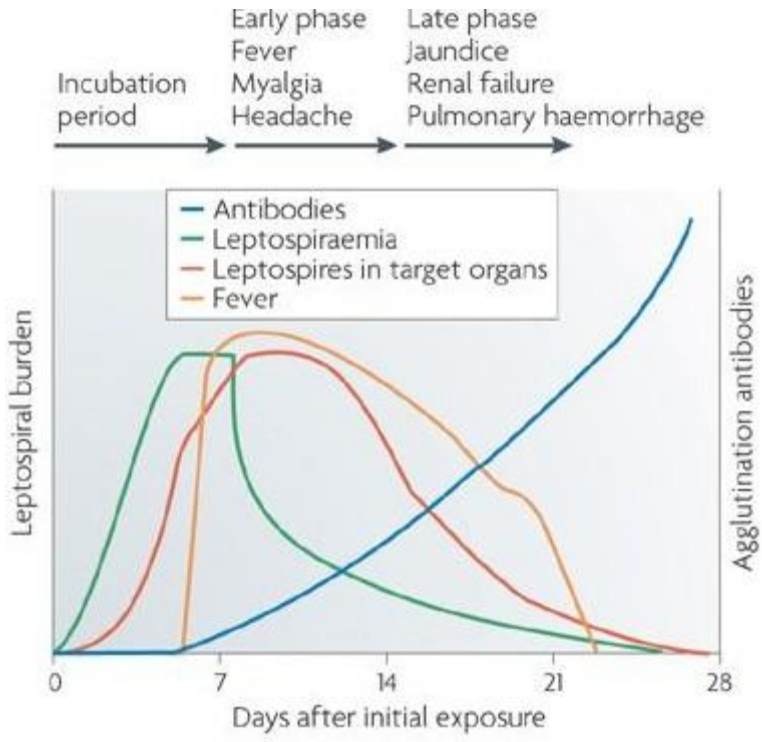

Figure 2-3 Leptospiral infection dynamic. Reprinted from Ko et al. (2009) with permission from Nature ©2009

2.4.2 Laboratory diagnosis

There are several confirmatory laboratory tests to ascertain leptospirosis, which can be grouped into direct and indirect approaches. Direct diagnostic techniques including microscopy, culture and molecular methods. Direct microscopy and dark field phase contrast microscopy can be performed to identify leptospires in blood, urine and cerebrospinal fluid (CSF). However, the weakness of this technique is that it needs certain number of Leptospira to be examined (about 10 cells/ml) and it is very hard to assure false positives and false negatives (Picardeau et al., 2014). Leptospires can also be isolated from blood, urine and CSF samples. However, the culture method is technically complicated and time-consuming, requires several weeks of incubation at 28–30°C, needs routine dark-field microscopic examination, has low sensitivity and Biosafety cabinet level 2 (BSL-2) laboratory. Alternatively, Leptospiral DNA in clinical material can be tested by molecular diagnosis using polymerase chain reaction (PCR) (Merien et al., 1995; Fonseca et al., 2006). This method offers a rapid test with high sensitivity and specificity. Recently, several developments of conventional PCR have been performed, such as multiplex PCR assay and 16s rRNA-PCR, followed by restriction fragment length polymorphism (RFLP), which potentially can be used for early detection of leptospirosis (Ahmed et al., 2012;

GÖKmen et al., 2016). However, it is costly and not widely available in most primary healthcare in developing countries.

Indirect diagnostic approaches can also be used to detect *Leptospira*. These include microscopic agglutination test (MAT), enzyme-linked immunosorbent assay (ELISA) and indirect haemagglutination assay (IHA). So far, due to its high sensitivity and specificity, MAT is considered as the 'gold-standard' technique to serologically confirm leptospirosis (Goris and Hartskeerl, 2014). A standard criterion for a positive MAT is a fourfold increase in antibody titre or a conversion from seronegativity to a titre of 1/400 or above. However, this could be varied between countries depending on the local epidemiological conditions. In fact, MAT has also limitations. This test requires live cultures of leptospires which may not be available in resource-constrained countries. Substantial resources and qualified technicians are essentially required to perform MAT requires. Moreover, cross-reaction could occur between serovars in each serogroup, so that additional testing might be needed to determine the exact serovar causing infection (WHO, 2011).

Another serological test including IgM ELISA, macro-agglutination, immunofluorescence assay (IFA), indirect hemagglutination assay (IHA), latex agglutination, lateral flow assays (LFA) and IgM dipstick can be used as screening test (McBride et al., 2005). Several antibody-based kits have been trialled to help quickly detect clinically suspected leptospirosis infection at the early acute stage, so that primary healthcare doctors can administer antibiotics promptly to prevent further complications which also reduces the cost for hospitalisation. However, the sensitivity and specificity for each test is inconsistent. If possible, further diagnosis should be done by using MAT test to confirm leptospirosis. To date, none of these available tests have fulfilled the principle of rapid diagnostic tests: accurate, user-friendly, low-cost, interpretable, consistent, and timely (Picardeau et al., 2014).

2.5 Prevention and control

2.5.1 Managing risks in human

Several preventive actions have been recommended to minimising the risk of infection in humans. Leptospirosis can be avoided by a combination of mechanical and social approaches. As leptospirosis is commonly known as an occupational hazard, prevention can be mechanically applied by using personal protective equipment (PPE), such as boots, gloves, goggles, clothes. While there is discrepancy in the effectiveness of PPE on

preventing *Leptospira* infections (Dreyfus et al., 2015; Pittavino et al., 2017), studies have shown the benefits of using PPE in preventing leptospirosis infection (Phraisuwan et al., 2002; Tomcyzk et al., 2014). Based on meta-analysis, it shows that using footwear is a robust protective measure for leptospirosis infection (OR = 0.59; 95% CI: 0.37–0.94) (Tomcyzk et al., 2014).

In addition to promoting PPE in high-risk populations to prevent leptospirosis, chemoprophylaxis could be one of the preventive strategies. The use of antibiotic prophylaxis to prevent leptospirosis infection has been documented in previous studies (Takafuji et al., 1984; Gonsalez et al., 1998; Sehgal et al., 2000; Agampodi et al., 2008; Bhardwaj et al., 2008; Dechet et al., 2012; Chusri et al., 2014; Fonseka et al., 2019). So far, doxycycline (200 mg orally once per week) is thought to be a significant chemoprophylactic for preventing leptospiral infection but the protective level is considerably varied among studies. Although researches have reported success in some studies (Takafuji et al., 1984, Dechet et al., 2012), the application of a chemoprophylaxis approach to the general population during an outbreak or when there is flooding is challenging without adequate awareness among the high-risk population (Sehgal et al., 2000; Bhardwaj et al., 2008; Fonseka et al., 2019). Also, a systematic review indicates that doxycycline may not be appropriate in the long term for the general population as it could lead to many contraindications (e.g., nausea, vomiting, allergies) (Brett-Major and Lipnick, 2009).

Using such approaches alone, however, might not be effective during flooding or a post-disaster scenario where the risk of exposure to an environment containing *Leptospira* is so high. Therefore, behavioural change should be followed by social approaches, primarily through improving the level of awareness about leptospirosis. Better understanding about the risk, symptoms, and modes of transmission can help improve initial preventive measures and appropriate treatment among at-risk populations and by local health workers. Health education packages, for example, could be delivered through school curiculla. Such an approach with other diseases, such as worm infections, has been demonstrated to significantly improve children's knowledge about the disease and help in reducing infections (Bieri et al., 2013; Al-Delaimy et al., 2014). A cluster-randomised intervention trial conducted by Bieri et al. (2013) at Chinese schools in the Hunan province, for instance, showed that the health education packages (e.g., workshops, video, pamphlet, classroom discussions) successfully increased student's knowledge about soil-transmitted helminths, resulting in a change in hand-washing behaviour and a 50%

reduction in the incidence of infection. In the leptospirosis context, there are examples from La Reunion Islands and French Polynesia in which leptospirosis awareness materials (e.g., leaflets, posters) were distributed in schools in addition to general hygiene education (Goarant, 2016).

Immunisation is another preventive measure that has potential and may be the most effective way to prevent leptospirosis, especially for those populations at greatest risk. Yet, there are still key issues that impede the development and implementation of human vaccines, including serovar-specific effectiveness, side-effects, and short duration of protection (Koizumi and Watanabe, 2005; Adler, 2015). To date, several vaccines—including whole cell attenuated and inactivated vaccines, leptospiral lipopolysaccharides (LPS) vaccines, and recombinant DNA vaccines—are available (Martinez et al., 2004; Laurichesse et al., 2007; Wang et al., 2007; Adler, 2015; Rajapakse et al., 2015; Xu and Ye, 2017; Laurichesse et al., 2007). So far, a well-established vaccine is the whole cell monovalent vaccine, but it is not effective against different serovars. Immunisation may not be effective in massive areas where the epidemiology (e.g., reservoir hosts) and risks could be varied. To develop effective vaccines, an improved understanding on *Leptospira* diversity and its genetic characters is therefore essential.

Licensed human *Leptospira* vaccines are limited and are now only available in a few countries, including in China (Hu et al., 2014; Xu and Ye, 2017). Currently, a single multivalent, inactivated leptospirosis vaccine is used in China. This vaccine uses seven strains of the main *L. interrogans* serogroups, including three highly virulent (serogroup Icterohaemorrhagiae, Grippotyphosa, and Autumnalis) and four low-virulence strains (serogroup Canicola, Pomona, Australis, and Hebdomadis), and it is still applied to populations at-risk during annual epidemic periods (Xu and Ye, 2017, Zhang et al., 2019a). Notably, the most important preventive measure in the absence of vaccines is prompt diagnosis followed by immediate treatment.

2.5.2 Managing risks in animals

Livestock biosecurity and animal husbandry

Food producing animals, such as cattle, pigs, and sheep, also play a significant role in leptospirosis transmission—either as maintenance host or accidental host for *Leptospira*. As aforementioned, a wide range of serogroups and serovars can harbour and infect livestock. It has been suggested that rodents are a major pest in farms and are a causative

agent of leptospirosis in animals (Webster et al., 1995; Backhans and Fellstrom, 2012). At farm level, biosecurity measures (e.g., livestock management, vaccination, antibiotic use/ metaphylactic protocol, quarantine, animal-health monitoring, rodent control) have an important role in controlling *Leptospira* spillover from animal to human (Graham et al., 2008; Mughini-Gras et al., 2014; Ellis, 2015). An integrated strategy to control leptospirosis in livestock by combining extensive biosecurity measures, vaccination, and antibiotic metaphylaxis has successfully reduced outbreaks of the infection at farm level (Mughini-Gras et al., 2014; Pimenta et al., 2019). For instance, in Brazil, a recent study by Pimenta et al. (2019) highlighted that integrating immunisation and antibiotic therapy and improving management practices has efficiently reduced reproductive failure in dairy cattle due to leptospirosis.

Although there is variation in the findings regarding the effect of vaccination on animals (Adler and de la Pena Moctezuma, 2010; Ayral et al., 2014), vaccination seems to be the most feasible and effective way to lower the risk of infection in livestock and domestic animals. Vaccination has effectively reduced the incidence of abortion in herds due to *Leptospira* infection (Jacobs et al., 2015). It has also potential to reduce urinary shedding and renal carriage in livestock; although the rate of efficacy varies among studies (Allen et al., 1982; Hodges et al., 1985; Vallée et al., 2016). A study in New Zealand showed that a campaign for vaccination of dairy cows helped to reduce leptospirosis among dairy farmers by more than 80% (Marshall, 1987). Based on recent Bayesian random effect meta-analysis, the vaccine efficacy against *Leptospira* serovar Hardjo in cattle was 89.9% (95% probability interval 80.6%–94.9%), suggesting that vaccine could be used to prevent leptospirosis incidence both in animals and humans working with livestock (Sanhueza et al., 2018).

2.5.3 Managing environmental risks

The environmental driver of leptospirosis is multifactorial as discussed in earlier sections. The emergence of leptospirosis is associated with poor living conditions (e.g., unsafe water and poor sanitation, poor waste management, improper drainage or sewage system) that favour rodent infestation of human dwellings. During the rainy season, flooding amplifies the exposure risk as it helps spread the *Leptospira*-contaminated urine of rats or infected animals as well as disrupting basic services. Controlling environmental risks needs to be directed towards improving environmental conditions and basic infrastructure,

such as providing water, sanitation and hygiene (WASH), a drainage system, rodent control, and flood management (Lau et al., 2010, 2012; Alderman et al., 2012). Furthermore, knowing when interventions should be implemented and a better understanding of the local climate variability and the environmental conditions that signal the highest risk to *Leptospira* exposure is essential. To help improve timely outbreak prevention and control, a study on understanding the short-term association between climate and physical environmental indicators and human leptospirosis emergence is discussed in Chapter 8.

2.5.4 Surveillance

The objective of disease surveillance is to provide accurate, complete, and representative data on disease incidence and burden, high-risk areas, and potential upcoming outbreaks (Jena et al., 2004). Such information is needed to guide policy makers and health authorities at every level to effectively plan and implement leptospirosis control strategies. However, surveillance for leptospirosis in most of the endemic countries, especially in developing countries, is restricted by the lack of good performance and coverage of diagnostic tools, and epidemiological data. In addition, there are no tools that can help to locate and forecast high-risk areas for leptospirosis and to detect outbreaks (WHO, 2010, 2011). Geographical information system (GIS) in combination with statistical modelling could be used to identify areas most at risk, quantify risk, and forecast outbreaks by taking into account, at least, climatic and environmental data. However, to date, the use of such approaches for leptospirosis control and surveillance is still poorly documented and there is no available comprehensive evaluation regarding its application. The general importance of GIS for understanding disease epidemiology and control is elaborated in the next section.

Early warning systems (EWSs) are at the forefront of modern infectious disease surveillance systems. EWSs strengthen surveillance as they can help to anticipate excesses in disease incidence that can lead to large outbreaks. To date, methods for effectively forecasting leptospirosis outbreaks for geographically targeted prevention, case detection, and response is still lacking (WHO, 2010, 2011). A few studies have been initiated to forecast leptospirosis outbreaks based on climate variables or seasonality as part of developing an EWS (Chadsuthi et al., 2012; Weinberger et al., 2014). All of these studies, however, were solely based on weather data. Future outbreak-prediction models should explore the

opportunity to incorporate environmental indicators (e.g., abundance of rodents, flooding) (Goarant et al., 2016). Research outlined in Chapter 8 shows how I developed temporal models by incorporating both weather and remotely sensed environmental data to estimate risk and lagged effects, which lay the foundation for an EWS of leptospirosis in China.

2.6 The importance of a spatial analytical approach and a spatial decision support system (SDSS) for disease control

2.6.1 Spatial epidemiology

To support effective leptospirosis surveillance and control, health authorities need tools to guide them to where interventions are needed the most. One of the specific branches in epidemiology, which pinpoints on analysing the spatial pattern of the disease of interest and its association with sociodemographical, environmental, genetic and other risk factors with particular emphasis on the small-area level, is known as spatial epidemiology (Elliott and Wartenberg, 2004). This involves visualisation or mapping, exploration of spatial clusters, and spatial modelling (Pfeiffer et al., 2008). Spatial epidemiological tools can be used as decision tools which can provide evidence to effectively guide public health authorities in planning, implementing, and evaluating disease control and prevention at specific areas (Rezaeian et al., 2007; Caprarelli and Fletcher, 2014).

Recently, spatial epidemiological approaches have been extensively used to explain the epidemiology of various kinds of infectious diseases: vector-borne diseases, such as malaria (Hay et al., 2000; Bi et al., 2013; Houngbedji et al., 2016) and dengue (Eisen and Lozano-Fuentes, 2009; Fan et al., 2014; Dhewantara et al., 2015, 2019; Astuti et al., 2019); zoonotic waterborne diseases, such as schistosomiasis (Soares Magalhaes and Clements, 2011; Hodges et al., 2012; Soares Magalhaes et al., 2014; Lai et al., 2015; Wang et al., 2016); and rodent-borne diseases, such as scrub typhus (Wu et al., 2016), hemorrhagic fever with renal syndrome (Wu et al., 2011), Lassa fever (Fichet-Calvet and Rogers, 2009) and plague (Qian et al., 2014).

2.6.2 Application of spatial epidemiology in leptospirosis

As high-quality spatial data become increasingly available there has been a growing interest in using spatial epidemiological analysis to acquire a better understanding of leptospirosis epidemiology. Basic spatial analytical techniques through visualisation of the

georeferenced point or areal data to map the distribution of leptospirosis incidence or prevalence and attributable risks (e.g., environment, socioeconomic data) have been used in previous studies (Barcellos and Sabroza, 2000, 2001; Stevens et al., 2011; Lau et al., 2015, 2016; Reis et al., 2008; Gracie et al., 2014; Garcia- Ramirez et al., 2015). For instance, Barcellos and Sabroza (2001) mapped the incidence and several environmental factors and found that higher incidence was observed in flood-risk areas and proximity to waste disposal sites. Reis et al. (2008) used 6-cm resolution of aerial photographs to confirm that elevation and proximity to open sewers and waste disposal were environmental risks for leptospirosis in slum communities in Brazil. Moreover, based on DALY estimates, Torgerson and colleagues (2015) produced the first global country-level map of the burden of leptospirosis. These maps are important as they can be used to support and guide health authorities to put into practice public- and animal- health interventions. Mapping risk at finer spatial resolution is essential for better informing policymakers in designing and implementing area-specifc public health interventions. In Chapter 5 to Chapter 7, I provide examples of mapping leptospirosis risk on a global and sub-national/local scale.

Spatial analytical tools can be used to investigate disease patterns, to help generate hypothesis, and to explain the potential drivers associated with disease distribution. In previous studies, spatial patterns of incidence or risk have been examined to ascertain whether the disease is clustered or randomly spread across space and time (Pfeiffer et al., 2008). For instance, Tassinari et al. (2008) used a space-time analysis and showed that leptospirosis incidence appeared to be geographically clustered in a given period of time and it was believed that it was explained by high rainfall intensity. Mohd Radi et al. (2018) used spatial analytical tools to determine the spatial-temporal pattern of leptospirosis incidence in Kelantan, Malaysia. They showed that the leptospirosis hotspots were more likely to be spatially clustered after flooding and that this correlated with distance to garbage refusal sites and land use. Research detailed in Chapter 6 describes the application of spatial analytical tools to investigate residual hotspots of leptospirosis in China and the use of GIS to help characterise the key demographical, environmental and socioeconomic conditions of high-risk areas.

Spatial analytical tools in combination with stastical modelling can also be used to estimate risk, generate predictive maps of incidence or prevalence, number the population-at-risk, and identify areas where risk at its highest. A few researchers have aimed to develop predictive risk maps for leptospirosis in their studies. For instance, using georeferenced

point data (surveyed households) and non-spatial logistic regression models, predictive maps for seroprevalence of leptospirosis were first developed by Lau et al. (2012a) in her study in American Samoa, by taking into account individual-level factors and four environmental factors (altitude, pig density, vegetation, and soil type). The maps showed that variation in seropositivity was indeed correlated with individual-level factors and environmental factors. Seroprevalence was predicted to be higher in those households residing in villages at low elevation, in rural areas, on clay soil, and with higher pig density. Rood et al. (2017) used simultaneous autoregression (SAR) to predict the incidence of leptospirosis by taking into account land use, type of soil, water infrastructure, cattle farm density, and the proportion of certain groups of the population. A recent study by Mayfield et al. (2018b) demonstrated the use of spatial Bayesian networks to produce probabilistic risk maps of leptospirosis infection under different epidemiological settings. The study showed that the effect of such factors on the probability of infection differed in both rural and urban areas—except for the effect of density of commercial dairy farms. The presence of pigs and high poverty rates was likely to increase the risk of infection, especially in rural areas. Although such an approach offers benefits concerning its capacity and flexibility to deal with a range of data, researchers using this technique do not fully take into account spatial dependency and uncertainties, and they assume that the spatial process was stationary.

Spatial autocorrelation is one crucial foundation of spatial epidemiology, and it should be adequately addressed in analysing the spatial variation. Spatial autocorrelation explains the degree of similarity between two observations at certain locations. It is important to note that two neighbouring locations are usually more identical than those the distant ones (Pfeiffer et al., 2008). This has been known as Tobler's First Law of Geography. Failing to account the spatial autocorrelation in the models' residuals could violate the assumption of independence and thus will generate inaccurate estimates. Also, uncertainties that may have resulted from the use of the data, models, analyses and predictions have to be considered in the modelling processes (Elith et al., 2002). Maps that provide estimates of uncertainty in model outputs can help inform health authorities to decide objectively in planning and implementing spatially targeted programs for disease control (Clements et al., 2006). Predictive tools for leptospirosis need to be developed to improve leptospirosis control (WHO, 2010, 2011).

One of the approaches that allow researchers to include spatial correlation and uncertainties is the Bayesian method. Recently, the Bayesian method has been widely

used in the spatial epidemiology of tropical diseases as it offers several benefits compared with traditional approaches (Best et al., 2005). First, the Bayesian spatial method is useful in minimising bias and variance compared with conventional statistical methods (Besag et al., 1991). It is a probabilistic likelihood-based method which is highly flexible and is able to adapt to data availability issues. Second, it provides suitable platforms for incorporating spatial correlation and uncertainty in the modelling process (Clements et al., 2006). While the Bayesian method offers such appealing advantages, it has scarcely been used in estimating and predicting the geographical variations in the risk of leptospirosis and there remains a need to document the applicability of GIS, RS, and spatial analytical tools for control and surveillance of leptospirosis. A critical review of the application of spatial analytical tools for leptospirosis is presented in Chapter 4. Moreover, the application of Bayesian spatial modelling to estimate the spatial risk of leptospirosis is illustrated in Chapter 7.

2.6.3 Spatial decision support system

While mapping leptospirosis and the use of spatial analytic tools in this field has been well documented, their full potential as tools to support decision-making processes has not been well recognised. The use of the spatial decision support system (SDSS) in public health contexts has been demonstrated in several countries to support vector-borne diseases and elimination program of malaria (Wangdi et al., 2016; Kelly et al., 2011), but it has not been applied to controlling leptospirosis. An SDSS provides a user-friendly computerised system, incorporating geographical or spatial data, disease notification data, and other attributes (e.g., resources, demographics). It can automatically analyse the available data to generate enriched and interactive visual graphics or maps and tables to guide decision making for planning and implementation of interventions (Kelly et al., 2011).

2.7 Summary

Based on the literature review above, the following gaps in knowledge have been identified in the context of leptospirosis epidemiology and control:

1. While there has been a growing number of studies on leptospirosis aimed at utilising the spatial analytical approaches to understand its epidemiology, a comprehensive evaluation of the use of such methods in existing studies is not available.

2. Torgerson and colleagues (2015) provided the first global country-level map of the burden of leptospirosis. However, this burden estimate may no longer be relevant for China as researchers argue in recent reports that the morbidity and mortality of leptospirosis in China have been gradually decreasing since the 1990s (Zhang et al., 2012). Most importantly, Torgerson's study did not adequately capture the variation within the country. To better inform policymakers in planning and implementing local specific public health interventions, recent estimates of the burden as well as its geographical distribution at more satisfactory spatial resolution is essential. Before this thesis, no one had estimated and mapped DALYs for leptospirosis at a sub-national level, especially in China.
3. In developing countries where topography, climatic, biodiversity, demographic and socioeconomic conditions are highly complex, such as in China, the epidemiology and geographical pattern of leptospirosis incidence are likely to be heterogeneous. This could make business-as-usual interventions inefficient. Thus, it is crucial to understand local epidemiology to better inform planning and implementation of targeted interventions that suit local conditions. However, the role of environmental and socioeconomic factors in the heterogeneity of distribution of leptospirosis incidence, especially in China, remains unknown.
4. The World Health Organization – Leptospirosis Research Group (LERG) recommends the development of predictive tools to support the identification of geographic areas that are at highest risk and the populations affected by leptospirosis (WHO, 2010). In recent years, a growing number of studies have developed predictive maps of leptospirosis incidence to assist leptospirosis control (Lau et al., 2012a, Rood et al., 2017, Mayfield et al., 2018b, Baquero and Machado, 2018). While leptospirosis is also an important public health problem in China, spatially explicit predictive maps for leptospirosis have not been developed.
5. While it is well established that leptospirosis outbreaks are strongly seasonal and influenced by weather (Chadsuthi et al., 2012; Weinberger et al., 2014; Matsushita et al., 2018), weather-based models to predict leptospirosis outbreak remain lacking (Goarant, 2016). Furthermore, there is limited research into predictive models incorporating environmental parameters.

Chapter 3 General methodology

3.1 Context

In this thesis, I used data from different sources. Chapter 4 consists of a systematic review of data retrieved from major online literature databases: Pubmed, Web of Science, Scopus, EMBASE, Zoological records and ScieLo. I obtained the leptospirosis data used in Chapter 5 to Chapter 8 from the China Center for Disease Control and Prevention (CDC). In addition, environmental and socioeconomic data were collected from several publicly available databases, including the United States Geological Survey (USGS) databases, China Resource and Environmental Science Data Center of the Chinese Academy of Sciences, China Meteorological Data Sharing Service System, WorldClim, WorldPop, China National Bureau of Statistics and Food and Agriculture Organization (FAO). In this chapter, I describe the data used in this thesis, and I provide a summary of all the data in Table 3-1.

Table 3-1 Epidemiological, environmental and socioeconomic data used in this thesis

Data	Description	Sources	Chapter 5	Chapter 6	Chapter 7	Chapter 8
Epidemiological data						
Human leptospirosis case	Notification data (2005–2016) containing information on age, gender, code of county, coordinates, date of onset of illness, date of death, case classification (suspected, probable, confirmed)	China Center for Disease Control and Prevention	√	√	√	√
Environmental variables						
Climatic data	Precipitation	China Meteorological Data Service Center.				√
	Relative humidity	China Meteorological Data Service Center.				√
	Gridded precipitation data (1-km x 1-km). Values were sampled at county-level using ArcGIS software	WorldClim		√	√	
Land surface temperature (LST)	Raster data with 1-km spatial resolution. Monthly LST for each county for 2005–2016 was sampled using ArcGIS software. Values were sampled at county-level using ArcGIS software	MODIS Terra, MODIS11A2 8-day, 1 km spatial resolution			√	√
Normalized Difference Vegetation index (NDVI)	Raster data with 250 metre spatial resolution. Monthly NDVI value for each county for period of 2005–2016 was sampled using ArcGIS software. The NDVI value ranges from -1 to 1. 250 metre spatial resolution	MODIS Terra 13Q1 v006 Vegetation Indices 16-Day L3 Global, 250 metre spatial resolution			√	√
Modified Normalized Difference Water Index (MNDWI)	Monthly NDWI value for each county for 2005–2016 was	MODIS Terra MOD09A1.V6 8-day, 500m spatial resolution			√	√

Data	Description	Sources	Chapter 5	Chapter 6	Chapter 7	Chapter 8
	sampled using ArcGIS software. NDWI calculated by using formula $(R_{GREEN}-R_{SWIR)} / (R_{GREEN} + R_{SWIR})$ The value of the index ranges from -1 to 1.					
Elevation	Shuttle Radar Topography Mission (SRTM)- Digital elevation model (DEM), 1-km (30-arc seconds) spatial resolution. Values were sampled at county-level using ArcGIS software	WorldClim		√	√	
Slope	Slope was calculated from the SRTM-DEM elevation data by using ArcGIS toolbox. The mean slope values for each county were sampled using ArcGIS software.	WorldClim			√	
Land cover	Land cover types for 2005 and 2015. Reclassified into 6 types: cultivated land, forested land, grassland, waterbodies, artificial surfaces and bare land.	Data Center for Resources and Environmental Sciences, Chinese Academy of Sciences (RESDC)			√	
Hydrological features	River basin boundaries and streams	GTOPO Hydro1K, HydroSHEDS, SRTM, 3 arc-second resolution			√	
Livestock density	Gridded pig and cattle density with 2010 as year of reference. Cell resolution 0.00833 (1-km x 1-km). Values were sampled at county-level using ArcGIS software.	FAO-GeoNetwork model of livestock density (GLW 2.01)			√	

Data	Description	Sources	Chapter 5	Chapter 6	Chapter 7	Chapter 8
Socioeconomic variables						
Population	Annual population data by county (2005–2015)	China National Bureau of Statistics	√	√	√	√
Population density	Population density v4 (2005, 2010, 2015) (raster data). Values were sampled at county-level using ArcGIS software.	Socioeconomic Data and Applications Center (SEDAC)			√	
Farmland/crop production	Raster data for crop production (in kg per ha). Values were sampled at county-level using ArcGIS software.	Resource and Environmental Science Data Center of the Chinese Academy of Sciences (http://www.resdc.cn)		√	√	
Type of county (residence)	Urban or rural type	A 5x5 km resolution rural/urban surface derived from the Global Rural-Urban Mapping Project (GRUMP),		√	√	
Gross Domenstic Product (GDP)	Gridded GDP per capita (2010). Values were sampled at county-level using ArcGIS software.	(http://www.geodoi.ac.cn/weben/doi.aspx?Id=125) (Huang Y et al. 2014).		√	√	

3.2 Leptospirosis data

Leptospirosis notification data from 2005 to 2016 were provided by the China CDC. The data are publicly available upon request to the data center of the CDC. In China, leptospirosis is classified as Class B Notifiable Disease since 1955, hence all suspected and confirmed leptospirosis cases must be reported by all health providers at county-level to the CDC through the web-based reporting system, the China Information System for Diseases Control and Prevention (CISDCP). Notified leptospirosis cases include information about sex, age, occupation, date of onset of illness, date of diagnosis, date of death, case classification (suspected, clinical, and laboratory-confirmed), and address. All records were anonymised prior to the commencement of analysis. Ethics clearance for the use of these leptospirosis data was provided by the Medical Research Ethics Committee of the University of Queensland (Number 2016001608) and the Ethics Committee of Beijing Institute of Disease Control and Prevention (*see* Appendix A)

Leptospirosis cases are classified into three categories: suspected, clinically diagnosed, and confirmed. Suspected cases are defined as an individual with: i) a clinical symptom such as acute fever (up to 39 °C), which may be accompanied by chills, myalgia, or malaise; and ii) history of exposure within a month before the onset of illness to the following risk factors: epidemic season, reside in the epidemic area, either direct or indirect contact with suspected animals and their urine or faeces or with contaminated water and soil. Clinical (probable) cases are defined as suspected cases with at least one of the following clinical manifestations: conjunctival hyperemia, gastrocnemius tenderness, or enlargement of the lymph nodes. Whereas a confirmed case is defined as a suspected case with one or more any of the following laboratory results: i) positive culture of *Leptospira* from blood, urine, tissues, or cerebrospinal fluid (CSF); ii) microscopic agglutination test (MAT) titre of ≥400 in single or paired serum samples; iii) a fourfold or greater rise in MAT titres between acute and convalescent-phase samples; iv) the presence of pathogenic *Leptospira* spp detected by polymerase chain reaction (PCR); v) the presence of IgM antibodies by enzyme-linked immunosorbent assay (ELISA). Indeed, the IgM ELISA is not a ‘gold-standard’ serological test. While it has limited sensitivity and specificity, it has been useful especially in resource-poor areas in China. Additionally, as MAT is not sensitive for early infection and is not available in hospitals in remote areas, IgM ELISA has been used routinely in general laboratories. The national diagnostic criteria

for leptospirosis issued by the National Health and Family Planning Commission (NHFPC) (Ministry of Health of China, 2008).

3.3 Environmental indicators

Environmental indicators are grouped into climatic, physical environmental, and animal host data.

3.3.1 Climatic data

I used meteorological data, such as precipitation and relative humidity, from various sources depending on the scale of study. For country- and region-level analysis (Chapter 6 and 8), I used gridded raster meteorological data (i.e. precipitation) with 30 arc-seconds (~ 1-km) spatial resolution, which was extracted from WorldClim (v.2) (available at www.worldclim.org) (Hijmans et al. 2005; Fick and Hijmans 2017). For county-level analysis (Chapter 7), I used daily meteorological records from local weather stations that are made available by the China Meteorological Data Sharing Service System (http://cdc.cma.gov.cn/).

3.3.2 Physical environmental data

Elevation and slope at 30 arc-seconds (~ 1-km) spatial resolution was extracted from WorldClim (v.2) (available at www.worldclim.org) digital elevation model (DEM). Data for the normalized difference vegetation index (NDVI) with 250 metre spatial resolution were retrieved from MODIS Terra 13Q1 v006 Vegetation Indices 16-Day L3 Global. I used MODIS Terra 09A1 v006 with 500-meter spatial resolution to calculate a modified normalised water difference index (MNDWI) as a waterbodies or flood indicator. Land surface temperature (LST) (°C) data were extracted from MODIS Terra MOD11A2, with an 8-day composite and 1-km resolution. All MODIS products were downloaded from the United States Geological Survey (USGS) Earth Resources Observation and Science (EROS) Center (https://eros.usgs.gov/). Land cover data were obtained from the Data Center for Resources and Environmental Sciences, Chinese Academy of Sciences (RESDC) (http://www.resdc.cn).

3.3.3 Animal hosts data

I used data for livestock density (pig and cattle) from Gridded Livestock of the World version 2.01 with 1-km spatial resolution retrieved from FAO-GeoNetwork (http://www.fao.org/geonetwork/srv/en/main.home)(Robinson et al. 2014).

3.4 Socioeconomic data

I used county-level population data, for 2005 to 2016, from the China National Bureau of Statistics. Population density data were obtained from WorldPop, with 100-metre spatial resolution (http://www.worldpop.org.uk/data).An urban extent grid (v.1) raster dataset was obtained from the Global Rural-Urban Mapping Project (GRUMP v.1) (Center for International Earth Science Information Network - CIESIN - Columbia University et al. 2011) and used to determine the proportion in each county of urbanised and rural areas (http://sedac.ciesin.columbia.edu/data/set/grump-v1-urban-extents). I used a farmland productivity raster map, obtained from the Resource and Environmental Science Data Center of the Chinese Academy of Sciences (http://www.resdc.cn). Data for county-level gross domestic product (GDP) were obtained from gridded GDP of China with 1-km resolution (http://www.geodoi.ac.cn/weben/doi.aspx?Id=125) (Huang Y et al. 2014).

3.5 Methods

Data and methods used in each chapter are detailed in Table 3-2.

Table 3-2 Data and methods used in each chapter

Chapter	Data and methods
Chapter 4 **Objectives:** • To identify and critically appraise published literature reporting on the use of spatial tools for leptospirosis control • To formulate guidelines for the application of spatial analytical tools for leptospirosis control and surveillance	• Six databases were searched (Pubmed, Web of Science, EMBASE, Scopus, SciELO, and Zoological Record) from the 1930s to October 2018; • Articles that met inclusion and exclusions criteria are reviewed (*see* Section 4.3.2); • Data for study site, year of publication, study design (cross-sectional, case-control, cohort, etc.), infection data used (e.g. human, animal, or both), study objective (e.g. disease mapping, detect clustering, spatial and/or temporal modelling), methodologies (e.g. spatial/temporal analyses techniques, data sources, spatial and temporal resolution), predictors (e.g. environmental, climatic, socioeconomic, demographic), and outcomes (e.g. type of maps, findings) were extracted and summarised.
Chapter 5 **Objectives:** • To investigate the changes in notified morbidity and mortality of leptospirosis • To quantify the demographical, temporal and geographical heterogeneity of the burden during 2005 to 2015.	• Province-level leptospirosis case data from 1 January 2005 to 31 December 2015 were used. It included information about age, gender, occupation, date of onset of illness, diagnosis and death, place of residence (i.e. county and province) and case classification (suspect, clinical, and confirmed). • Yearly demographic data, including population data by age, sex, and occupation, were collected from the National Bureau of Statistics of China for each province from 2005 to 2015. • Incidence rate and mortality rate (per 100,000 people) was calculated. • Burden in terms of Disability-adjusted life-years (DALY) was estimated based on Torgerson et al. (2015) and Global Burden of Disease framework. • Changes in incidence, mortality, and burden were mapped using GIS software. • Simple linear regression was performed to detect trends. • A chi-square ($\chi 2$) test was performed to determine the difference in incidence, mortality rate, and burden by age, sex, and occupation in different time periods. P values of < 0.05 were considered statistically significant. • A multiplicative seasonal decomposition analysis was conducted using SPSS version 24 (IBM Corp., Armonk, NY, USA) to examine seasonality of leptospirosis incidence.
Chapter 6 **Objectives:** • To describes the spatiotemporal pattern of leptospirosis during 2005 to 2016 in China (global analysis) • To determine high-risk and low-risk counties • To examined whether the	• County-level leptospirosis case data from 1 January 2005 to 31 December 2016 were used. It included information about age, gender, occupation, date of onset of illness, diagnosis and death, place of residence (i.e. county and province) and case classification (suspect, clinical, and confirmed). • County-level population data were collected from the National Bureau of Statistics of China. • The disease standardized morbidity ratio (SMR) was calculated. • Spatial smoothing based on the empirical Bayes method was applied. R software package '*DCluster*' was used. • Spatial analyses involved tests for (i) global spatial autocorrelation Moran's I for each year and (ii) local indicators of spatial association (LISA) to determine cluster of counties with high or low rates (for each year). R software package '*spdep*' and GeoDA software were used.

Chapter	Data and methods
spatial pattern of leptospirosis has changed over the period • To characterise environmental and socio-demographic factors specifically attributed to high-risk and low-risk areas	• Descriptive analyses were performed to profile and compare demographical, ecological, and socioeconomic conditions of all cluster categories. Chi-square tests (for categorical variables) or one-way ANOVA or Kruskal-Wallis test with post hoc Tukey's honestly significant difference (HSD) test (for continuous variables) were performed. • Maps were created using GIS software
Chapter 7 ***Objectives:*** • To quantify the effect of environmental and socio-economic factors on the spatial variation of incidence of leptospirosis • To generate smoothed incidence of leptospirosis	• County-level leptospirosis infection data for 2005–16 were used and restricted to two regions: Upper Yangtze River Basin (UYRB) and Pearl River Basin (PRB). • County-level environmental and socioeconomic data were sampled: precipitation, LST, NDVI, MNDWI, elevation, slope, livestock density, crop production, population density, urban-rural, and GDP. • Non-spatial model: Spearman's correlation, univariate analysis Poisson Generalized Linear Model (GLMs). • Spatial autocorrelation in the residuals of the final models was examined using Moran's I analysis. • Bayesian conditional autoregressive - zero-inflated Poisson regression (CAR-ZIP) was constructed for each region. The ZIP approach was selected to overcome issues associated with excess zero counts in leptospirosis notifications (Lambert 1992; Agarwal et al. 2002). • Spatial effects of covariates on leptospirosis distribution was estimated for each region using Bayesian software OpenBUGS. • Maps of posterior mean and standard deviation were developed using GIS software.
Chapter 8 **Objective*:*** • To assess the short-term effect of climate variability and satellite-based physical environmental parameters on incidence of leptospirosis	• Monthly leptospirosis cases (1 January 2006 to 31 December 2016) were used. • Monthly meteorological data (precipitation and relative humidity) for the same period were used. • Monthly remote-sensed environmental data (NDVI, MNDWI, LST) for the same period were used. • Spearman's correlation, cross-correlation analysis, and seasonal decomposition analysis were performed. • Negative Binomial - Poisson Generalize linear model (GLM) was used to estimate the effects of climatic and environmental factors on the incidence of leptospirosis, controlling for seasonality. This approach was used to overcome issues related with overdispersion in the count data. • The goodness-of-fit of the models was examined based on Bayesian Information Criterion (BIC) and deviance. The model with lower BIC and deviance was chosen as the final model. • The seasonality and autocorrelations of the deviance residuals of the final models were checked by visually examining the sequence charts and partial autocorrelation function over time lags.

Chapter 4 Spatial epidemiological approaches to inform leptospirosis surveillance and control: a systematic review and critical appraisal of methods

This chapter has been published in *Zoonoses and Public Health* as a review paper. The concept and design of the methodology of the study was formulated by PWD (80%) with the assistance of RJSM (20%). PWD was responsible for data management (100%), data analyses (100%) and the interpretation of results (80%) was discussed in consultation with RJSM (10%) and all co-authors (10%). PWD was responsible for drafting the manuscript (100%). PWD was responsible for revision of the final version of the manuscript (90%), taking into account the comments and suggestions of RJSM (5%) and all co-supervisors (5%).

Reprinted from Zoonoses and Public Health, March 2019; Volume 66 Issue 2, pp.185-206. **Dhewantara, P.W.**, Lau, C.L., Allan, K.J., Hu, W., Zhang W., Mamun, A.A. and Soares Magalhães, R.J. Spatial epidemiological approaches to inform leptospirosis surveillance and control: A systematic review and critical appraisal of methods. Permission to reprint has been obtained from John Wiley and Sons.

4.1 Context

Spatial epidemiology is a specialist branch of epidemiology that deals with 'the description, analysis and interpretation of geographic variation in disease with respect to demographic, environmental, behavioral, socioeconomic, genetic, and infectious risk factors particularly at small-area level, involving disease mapping, geographic correlation studies, disease cluster and clustering' (Elliott and Wartenberg, 2004, p.998). Considering the role of place together with person and time in disease transmission is a valuable approach for generating and testing aetiological hypotheses about environmental determinants of disease. Moreover, spatial epidemiology can provide evidence to effectively guide public health agencies in distributing and improving resources for disease control and prevention in specific areas (Rezaeian et al., 2007). The literature review in Chapter 2 revealed that there are a considerable number of epidemiological studies aimed at understanding factors associated

with leptospirosis transmission, but few that have utilised a spatial analytical approach to explore and provide a better knowledge of the disease and to generate tools to support leptospirosis control. At the time when the research plan for this chapter was developed, there was no study that documented, reviewed, and comprehensively evaluated the application of spatial analytical techniques in the available leptospirosis studies. Therefore, in this chapter, I set out to perform a systematic review of studies to look at the general application of spatial analytical tools in the field of leptospirosis and the relative importance of such tools in supporting leptospirosis disease control programs. I also critically assess gaps in the methodology that could limit the benefits of these tools in helping health authorities to design targeted interventions for reducing the burden of leptospirosis.

The systematic review was conducted by following the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (Moher et al., 2009). At the first stage, I set out several keywords to search the literature in six databases: Scopus, Web of Science, Pubmed, EMBASE, SciELO and Zoological Records. Subsequently, I screened and identified studies that were eligible for review based on the predefined inclusion and exclusion criteria. At the second stage, I reviewed and critically evaluated the methods used in those studies regarding the source of epidemiological data as well as analytical approaches (e.g., the spatial unit of analysis, visualisation, spatial exploration tools and modelling techniques). The systematic review demonstrated that in recent years we have seen a substantial growth in leptospirosis studies that use spatial epidemiological approaches, highlighting the relative importance of such approaches to better understand patterns and their underlying factors. However, while there has been an increase in number, I found that only a few studies had generated spatially explicit predictive maps for leptospirosis. In addition, the quality of the epidemiological data, the relevance and complexity of factors incorporated in the analysis, and the spatial analytical methods used among studies differed widely, which prevented comparison between studies. Therefore, based on these findings and to improve the value and practicality of maps in supporting leptospirosis disease control and surveillance, I proposed a general framework which provides clear guidance to adequately design and apply spatial analyses.

4.2 Introduction

Leptospirosis is a zoonotic disease of major public health and animal health importance caused by pathogenic spirochete belonging to the genus *Leptospira* that is common in tropical and sub-tropical countries (Faine et al., 1999; Bharti et al., 2003). Annually worldwide, it is estimated that at least one million human cases and 58,900 deaths occur leading to the loss of approximately 2.9 million DALYs (Costa et al., 2015; Torgerson et al., 2015). In animals, *Leptospira* infection can lead to reproductive failure in livestock (e.g., abortion, premature progeny, stillbirths, infertility, and fetal mummification), decreased milk production and systemic illness, which may be fatal and cause significant economic losses (Donahue et al., 1995; Martins et al., 2012; Ellis, 2015). Hence, it is imperative to improve the delivery of disease control strategies in both human and animals.

Leptospirosis transmission is driven by a complex interaction of environmental, socioeconomic, demographic and individual determinants which result in considerable geographical and temporal variation in infection risk (Lau et al., 2010; Mwachui et al., 2015). Infection may occur through contact with infected reservoir animals' urine and tissues, or with *Leptospira*-contaminated soil or water. More than 300 serovars of *Leptospira* spp, categorised into 25 serogroups, have now been identified worldwide (Levett, 2001). There are 10 pathogenic species and five intermediate species which occasionally cause mild clinical manifestations (Xu et al., 2016b). A wide range of animals including domestic (e.g., livestock and companion animals), wildlife, and rodents have been identified as *Leptospira* carriers (Adler and de la Pena Moctezuma, 2010; Haake and Levett, 2015).

The incidence of leptospirosis is geographically and temporally varied, and it is strongly associated with climatic, environmental and local socioeconomic factors (Cosson et al., 2014). A higher incidence is reported in tropical, humid and temperate regions, especially during the wet season, disproportionately affects deprived populations both in rural and urban areas (Ko et al., 1999). Numerous leptospirosis outbreaks, particularly in urban setting are often linked with severe flooding resulting from heavy rainfall or cyclones (Ko et al., 1999; Amilasan et al., 2012; Dechet et al., 2012). In rural areas, leptospirosis is closely correlated with agricultural processes such as rice paddy harvesting and livestock husbandry (Prabhakaran et al., 2014; Ellis, 2015). Ecological degradation of living conditions due to rapid population growth and urbanisation coupled with climate change are considered to be some

of the most important driving forces behind current and future leptospirosis outbreaks (Lau et al., 2010)

The complexity in transmission pathways for leptospirosis constitutes a significant challenge for control strategies, especially in remote and poor resource endemic areas. There is a need to develop accurate and cost-effective tools to improve existing surveillance and strengthen control strategies. Geographic information systems (GIS), remote sensing (RS), and geospatial statistics tools have now been greatly enhanced and used in public health studies and have the potential to help improve disease epidemiology and control. The present paper is aimed to comprehensively review the use of spatial analytical methods in leptospirosis studies to help improve research designs and lay the foundation for further leptospirosis studies to support more effective surveillance and control programs. Leptospirosis transmission strongly involves interdependent interaction between animals, humans, and the environment (Rabinowitz et al., 2013). Hence, in this paper, we focused on how spatial and temporal approaches have been used in leptospirosis studies of both animals and humans. Future research directions on the application of spatiotemporal analysis in leptospirosis are also discussed.

4.3 Methods

4.3.1 Search strategy

Using standard systematic review and meta-analysis (PRISMA) guidelines (Moher et al., 2009), I searched Pubmed, Web of Science, EMBASE, Scopus, SciELO, and Zoological Record for peer-reviewed articles published until 31 October 2018. In order to identify other relevant articles not captured by the initial searches, I manually searched the reference lists of included articles (Hopewell et al., 2007). To retrieve relevant articles, I used a combination of the following search terms: spatial, spatiotemporal, geographical information system, mapping, remote sensing, prediction, outbreak, cluster, and leptospirosis (Appendix B: Table B-1). No restrictions on language or publication date were applied.

All articles retrieved from the databases were stored and checked for duplicates using EndNote™ (Thomson Reuters, Philadelphia, PA, USA) reference manager. All unique titles and abstracts (when available) were screened to identify relevant publications that met

inclusion criteria by one reviewer (PWD). Full review was then applied to all articles available in a full text for eligibility by two reviewers (PWD and RJSM). Eligible articles were grouped into three categories: studies that used data on (i) human, (ii) animal, or (iii) both human and animal infection.

4.3.2 Inclusion and exclusion criteria

Studies were eligible for inclusion if they applied one or more spatial analyses techniques including visualisation (defined as mapping leptospirosis infection data to illustrate spatial patterns of disease distribution), exploration (defined as applying statitistical tools to analyse such patterns, including whether the infection data were clustered or random), and modelling (e.g., utilise spatial and non-spatial data to explore associated risk factors for infection, to quantify spatial variation in risk, and to develop spatial and/or temporal predictive models).

Papers were excluded if: (i) abstract or full paper not available; (ii) experimental design studies, case series or case reports, studies on the genetic characterisation of *Leptospira* spp. without involving spatial analyses; (iii) ecological or environmental surveys associated with animal reservoirs without providing *Leptospira* infection data; (iv) non-spatial studies; (v) studies that dealt with seasonality with no further attempt to develop temporal predictive models; or (vi) short communications, conference proceedings, commentaries, review articles, books or book sections.

4.3.3 Data extraction

For each eligible article, I extracted and summarised data on study location, year of publication, study design (e.g., cross-sectional, case-control, cohort), leptospirosis epidemiological data (e.g., human, animal, or both) and diagnostic methods used, study objective (e.g., disease mapping, detect clustering, spatial and/or temporal modelling), spatial and/or temporal analysis methods (e.g., visualisation, exploration, modelling), predictors (e.g. environmental, climatic, socioeconomic, demographic), and outcomes (e.g. maps, findings).

4.4 Results

4.4.1 General characteristics of studies included in the review

A total of 1468 records were identified from six databases and 23 additional records were identified through manual searches from bibliographic lists of included papers. A total of 690 unique records remained after the removal of 778 duplicates. A total of 263 papers published until October 2018 met our inclusion criteria and were included for full-text review. After full-text review, a total of 115 articles from 41 countries were finally included in our systematic review (Figure 4-1).

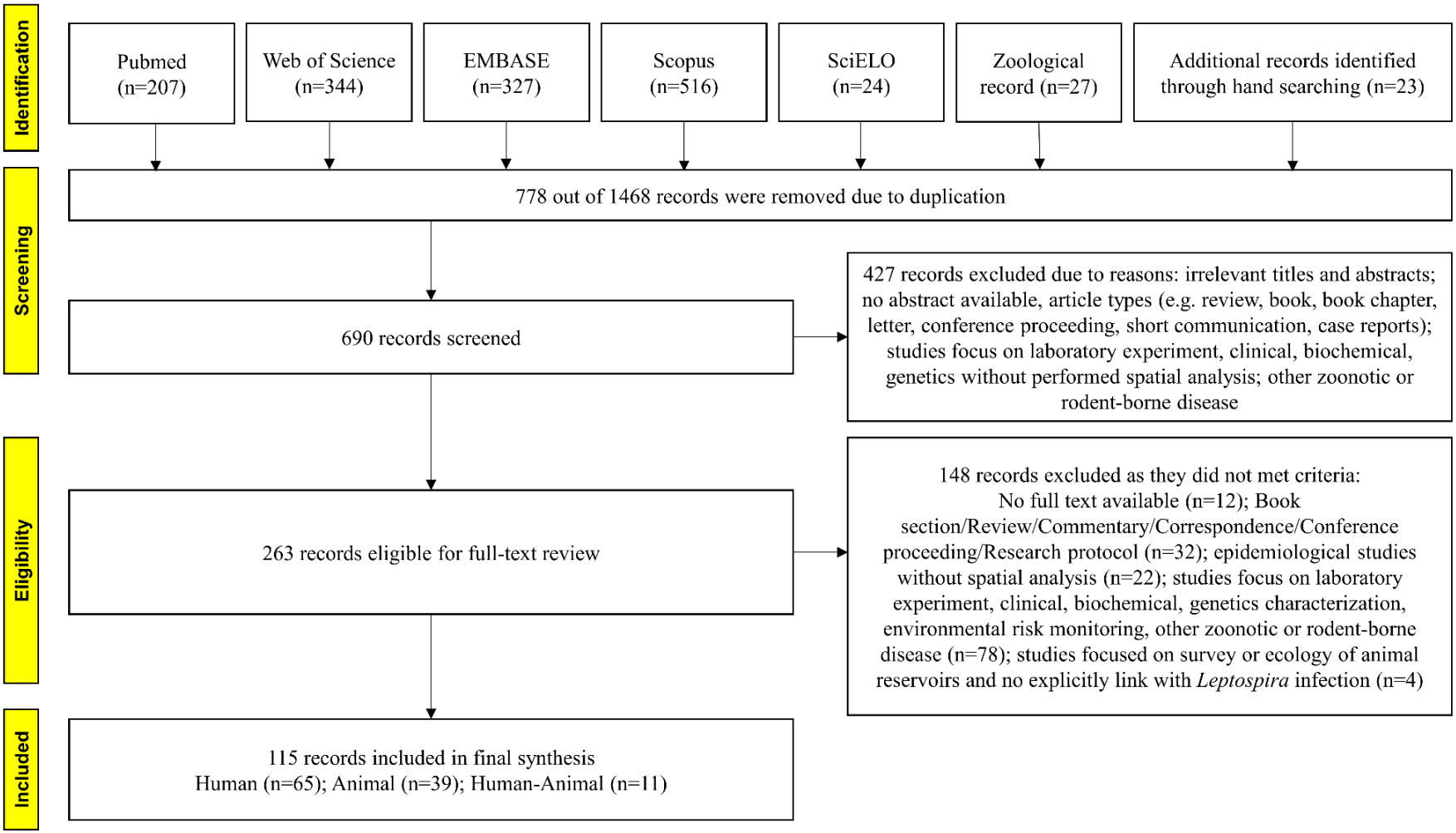

Figure 4-1 Search and selection process based on PRISMA framework (Moher et al., 2009). Total of 115 records published until 31 October 2018 were reviewed.

The trend in number of publications reporting the use of spatiotemporal approaches to understand the epidemiology of human and/or animal leptospirosis has been increasing with most studies occurring after 2010 (Figure 4-2). A total of 65 studies used data on human infection, 39 studies used animal infection data, and 11 studies used data on both human and animal infection. Studies were performed either at the sub-national (n = 79/115) level, national level (n = 35/115) or regional level (n = 1/115). No global or continental-scale studies were reported in any of the papers included in our review.

The majority of leptospirosis studies were reported from the Americas, especially in Brazil (24.61%, n = 16/65) for human leptospirosis studies and the United States (28.20%, n = 11/39) for animal leptospirosis studies (Figure 4.3). Studies using both human and animal infection data were conducted in eight countries, mainly in Southeast Asia (45%, n = 5/11), including Thailand, Indonesia, and the Philippines.

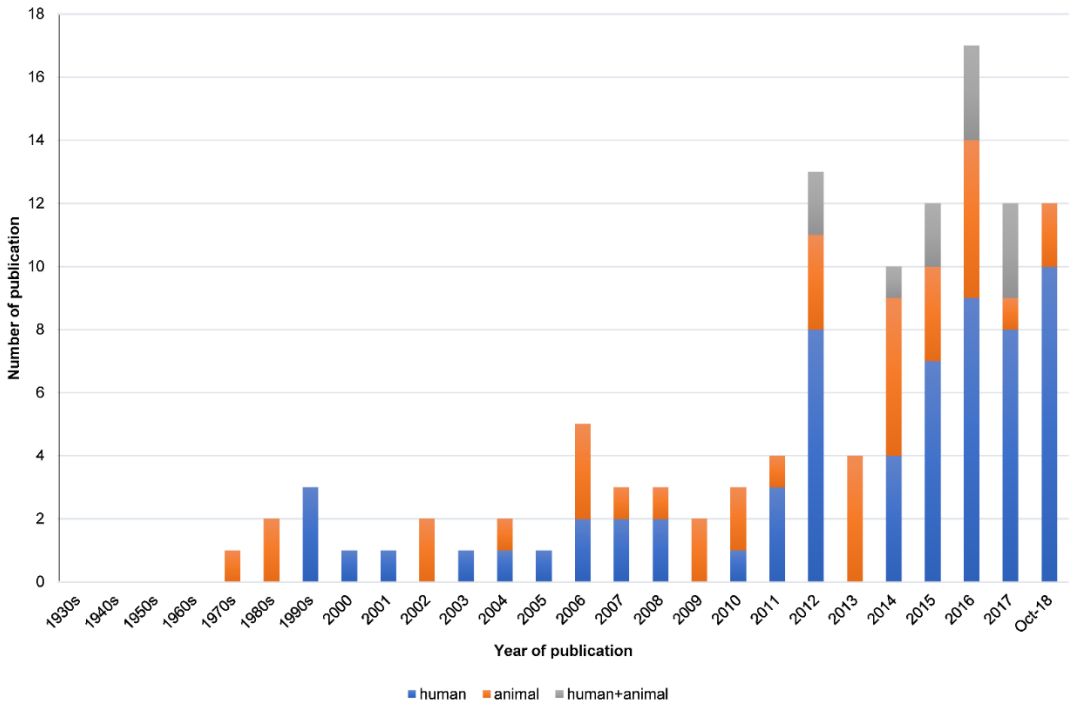

Figure 4-2 Number of included articles in the review classified by time period. Articles were grouped into three categories based on the epidemiological data used: human, animal, and both human and animal infection data. The use of spatial analytical methods in the field of leptospirosis appears to grow since 1970.

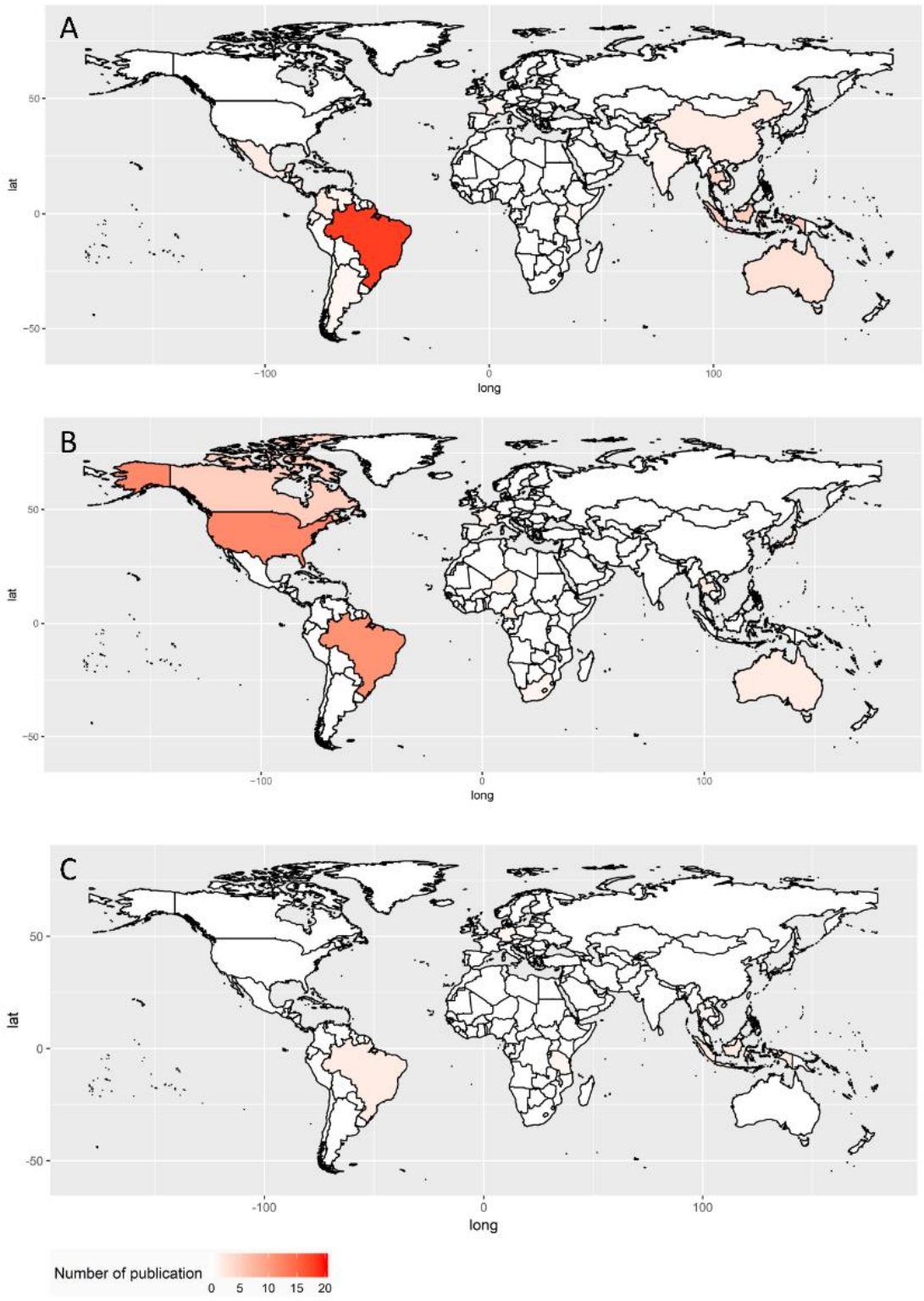

Figure 4-3 Distribution of selected papers on spatial and/or temporal analysis of human leptospirosis (A), animal leptospirosis (B), and both human and animal leptospirosis (C).

From the total of 115 eligible articles, 106 (92.17%) studies in 37 countries dealt with spatial analyses which included visualisation (90.56%, n = 97/106), exploration (33.01%, n = 35/106), and modelling (47.16%, n = 50/106). Whereas, nine articles applied temporal or time-series modelling techniques as tools to predict human (n = 7) and animal (n = 2) leptospirosis incidence. Among those studies that included spatial analysis, few studies (15.09%, n = 16/106) conducted visualisation, exploration, and modelling concurrently (Della Rossa et al., 2016; Gracie et al., 2014; Lau et al., 2012a; Mayfield et al., 2018a; Miyama et al., 2018; Mohd Radi et al., 2018; Raghavan et al., Brenner, 2012; Robertson et al., 2012; Soares et al., 2010; Suwanpakdee et al., 2015; Tassinari et al., 2008) (Appendix B: Table B-2).

4.4.2 Leptospirosis infection data sources, case definitions and diagnostic tests

Leptospirosis infection data were mostly obtained from national notification system (45.21%, n = 52/115), medical records or laboratory databases (include hospital admission database) (22.60%, n = 26/115). Only 40 studies (34.78%, n = 40/115) used infection data generated by surveys. Most studies were cross-sectional (86.95%, n = 100/115), few (6.08%, n = 7/115) were case-control studies (Ghneim et al., 2007; Hennebelle et al., 2013; Raghavan et al., 2011, 2013; Suryani et al., 2016; Ward, 2002a; Ward et al., 2004) and only six studies (5.21%) employed a prospective cohort design (Deshmukh et al., 2019; Hagan et al., 2016; Ko et al., 1999; Ledien et al., 2017; Mišić-Majerus, 2014; Reis et al., 2008).

In terms of diagnostic approaches, human infection data used were most commonly based on microscopic agglutination test (MAT) (50.76%, n = 33/65), enzyme linked immunosorbent assay (ELISA) (33.84%, n = 22/65) or polymerase chain reaction (PCR) (13.84%, n = 9/65). Eleven studies used culture in combination with serological tests or PCR (Biscornet et al., 2017; Desvars et al., 2011; Jansen et al., 2005; Pijnacker et al., 2016; Rood et al., 2017; Slack et al., 2006, 2007; Soares et al., 2010; Suwanpakdee et al., 2015; Tassinari et al., 2008; Weinberger et al., 2014) to diagnose human infection. As with human studies, the majority of animal studies also used MAT (53.84%, n = 21/39) to determine animal infection status, and three studies used ELISA only (Miyama et al., 2018; Pijnacker et al., 2016; Soares et al., 2010). Eight studies used culture in combination with serological tests or PCR.

Thirty-one (47.69%, n = 31/65) human leptospirosis studies, four studies (10.25%, n = 4/39) on animal leptospirosis, and four studies (36.36%, n = 4/11) that used animal and human

infection data did not clearly describe the case definitions of leptospirosis infection. And, 28 studies did not specifically describe the diagnostic techniques used.

4.4.3 Mapping the geographical distribution of leptospirosis

Mapping human leptospirosis data

Most spatial studies (96.55%, n = 56/58) produced human infection maps and most utilised data obtained from the national disease surveillance notification systems (73.21%, n = 41/56). Maps were produced to depict incidence or prevalence in certain administrative areas (48.21%; n = 27/56) either at regional (n = 1) (Schneider et al., 2017), national (n = 11) (Gonwong et al., 2017; Jansen et al., 2005; Lau et al., 2012a; Massenet et al., 2015; Robertson et al., 2012; Rood et al., 2017; Schneider et al., 2012; Shi et al., 1995; Stevens et al., 2011; van Alphen et al., 2015; Zhao et al., 2016) or sub-national scales (n = 15) (Barcellos et al., 2000, 2003; Chaiblich et al., 2017; Garcia-Ramirez et al., 2015; Gracie et al., 2014; Herbreteau et al., 2006; Ko et al., 1999; Lau et al., 2015; Mišić-Majerus, 2014; Mohammadinia, 2017; Mohd Radi et al., 2018; Myint et al., 2007; Schneider et al., 2015; Soares et al., 2010; Vega-Corredor and Opadeyi, 2014). Twelve studies used Kernel density estimation technique to generate smoothed distribution maps of disease counts, risk or population density (Chaiblich et al., 2017; Cook et al., 2017; de Melo et al., 2011; Deshmukh et al., 2019; Filho et al., 2014; Lau et al., 2012b, 2012c; Mohd Radi et al., 2018; Reis et al., 2008; Rood et al., 2017; Tassinari et al., 2004; Vega-Corredor and Opadeyi, 2014). Two studies constructed suitability maps for leptospirosis occurrence at national level (Sanchez-Montes et al., 2015; Zhao et al., 2016).

Seroprevalence maps were produced by three studies (5.35%, n = 3/56) based on ELISA (Gonwong et al., 2017) or MAT (Lau et al., 2012a; Lau et al., 2016). Seropositivity maps were created based on serological (MAT) data collected from the field surveys (Lau et al., 2012b, 2012c). Six studies mapped the distribution of predominant serovars identified from field studies (Lau et al., 2012a, 2012b, 2012c, 2015; Myint et al., 2007; Slack et al., 2007). No serogroup or serovar distribution maps at regional and global scale were reported. Spatiotemporal maps were created (21.42%, n = 12/56) (Baquero and Machado, 2018; Dhewantara et al., 2018; Garcia-Ramirez et al., 2015; Gracie et al., 2014; Hagan et al., 2016; Lau et al., 2015; Robertson et al., 2012; Soares et al., 2010; Sulistyawati et al., 2016;

Suwanpakdee et al., 2015; Tassinari et al., 2004, 2008; van Alphen et al., 2015) to illustrate changes in distribution (Della Rossa et al., 2016; Gracie et al., 2014; Lau et al., 2015; Schneider et al., 2012; Soares et al., 2010; Sulistyawati et al., 2016; Suwanpakdee et al., 2015; Tassinari et al., 2004, 2008), disease rates/risks (Baquero and Machado, 2018; Garcia-Ramirez et al., 2015; Hagan et al., 2016; Robertson et al., 2012; Suwanpakdee et al., 2015; van Alphen et al., 2015), or burden in terms of disability-adjusted life years (DALYs) (Dhewantara et al., 2018). One set of sub-national spatiotemporal maps describing changes in serovar-specific cases was produced at state level in Australia (Lau et al., 2015). Summary of the studies on mapping leptospirosis is provided in Appendix B: Table B-3 and Table B-4.

Mapping animal leptospirosis data

Thirty-four studies used mapping approaches to describe spatial heterogeneity in incidence/prevalence, serostatus, or distribution of *Leptospira* infections among various reservoir animals including companion animals, livestock, rodents, and wildlife. Few studies created prevalence maps at national (2.94%; n = 1/34) (Suwancharoen et al., 2016) or sub-national (14.70%; n = 5/34) (Filho et al., 2014; Hesterberg et al., 2009; Machado et al., 2016; Scolamacchia et al., 2010; Silva et al., 2018) levels. The infection data of companion animals (e.g., dogs) were obtained commonly from laboratory databases/medical records deposited at veterinary clinics (32.35%, n = 11/34). Serovar-specific prevalence in livestock was mapped (8.82%, n = 3/34) in Australia (Elder et al., 1986; Elder and Ward, 1978) and Japan (Miyama et al., 2018). Livestock, rodents, or wildlife-animals infection data were often collected from animal sampling. Few studies reported the use of Kernel density risk maps (n = 2) (Filho et al., 2014; Hashimoto et al., 2015) and suitability maps (n = 1) (Dobigny et al., 2015). No spatiotemporal maps for animal leptospirosis was reported.

Mapping human and animal infection data

Eleven articles used both human and animal infection data (Assenga et al., 2015; Biscornet et al., 2017; Chadsuthi et al., 2017; Cipullo and Dias, 2012; Della Rossa et al., 2016; Fonzar and Langoni, 2012; Hurd et al., 2017; Pijnacker et al., 2016; Sumanta et al., 2015; Villanueva et al., 2014; Widiastuti et al., 2016), but only 64% (n = 7/11) of studies incorporated both human and animal infection data into their maps. One study created a national level seroprevalence

map for both humans and animals (Chadsuthi et al., 2017). At the sub-national level, six studies mapped the geographic co-distribution of serogroups (Assenga et al., 2015; Villanueva et al., 2014) or *Leptospira* seropositivity (Cipullo and Dias, 2012; Fonzar and Langoni, 2012; Sumanta et al., 2015; Widiastuti et al., 2016) in both humans and animals. No maps have been produced on describing spatial-temporal changes in risks were identified in this group of study.

4.4.4 Exploratory analysis: detecting spatial autocorrelation and disease clustering

On studies that used human infection data

A wide range of classic global and local spatial clustering analyses were used to investigate large-scale and small-scale variations in patterns of disease distribution (Table 4-1; Appendix B: Table B-5). Eight studies used global Moran's *I* to test spatial clustering on areal data (Cook et al., 2017; Della Rossa et al., 2016; Goncalves et al., 2016; Gracie et al., 2014; Mohammadinia et al., 2017; Rood et al., 2017; Soares et al., 2010; Suryani et al., 2016). Two studies analysed clustering of point data by using global Moran and average nearest neighbour methods (Mohd Radi et al., 2018; Suryani et al., 2016). While Knox test was used to assess global spatial clustering of the leptospirosis over space and time (Bennett and Everard, 1991). Localised spatial clustering techniques were applied to determine hotspots, including Local Indicators of Spatial Association (LISA) (n = 3) (Mohd Radi et al., 2018; Rood et al., 2017; Soares et al., 2010) and Getis and Ord's (G_i^*) (n = 3) (Hassan and Tahar, 2016; Mayfield et al., 2018a; Suwanpakdee et al., 2015). Both global and local tests for clustering were only applied in a few studies (14.28%) (n = 3/21) (Lau et al., 2012a; Rood et al., 2017; Soares et al., 2010).

Locating the high-risk clusters across space, seven studies used SaTScan (Kulldorff and Nagarwalla, 1995) at national (Gutierrez and Martinez-Vega, 2018; Lau et al., 2012a; Massenet et al., 2015; Robertson et al., 2012) and sub-national scale (Deshmukh et al., 2019; Sulistyawati et al., 2016; Tassinari et al., 2008). The maximum circular spatial window was often set at 50% (Gutierrez and Martinez-Vega, 2018; Lau et al., 2012a; Massenet et al., 2015; Sumanta et al., 2015) of the population at risk. The temporal window used ranged from 30 days (Tassinari et al., 2008) to one year (Massenet et al., 2015); although five studies did

not explicitly define spatial or temporal windows (Deshmukh et al., 2019; Robertson et al., 2012; Sulistyawati et al., 2016).

Table 4-1 Summary of approaches used to measure spatial clustering in human, animal, and both human-animal leptospirosis studies

Spatial clustering methods		N	Infection data		
			Human (n=21)	Animal (n=13)	Both human and animal (n=1)
Global measures	Moran's I / Global Moran	11	Cook et al. (2017); Della Rossa et al. (2016); Goncalves et al. (2016); Gracie et al. (2014); Mohammadinia et al. (2017); Mohd Radi et al. (2018); Rood et al. (2017); Soares et al. (2010); Suryani et al. (2016)	Alton et al. (2009)	Hurd et al. (2017)
	Geary's c	1			Hurd et al. (2017)
	Cuzick-Edwards *K*th neighbour test	3		Hennebelle et al.(2013); Raghavan et al., (2012); Scolamacchia et al. (2010)	
	Average nearest neighbour	2	Mohd Radi et al. (2018); Suryani et al. (2016)		
	Knox test	1	Bennett and Everard (1991)		
	Semivariogram/Empirical variogram	6	Lau et al. (2012a)	Alton et al. (2009); Raghavan et al. (2011, 2012, 2013)	Hurd et al., 2017
Local measures / cluster detection	LISA / Local Moran	3	Mohd Radi et al. (2018); Rood et al.		

Spatial clustering methods		N	Infection data		
			Human (n=21)	Animal (n=13)	Both human and animal (n=1)
			(2017); Soares et al. (2010)		
	Getis-Ord G*	3	Hassan and Tahar (2016); Mayfield et al. (2018a); Suwanpakdee et al. (2015)		
	Bernoulli/Poisson spatial scan statistics	10	Cipullo and Dias (2012); Deshmukh et al. (2019); Lau et al. (2012a)	Alton et al. (2009); da Silva et al. (2006); Hennebelle et al. (2013); Himsworth et al. (2013); Miyama et al. (2018); Nicolino et al. (2014); Sumanta et al. (2015)	
	Poisson/Binomial/Multinomial space-time scan statistics	8	Gutierrez and Martinez-Vega (2018); Massenet et al. (2015); Robertson et al. (2012); Sulistyawati et al. (2016); Tassinari et al. (2008)	Alton et al. (2009); Gautam et al. (2010); Hennebelle et al. (2013); Ward, (2002a)	
	FlexScan spatial cluster test	1			Hurd et al. (2017)

On studies that used animal infection data

Eleven articles tested for global or local spatial clustering on the animal infection data. Few studies applied both global and local tests (n = 2) (Alton et al., 2009; Hennebelle et al., 2013). A variety of methods were used including global Moran's *I* (n = 1) (Alton et al., 2009), Cuzick and Edwards' *k*-nearest neighbour and variogram (n = 3) (Hennebelle et al., 2013; Raghavan et al., 2012; Scolamacchia et al., 2010) to detect spatial clustering of infected animals. Nine studies investigated clusters of infected animals using scan statistics, including spatial scan test, temporal and spatial scan statistics, spatial permutation test (69.23%, n = 9/13) (Alton et al., 2009; da Silva et al., 2006; Gautam et al., 2010; Hennebelle et al., 2013; Himsworth et al., 2013; Miyama et al., 2018; Nicolino et al., 2014; Sumanta et al., 2015; Ward, 2002a).

On studies that used both human and animal infection data

Only one study explored spatial pattern of both human and animal infection data. This study used a variety of spatial clustering methods including Moran's *I* and Geary's c as well as employing several different cluster detection techniques using SaTScan and FlexScan software (Hurd et al., 2017).

4.4.5 Modelling risk of leptospirosis infection and spatial risk prediction

Modelling risk of human infection

Thirty-one studies (53.44%, n = 31/58) quantified the effect of a set of selected explanatory variables on leptospirosis incidence/prevalence, at national-level (n = 15/31) and sub-national level (n = 17/31) (Table 4-2). The summary of studies on modelling leptospirosis risk and covariates used in the study was detailed in Appendix B (Table B-6 and Table B-7, respectively). Most studies assessed the association between environment (e.g., land use, altitude, flood risk) (n = 29/31) or climatic factors (e.g., precipitation) (n = 18/31) and leptospirosis incidence/prevalence (Figure 4-4). Half of the studies utilised environmental data, including land cover, elevation, Normalized Difference Vegetation Index (NDVI) Normalized Difference Water Index (NDWI) and climatic data obtained from remote-sense databases (e.g. MODIS, Landsat) (Baquero and Machado, 2018; Gracie et al., 2014; Lau et al., 2012a, 2012b, 2016; Schneider et al., 2012; Suwanpakdee et al., 2015; Vega-Corredor

and Opadeyi, 2014; Zhao et al., 2016) (Appendix B: Table B-8). A recent study proposed the use of modified NDWI (MNDWI) to estimate the risk of *Leptospira* infection following flood (Ledien et al., 2017).

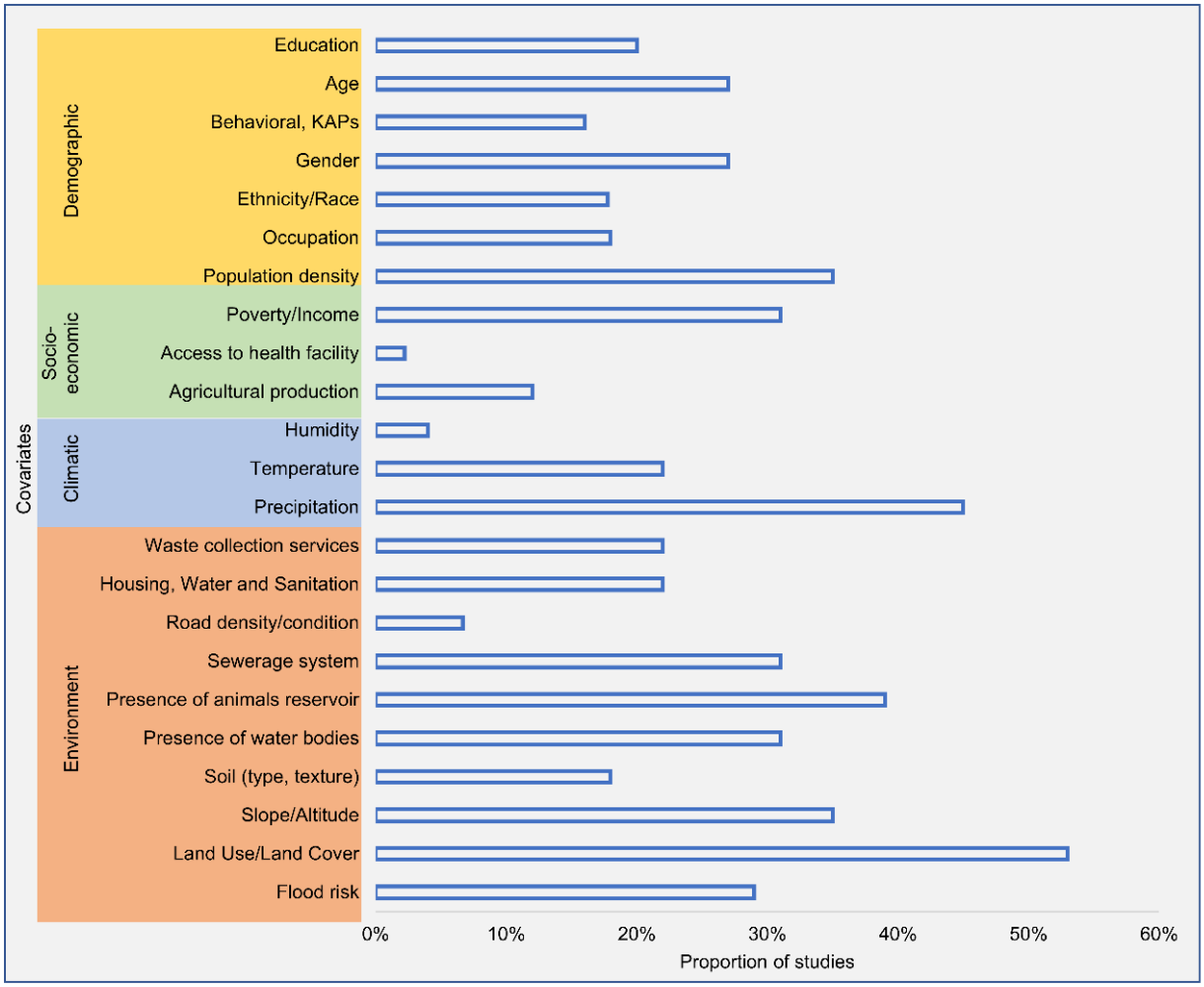

Figure 4-4 Covariates included in the models and the proportion of studies that incorporated those variables. Land-use/land cover (e.g., NDVI, type of residence, presence of paddy field), precipitation, altitude, presence of animal reservoirs, population density, and poverty were the most common predictors included in the models to estimate risk of leptospiral infection.

Table 4-2 Summary of modelling techniques used in eligible leptospirosis studies

Modelling approach		N	Leptospirosis epidemiological data		
			Human (n=31)	Animal (n=17)	Human and animal (n=3)
Regression	Linear regression/Generalized linear models (GLMs) /Poisson regression/Binomial GLM/Quadratic regression	14	Ledien et al. (2017); Mohd Radi et al. (2018); Reis et al. (2008); Schneider et al. (2012); Vega-Corredor and Opadeyi (2014)	Biscornet et al. (2017); Elder et al. (1986); Himsworth et al. (2013); Ivanova et al. (2012); Major et al. (2014); Miyama et al. (2018)	Chadsuthi et al. (2017); Della Rossa et al. (2016); Hurd et al. (2017)
	Logistic regression/multilevel mixed-effect logistic models/multinomial logistic models	17	Cook et al. (2017); Lau et al. (2012a, 2012b, 2016); Robertson et al. (2012); Schneider et al. (2012); Tassinari et al. (2008); Zhao et al. (2016)	Alton et al. (2009); Ghneim et al. (2007); Himsworth et al. (2013); Raghavan et al. (2011, 2012, 2013); Silva et al. (2018); Ward et al. (2004)	Chadsuthi et al. (2017)
	Generalized additive models (GAMs)	3	Hagan et al. (2016); Reis et al. (2008)	Bier et al. (2013)	
	Negative binomial (NB)/Zero-inflated negative binomial regression models	2	Schneider et al. (2015); Suwanpakdee et al. (2015)		
	Geographical weighted regression (GWR)	5	Mayfield et al. (2018a); Mohammadinia et al. (2017); Mohd Radi et		

Modelling approach		N	Leptospirosis epidemiological data		
			Human (n=31)	Animal (n=17)	Human and animal (n=3)
			al. (2018); Vega-Corredor and Opadeyi (2014); Widayani et al. (2016)		
	Generalized linear mixed models (GLMMs)	2	Tassinari et al. (2008)	Alton et al. (2009)	
	Boosted regression trees (BRTs)	2	Ledien et al. (2017)	White et al., (2017)	
Autoregressive models	Simultaneous Auto Regression (SAR)	1	Rood et al. (2017)		
Disease distribution modelling	Maximum entropy (MAXENT) Ecological niche models, Genetic Algorithm for Rule Set Production (GARP)	2	Sanchez-Montes et al. (2015); Zhao et al. (2016)		
Bayesian approach	Integrated Nested Laplace Approximation (INLA) + Stochastic Partial Differential Equations (SPDE); Bayesian inference; Besag, York and Mollie (BYM) model; Spatial Bayesian Networks	4	Baquero and Machado (2018); Hagan et al. (2016); Reis et al. (2008); Mayfield et al. (2018b)		
Interpolation technique	Kriging	3	Deshmukh et al. (2019); Dozsa et al. (2016); Goncalves et al. (2016)		
Correlation	Pearson correlation / Spearman's correlation	4	Gonwong et al. (2017); Gracie et al.	Elder and Ward (1978)	

Modelling approach		N	Leptospirosis epidemiological data		
			Human (n=31)	Animal (n=17)	Human and animal (n=3)
			(2014); Soares et al. (2010)		
	Chi-square test	3	Barcellos and Sabroza (2001); Goncalves et al. (2016)	Ghneim et al. (2007)	
	ANOVA/Bivariate analysis	3	Barcellos and Sabroza (2000); Schneider et al. (2012); Suryani et al. (2016)		
	Mallow's Cp statistics	1		Elder et al. (1986)	
Decision analysis	Decision tree analysis	1		Bier et al. (2012)	

About half of modelling studies included host-related variables such as the presence of animals (e.g., rodents, pigs, dogs, livestock) or animal population size or density into the models (Cook et al., 2017; Dozsa et al., 2016; Hagan et al., 2016; Lau et al., 2012a, 2012b; 2016; Mayfield et al., 2018a, 2018b; Reis et al., 2008; Schneider et al., 2012; Suwanpakdee et al., 2015; Zhao et al., 2016). Animal hosts data were collected either from animal surveys (e.g., trapping), livestock census data, or from publicly available GIS databases (e.g., Food and Agricultural Organization-GeoNetwork).

Twenty-one studies (67.72%, n = 21/31) included socioeconomic variables (e.g., population density, income, agricultural production and urbanization) into their models. Population density (Ledien et al., 2017; Zhao et al., 2016) and socioeconomic indicators (e.g., GDP or poverty rate) (Baquero and Machado, 2018; Mayfield et al., 2018a, 2018b; Schneider et al., 2015; Zhao et al., 2016) were the most common predictors included in the models. Individual-level variables (e.g., age, gender, occupation, education/literacy, behavioral risk, or ethnicity) were incorporated in 16 out of 31 (51.61%) studies.

Traditional regression analyses were the most common statistical modelling technique used to quantify the association between these variables and leptospirosis incidence/prevalence (Table 4-2). Simultaneous autoregressive models (n = 1) (Rood et al., 2017) and boosted regression tree (BRT) models (n = 1) (Ledien et al., 2017) were also reported. To address the spatial non-stationarity of relationships between the spatial distribution of leptospirosis incidence and environmental and sociodemographic factors, five studies applied geographically weighted regression (GWR) (Mayfield et al., 2018a; Mohammadinia et al., 2017; Mohd Radi et al., 2018; Vega-Corredor and Opadeyi, 2014; Widayani et al., 2016). Two studies used ecological niche modelling using Maxent (Zhao et al., 2016) and Genetic Algorithm for Rule-set Production (GARP) (Sanchez-Montes et al., 2015) at a national scale (Sanchez-Montes et al., 2015; Zhao et al., 2016), and three studies applied a Bayesian approach to their analyses (n = 3) (Baquero and Machado, 2018; Hagan et al., 2016; Reis et al., 2008). In addition, the spatially explicit Bayesian Networks (BNs) have been introduced by one Fijian study (Mayfield et al., 2018b). Overall, only two studies completely constructed spatially-structured models (n = 2/31) (Lau et al., 2012a; Rood et al., 2017) in which model parameters were estimated (SAR and logistic regression, respectively), global and local

spatial autocorrelation in the residuals of the models were tested (using global Moran's *I* and semi-variogram), and spatial predictive maps were generated.

Modelling risk of animal infection

Seventeen studies (43.36%, n = 17/39) conducted in six countries assessed the association between incidence (n = 7) (Ghneim et al., 2007; Major et al., 2014; Raghavan et al., 2011, 2012, 2013; Ward et al., 2004; White et al., 2017) or prevalence (n = 10) (Alton et al., 2009; Bier et al., 2012, 2013; Biscornet et al., 2017; Elder et al., 1978, 1986; Himsworth et al., 2013; Ivanova et al., 2012; Miyama et al., 2018; Silva et al., 2018) with various predictors at national (n = 6) and sub-national (n = 11) levels. As with human studies, the effect of physical environmental (64.70%, n=11/17) (Alton et al., 2009; Biscornet et al., 2017; Elder et al., 1986; Ghneim et al., 2007; Ivanova et al., 2012; Raghavan et al., 2011, 2012, 2013; Silva et al., 2018; Ward et al., 2004; White et al., 2017) and climatic factors (52.94%, n=9/17) (Elder et al., 1978, 1986; Ghneim et al., 2007; Himsworth et al., 2013; Ivanova et al., 2012; Major et al., 2014; Silva et al., 2018; Ward et al., 2004; White et al., 2017) on animal infections was the most commonly studied. Nine studies used RS-based environmental data (Dobigny et al., 2015; Ghneim et al., 2007; Ivanova et al., 2012; Raghavan et al., 2011, 2013; Silva et al., 2018; Ward et al., 2004; White et al., 2017) including land cover/land use, elevation, or slope (Appendix B: Table B-7). Eight studies included parameters on the presence of other animal species in their models (Bier et al., 2012, 2013; Ghneim et al., 2007; Miyama et al., 2018; Raghavan et al., 2012; Silva et al., 2018; Ward et al., 2004; White et al., 2017). Only three studies assessed the role of socioeconomic covariates (e.g., household income of the owner) on animal infection (n = 2) (Raghavan et al., 2012; Silva et al., 2018; White et al., 2017). The individual-level variables, such as animal age, sex, breed, and behaviours, were less reported (n = 4) (Alton et al., 2009; Bier et al., 2013; Himsworth et al., 2013; Silva et al., 2018).

In terms of modelling techniques, regression models were most commonly used (n = 12/17) (Table 4-2). Among those, only three studies accounted for spatial autocorrelation in the residual of the models (Raghavan et al., 2011, 2012, 2013). Using a boosted regression tree, one study generated a national-scale predictive map of canine leptospirosis in the United States (White et al., 2017), but this study did not address spatial autocorrelation in the

residuals or prediction uncertainty. None of studies generated spatially structured prediction maps for animal leptospirosis incidence/prevalence.

Modelling risk of both human and animal infection

Three articles from three countries assessed the effect of various covariates on both animal and human infection (n = 3/11) (Chadsuthi et al., 2017; Della Rossa et al., 2016; Hurd et al., 2017). All of them focused on the role of environmental factors and climate on human and animal infection. Of these, only two studies generated spatially structured models and addressed spatial autocorrelation (Della Rossa et al., 2016; Hurd et al., 2017). No reviewed studies generated spatial prediction maps for both human and animal incidence/prevalence.

Temporal modelling as tools for leptospirosis outbreak detection

Nine studies performed time-series (temporal) regression at national (Chadsuthi et al., 2012; Desvars et al., 2011; Joshi et al., 2017; Lee et al., 2014; Ward, 2002b; Weinberger et al., 2014) and sub-national levels (Coelho and Massad, 2012; Deshmukh et al., 2019; Matsushita et al., 2018) to assess the effect of climatic variables and forecast leptospirosis outbreaks for humans (n = 7) (Chadsuthi et al., 2012; Coelho and Massad, 2012; Deshmukh et al., 2019; Desvars et al., 2011; Joshi et al., 2017; Matsushita et al., 2018; Weinberger et al., 2014) and canine infection (n = 2) (Lee et al., 2014; Ward, 2002b) (Table 4-3). Various temporal resolutions ranging from daily to monthly infection data were used with various timespans ranging from 7 to 16 years. Most studies included climatic factors such as precipitation, temperature, and humidity as predictors (n = 8/9) in the models. One study investigated the effect of El-Nino Southern Oscillation (ENSO) components (e.g., sea surface temperature anomaly, southern oscillation index, and oceanic Nino index) on human leptospirosis incidence in New Caledonia (Weinberger et al., 2014). Autoregressive models were used in three studies: human leptospirosis (n = 2) (Chadsuthi et al., 2012; Desvars et al., 2011) and canine leptospirosis (n = 1) (Ward, 2002b). One sub-national study in the Philippines employed a distributed lag non-linear (quasi-Poisson) model to assess non-linear relationships between rainfall and leptospirosis and the role of flood events (Matsushita et al., 2018).

Table 4-3 Summary of papers dealing with temporal time-series modelling

Reference	Objective	Location (spatial scale)	Study period (temporal scale)	Data source	Method(s)	Predictor(s)	Findings
Human leptospirosis (n=7)							
Weinberger et al. (2014)	To assess the relationships between climate and meteorological variables with leptospirosis cases; to develop a predictive model for timing of leptospirosis outbreaks	New Caledonia (national)	2000–2012 (monthly)	Laboratory-based passive surveillance notification	Negative Binomial Regression model (NBM), Principal component analysis, Bayesian information criteria (BIC), partial correlations, multivariate analysis, log-transformation, training tests, Serfling approach	Oceanic Nino Index (ONI), sea surface temperature, Southern Oscillation Index (SOI), rainfall, and temperature	Significant associations between leptospirosis incidence and El Nino indices, SST anomalies, and rainfall. SST anomaly could forecast an increase in leptospirosis cases with a 4-month lag.
Coelho and Massad (2012)	To examine the correlation between leptospirosis cases with climatic predictors	Sao Paolo, Brazil (sub-national)	1998–2005 (daily)	Hospital admission report	Negative binomial regression model (NBM)	Rainfall, Max-Min humidity, and temperature	Significant correlation between hospital admissions and rainfall intensity with lag of 14–18 days.

Reference	Objective	Location (spatial scale)	Study period (temporal scale)	Data source	Method(s)	Predictor(s)	Findings
Desvars et al. (2011)	To describe seasonality of leptospirosis and to test for correlation with meteorological factors	Reunion Island (national)	1998–2008 (monthly)	Hospital-based passive surveillance notification	Time-series analysis, log transformation, autocorrelation function (ACF), partial autocorrelation (PACF), augmented Dickey-Fuller test, ARIMAX, cross-correlations functions, goodness of fit criterion, AIC, Student's test	Rainfall, temperature, global solar radiation (GSR)	Monthly cases of leptospirosis influenced by cumulated rainfall with lag of 2 months and mean temperature and GSR during the month. Overall, the model could explain 67.7% of the variation of leptospirosis incidence.
Chadsuthi et al. (2012)	To determine and forecast the seasonal pattern of leptospirosis based on historical leptospirosis cases and meteorological data	Thailand (national)	2003–2009 (monthly)	Passive surveillance notification	Time-series analysis, log transformation, autocorrelation function (ACF), partial autocorrelation (PACF), augmented Dickey-Fuller test, ARIMAX, cross-	Rainfall, temperature	The role of rainfall and temperature on leptospirosis cases varied spatially across different regions. In the northern region, leptospirosis was driven by rainfall with a lag of 8-months; while in northeastern, rainfall and

Reference	Objective	Location (spatial scale)	Study period (temporal scale)	Data source	Method(s)	Predictor(s)	Findings
					correlations functions, goodness of fit criterion, AIC		temperature were found to be associated with leptospirosis incidence with 10-months and 8-months lag, respectively.
Joshi et al. (2017)	To estimate the influence of climatic variables on leptospirosis cases	Republic of Korea (national)	2001–2009 daily)	Passive surveillance notification	Time-series analysis, multivariate Poisson generalized linear models, variance inflation factor (VIF)	Daily minimum, maximum, and mean of temperature, minimum relative humidity, daily cumulative rainfall, solar radiation, total hours of sunshine	The minimum temperature, rainfall, and solar radiation were positively associated with leptospirosis cases with a lag of 0–11weeks.
Deshmukh et al. (2019)	To determine the association of climatic factors and leptospirosis incidence	Wardha district, India (sub-national)	2015–2016 (monthly)	Hospital-based surveillance	Poisson time-series regression	Minimum-maximum temperature, relative humidity, rainfall	Relative humidity in the month and rainfall in the previous month was the main determinant of leptospirosis incidence in a given month

Reference	Objective	Location (spatial scale)	Study period (temporal scale)	Data source	Method(s)	Predictor(s)	Findings
Matsushita et al. (2018)	To estimate the relationship between rainfall, flooding and leptospirosis infection	Manila, Philippines (sub-national)	2001–2012 (weekly)	Hospital-based surveillance	Distributed lag non-linear (quasi-Poisson) model, natural cubic spline, quasi-AIC, variance inflation factor (VIF)	Rainfall, flood	Rainfall were correlated with increased hospital admission for leptospirosis at a lag of 2 weeks. This association may partly be explain by flood events.
Animal leptospirosis (n=2)							
Lee et al. (2014)	To assess and compare regional seasonal patterns in seropositivity for canine leptospirosis	United States (national)	2000–2010 (monthly)	Laboratory database	Seasonal-trend decomposition analysis based on Loess (STL), logistic regression model	-	Each geographic region has distinctive seasonal patterns for seropositivity. In general, the highest positivity rates were reported in the fall.
Ward (2002b)	To describe the seasonal patterns of canine leptospirosis; to assess the role of rainfall on canine	United States and Canada (national)	1983–1998 (monthly)	Laboratory database	Time-series analysis, autocovariance (ACF), partial autocovariance (PACF), autoregression models, Akaike's information	Rainfall	Rainfall (lag of 3 months) could be used to predict canine leptospirosis incidence in the U.S and Canada.

Reference	Objective	Location (spatial scale)	Study period (temporal scale)	Data source	Method(s)	Predictor(s)	Findings
	leptospirosis incidence				criteria (AIC), cumulative spectrum, Box-Pierce, fluctuation tests, z-distribution, t-statistic,		

Model validation

Overall, model validation procedures to determine model accuracy were described in less than half of spatial modelling studies. Several measures were used to evaluate models including information criteria such as Akaike's information criterion (AIC), Bayesian information criterion (BIC), or deviance information criteria (DIC), Pearson chi-squared goodness-of-fit tests, and Hosmer-Lemeshow test. Data partitioning (e.g., splitting the data into training and testing subsets) was often used to validate the models as well as internal cross-validation (White et al., 2017). The Area Under the Receiver-operator curve (AUC ROC) analysis (Lau et al. 2012a; Mayfield et al., 2018b; Zhao et al., 2016) was applied to determine discriminatory performance and predictive accuracy of the models.

4.5 Discussion

This study is the first to review the application of spatial analytical methods in the field of leptospirosis epidemiology. The review demonstrates the potential of spatial-temporal epidemiological approaches to improve our knowledge of human and animal leptospirosis and its possible applications for assisting future intervention strategies to reduce leptospirosis burden. However, this review has identified some methodological limitations of existing studies that hinders their ability to provide a sound evidence base to guide local control efforts to reduce the burden of leptospirosis in humans and animals.

The source and quality of leptospirosis infection data substantially underpins the validity of spatial epidemiological studies. Indeed, my review noted that most studies have utilised leptospirosis notification data obtained from passive surveillance, which is likely to under represent the true incidence; although using notification data could be more feasible compared to conducting cross-sectional eco-epidemiological studies. It is noteworthy to acknowledge important disadvantages when using notification data, particularly for a disease such as leptospirosis, which is prone to being highly underreported. Of note, one concern with leptospirosis case ascertainment is that many endemic countries have limited laboratory capacity to undertake confirmatory diagnostic tests, so that the notification data may be primarily based on rapid diagnostic tests (RDT) or ELISA. Even these tests may not be routinely available throughout the country and this could lead to significant underdiagnosis and underreporting. In addition, other issues including the sensitivity and specificity of the

diagnostic methods used and discrepancies in reporting systems may also impede the quality of such notification data. To further compound this problem, this review identified several studies that did not clearly state the diagnostic tests or the case definitions used. These issues may greatly affect the clarity and quality of the data and thus lead to uncertainty about the geographical distribution of leptospirosis. This could misguide policy makers when developing strategies to efficiently target interventions to populations and areas at greatest risk. Given these limitations, future studies should carefully deal with the uncertainty in the epidemiological data.

In terms of spatial analysis approach, a considerable number of studies have used visualisation techniques to produce morbidity and mortality distribution maps. Indeed, such maps could be useful to assist health authorities to understand the geographical distribution of cases or risks. However, there are some common issues that needs to be carefully addressed when producing maps so that they are not misinterpreted. Besides the quality of data, the validity of the outcome of spatio-temporal analyses is greatly dependant on the spatial scale at which the analysis was performed, the type of data used (point or areal data), and how aggregation of areal data was conducted.

In particular, mapping geographical distribution of *Leptospira* serogroups or serovars identified in humans, host animals, and the environment is also of great importance; yet, this review indicates that this is still poorly explored. Such maps could be beneficial to support vaccine development (mainly for animals) and to better design control programs (e.g., identifying key animal sources of human infection to target One Health interventions). Of note, mapping the current distribution and future spread of pathogenic *Leptospira* may provide better understanding on the burden of leptospirosis. Further studies are therefore strongly encouraged to map the distribution of serogroups or serovars at various spatial-scales as it has important implications for understanding patterns of leptospirosis endemicity and aiding investigators to generate hypotheses on the potential source(s) of infection (host animals) as some specific serogroups/serovars are linked with specific host animals (e.g., serovars Canicola with dogs, Pomona with pigs, Hardjo with cattle) as well as disease severity and associated socioecological conditions.

Exploring spatial clustering of leptospirosis prior to modelling is fundamental for understanding spatial dependency of cases (Lawson, 2013). Furthermore, investigation of the

presence of spatial dependence is a first step for deciding the best modelling approach for quantifying predictors of disease and predictive risk mapping. This review demonstrates significant variation in the application of techniques used to test for spatial clustering, which requires systematic analysis as demonstrated by some of the studies reviewed here (Lau et al., 2012a; Rood et al., 2017). To detect spatial clustering, both global and local indices of spatial autocorrelation should be estimated, and it is also important to consider the type of the data (areal or point data) when choosing methods. This review highlights that almost all studies have overlooked the importance of assessing spatial autocorrelation in the residuals of non-spatial models. It also appears that most studies solely evaluated spatial autocorrelation, but when present, did not incorporate it into the modelling framework. Ignoring spatial dependence in the data can give rise to spurious associations, inaccurate and biased parameter estimations and spatial risk predictions (Dormann, 2007; Pfeiffer, 2008).

Another step for exploring spatial dependence involves the utilisation of spatial cluster detection techniques; by far the most commonly used by the studies reviewed here was Kuldorff's Spatial Scan statistic (SaTScan). This method allows researchers to estimate the relative risk inside and outside identified geographical clusters of disease by using predefined scanning windows and Monte Carlo simulation (Martin Kulldorff & Neville Nagarwalla, 1995). Despite its simplicity, there was no standard selection of thresholds across studies for the shape and size of the cluster scanning window (~10–50% of the population at risk) as the size and shape selection may depend on the nature of the data and their objectives. All studies assumed that disease clusters were circular, while ecologically, the disease often forms irregular shaped clusters (e.g., due to variation in a population or environmental characteristics). The use of circular scanning windows may reduce the chance to detect non-circular shaped clusters. To better detect and deal with irregularity of the disease clusters, alternative cluster detection tools could be used for future studies, such as FlexScan or a multidirectional optimal ecotope-based algorithm (AMOEBA) (Aldstadt and Getis, 2006; Ramis et al., 2014; Zhu et al., 2016).

This review shows that large number of spatial modelling studies assessed the association between physical environment (e.g., altitude, vegetation, proximity to waterbodies, sewerage systems or waste) and climatic factors on leptospirosis, suggesting the high importance of the environment on leptospirosis transmission, while factors associated with sociodemographic

conditions (e.g., urbanisation, poverty) and animal hosts appears to remain overlooked by many studies. In the context of zoonotic disease control, it has now been recognised that a One Health approach has greater potential to effectively control disease burden rather than focusing on human disease alone. Such framework should therefore be accommodated in future spatial models (i.e. the inclusion of animal host factors along with environment predictors and social determinants of health) to provide more comprehensive evidence for decision-making processes.

In terms of modelling methodology, the majority of spatial modelling studies reviewed here used a range of traditional regression models (frequentists) and very few have applied modelling techniques (e.g., Bayesian geostatistics methods) that fully address spatial autocorrelation. A disadvantage when using standard statistical modelling techniques is that they assume independence of observations and do not account for potential spatial dependency between neighbouring locations. When overdispersion or the effect of spatial dependence on the data are ignored, the standard errors could be underestimated and hence increase the risk of Type I errors (Pfeiffer, 2008). In addition, such traditional regression models are not able to identify variation in the relationships between the predictors and capture the complexity of disease transmission. There are several promising methods that could be used in future leptospirosis studies, such as Bayesian geostatistics, geographically weighted regression (GWR) and spatial Bayesian Belief Network (BBN). Recently, Bayesian geostatistics techniques have been widely used in various spatial epidemiological zoonotic diseases studies. This method has advantages over common frequentist regression models. Bayesian approaches are suitable when data are sparse and highly clustered. It allows accounting for spatial autocorrelation and adequately addresses uncertainties in the model design (Cressie et al., 2009; Diggle et al., 1998, 2007). Other methods such as geographically weighted regression (GWR) (Mayfield et al., 2018a) and Bayesian Belief Network (BBN) (Lau et al., 2017; Pittavino et al., 2017) have also been used in a few epidemiological studies in leptospirosis. The former provides opportunity to better deal with spatial non-stationarity of covariates in the models (Fotheringham et al., 2002), while the latter has the ability to effectively reveal and describe the complexity of relationships between variables in disease system (Landuyt et al., 2013; Lewis and McCormick, 2012). To help enhance understanding of leptospirosis transmission and predictive maps, further studies should be directed on exploring such non-traditional modelling techniques and incorporating spatial-temporal

elements into the models. All of these methods may allow researchers to produce more robust and better predictive risk maps for leptospirosis to better inform health managers on planning leptospirosis control. However, as the models become more complex and more advance modelling techniques are being used, it may greatly need considerable time, technical skill requirements, and computational capacity. For instance, using Bayesian geostatistical models could take hours or even days to run the model, while some techniques (e.g., spatial BNs) could be much faster and almost instantaneous. A recent study in Fiji offers a promising approach to better understand leptospirosis transmission under various socioecological scenarios by using spatial Bayesian Networks (Mayfield et al., 2018b)

Assessing the effect of climate variability (e.g., precipitation, temperature, ENSO) on leptospirosis risk allows researchers and public health officials to forecast when outbreaks may occur. It should be noted that one of the critical limitations of the conventional time-series modelling (e.g., ARIMA) is that it mainly assesses linear relationships of variables within the time series data (Zhang et al., 2014), while the relationships between variables and infection are commonly non-linear. To better address this non-linearity of associations, some techniques could be used in the future model such as distributed lag non-linear models (DLNM) (Gasparrini et al., 2010). Given the complexity of the leptospirosis infection pathway, future spatiotemporal models of leptospirosis distribution also need to incorporate the joint effects of multiple variables such as climatic and socioecological factors. One potential approach to better incorporate those complexities and enhance the predictive capability of leptospirosis forecasting models is machine learning. The application of machine learning algorithms such as Random Forest, Boosted Gradient and Neural Networks, have been demonstrated to have better performance and high predictive ability in several public health studies (Carvajal et al., 2018; Chen et al., 2018; Guo et al., 2017; Hu et al., 2018). Future studies should be directed to exploring such machine learning methods in modelling leptospirosis transmission.

4.5.1 Framework for the application of spatial analytical tools for leptospirosis studies

Based on the review, I proposed a general framework that could guide the application of spatial epidemiological methods for future leptospirosis studies (Figure 4-5). In general, there are three key components: input, spatial analytical processes, and output. Note that the first

stage (input) is a critical part of the inference as the analytical processes and the usefulness of the outputs (maps) greatly depends on the quality, type, and spatial and/or temporal scale of the infection data and attributes. This framework has potential to be adopted not only for leptospirosis but also for other diseases.

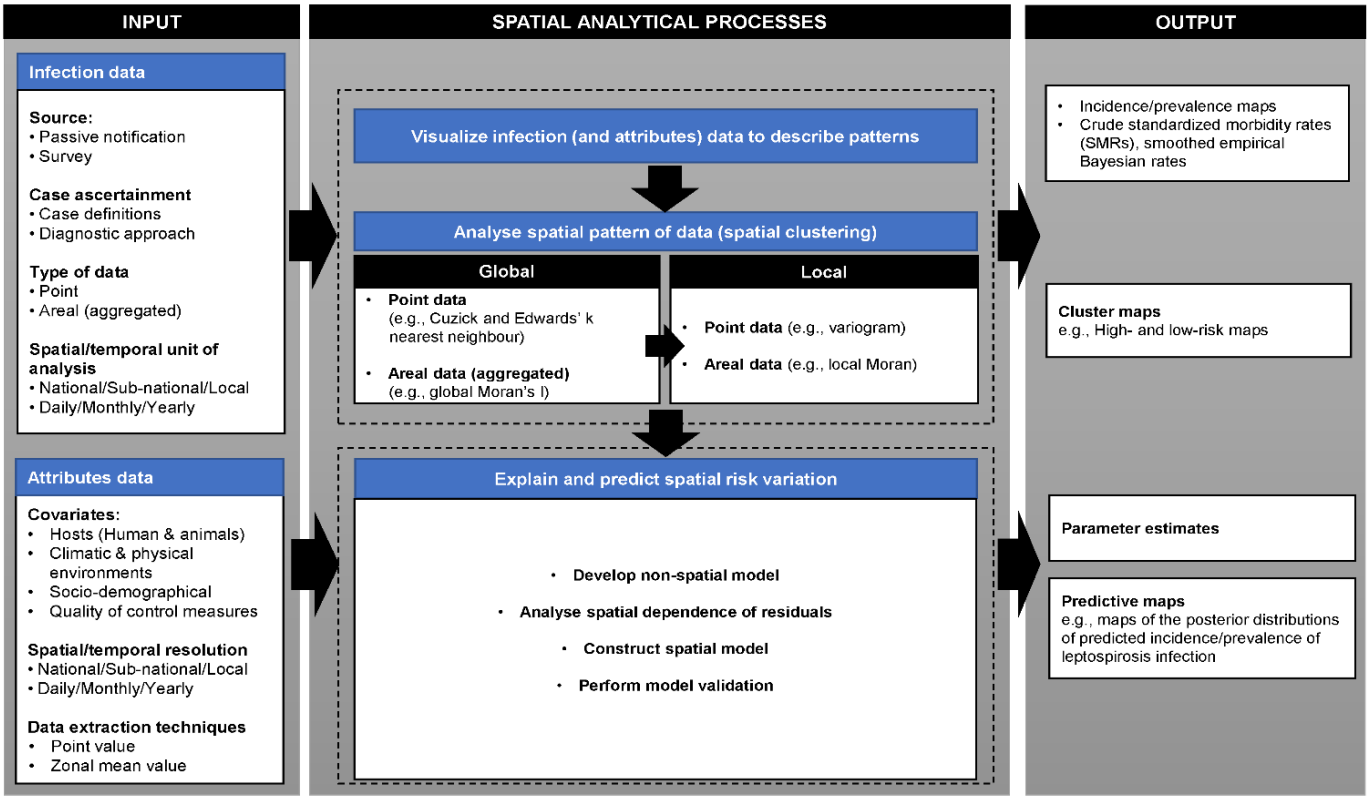

Figure 4-5 General framework for the application of spatial analytical tools for leptospirosis studies

Leptospiral infection data could be obtained from either notification or surveys. Case definitions and methods used to diagnose leptospiral infection should be clearly reported. Prior to the analysis, spatial data type should be determined as point or areal data (by aggregating the data into certain level of spatial unit) as well as the spatial and temporal unit of analysis. Incorporating wide-range covariates (e.g., human and animal hosts, climatic, physical environments, socioeconomic) into the analysis would improve understanding the determinants of the geographical variation of risk of leptospirosis. Geographical and temporal

patterns of disease risk is considered influenced by the heterogeneity in hosts (including humans and animals), climatic and physical environments, socio-demographical and also the quality of existing control measures. The spatial and temporal resolutions of those covariates should mirror the resolution of the epidemiological data. Based on the type of spatial data, using GIS tools (e.g., point or zonal mean statistics), the value of each covariate could be sampled.

The basic step of spatial analysis is visualisation, which aims to describe patterns in the infection data. Data could be presented as point or choropleth to describe prevalence/incidence or standardised morbidity ratio. To investigate the spatial pattern of the data, according to the type of the data (point or areal data), appropriate statistical tests are carried out to test global (first order) and local (second order) spatial clustering.

These tests are essential for exploring disease distribution over space (e.g., random or clustered over the space) and to locate high-risk areas. The ultimate objective of spatial and/or temporal analysis is to quantify risks and generate spatial and/or temporal prediction models. This stage employs both non-spatial and spatial regression techniques. All potential covariates are included and selected using fixed-effect regression model. Spatial autocorrelation in the residuals of the final models should be assessed, both by using global and local tests

Models with the ability to incorporate a spatial dependence component (i.e. Bayesian geostatistical model) are the most relevant to use when spatial autocorrelation is evident. Spatial regression models for risks (prevalence or incidence) could be constructed in Bayesian statistical software e.g. OpenBUGS version 1.4 (Medical Research Council Biostatistics Unit, Cambridge, UK and Imperial College London, London, UK). All models should include all selected covariates as fixed effects plus a geostatistical random effect, in which spatial autocorrelation between locations is modelled using an exponentially decaying autocorrelation function. The outputs of Bayesian models, including parameter estimates and spatial prediction at unsampled locations, are termed as “posterior distributions”. The posterior distributions in terms of the posterior mean and standard deviation then could be mapped using GIS software. This map is known as predictive risk maps. Further details on Bayesian model-based geostatistics techniques can be found elsewhere (Diggle and Ribeiro, 2007).

4.6 Limitations

Publication bias is an important limitation which should be considered when interpreting our findings. This review solely relied on published research manuscripts and we did not take into account other types of publications (e.g., theses or dissertations, conference proceedings). In addition, most studies captured by systematic search came from a limited set of countries; this may reflect substantial issues within the countries regarding the availability of the data due to technical issues (e.g., reporting systems, diagnostic capacity) in many endemic countries (Musso and La Scola, 2013; Schreier et al., 2013), poor public awareness and knowledge on the disease (Mohan and Chadee, 2011), and variation in surveillance systems (Costa et al., 2012).

4.7 Conclusions

While the use of spatial and temporal analyses has been greatly appreciated in the field of leptospirosis research, the quality of studies and analytical approaches varied significantly. To better understand the epidemiology and processes underlying leptospirosis transmission, appropriate spatio-temporal techniques should be chosen and applied taking into consideration quality and type of data, the geographical scale of analysis and type of covariates for inclusion. Uncertainty in disease modelling outputs should be carefully considered so that the model outputs can be effectively applied to support leptospirosis control interventions. Future work should be prioritised on optimising the potential of GIS/RS for developing a user-friendly and interactive decision-support system, providing an updateable map at local and national level at finer resolution as new data become available, and constructing more robust and reliable predictive models that account for spatial and temporal dependencies in leptospirosis transmission from different animal hosts and in different environments.

Chapter 5 Epidemiological shift and geographical heterogeneity in the burden of leptospirosis in China

This chapter has been published in *Infectious Diseases of Poverty* as an original peer-reviewed research paper. The concept and design of the study outlined in this Chapter 5 was formulated by PWD (80%) with the assistance of RJSM (20%). WYZ provided the data. PWD was responsible for data management (100%), data analyses (100%) and the interpretation of results (75%) was discussed in consultation with RJSM (15%) and all co-authors (10%). PWD was responsible for drafting the manuscript (100%). PWD was responsible for revision of the final version of the manuscript (90%), taking into account the comments and suggestions of RJSM (5%) and co-supervisors (5%).

5.1 Context

The literature review in Chapter 2 shows that leptospirosis is indeed a disease of public health importance, in that a total of 1.03 million cases and 58,900 deaths occur per year worldwide, resulting in the loss of roughly 2.9 million disability-adjusted life-years (DALYs) per year (Costa et al., 2015; Torgerson et al., 2015). In China, leptospirosis is of public health importance. Previous studies had indicated that leptospirosis outbreaks had been reported in more than 80% of the total provinces (34 provinces) and has caused more than 2.5 million cases and 20,000 deaths (Zhang et al., 2012; Shi et al., 2000). Nevertheless, since the 1990s the incidence of leptospirosis has been considerably declining, reaching a relatively low incidence of 0.70 cases per 100,000 people per year (Zhang et al., 2012; Hu et al., 2014). However, evidence on how the burden of leptospirosis in China has changed over time at sub-national level is lacking. In light of the gaps identified in the literature review (Chapter 2) and findings of the systematic review detailed in Chapter 4, and while numerous maps had been produced, no studies have attempted to map the burden of leptospirosis (in terms of DALYs) at sub-national level. A recent update of the spatiotemporal heterogeneity of the burden of leptospirosis in the country is essential to help policy decision makers and health authorities to guide the identification of areas and populations at highest risk for leptospirosis and resource allocation.

In this chapter, I utilised human leptospirosis data reported from 2005 to 2015 in China to explore the annual trend in morbidity and mortality both spatially (at province level) and temporally (yearly) and to demonstrate how this trend influences the distribution of the burden estimates of leptospirosis in terms of DALYs at sub-national level. In this study, I estimated that a total of 10,313 DALYs were lost during 2005–2015 due to leptospirosis infection. Most of the burden was attributable to mortality (~82.5% of DALYs). I also found that males (7,149 DALYs) and those aged 10–19 years (3,078 DALYs) were the most affected population by leptospirosis. I found that the geographical distribution of the burden estimates was heterogeneous at province level with the highest estimates identified in provinces within the Pearl River basin (Region A) and the Yangtze River basin (Region B). However, I also found that there was a significant decrease in morbidity and mortality of leptospirosis from 2005 to 2015, impacting a substantial decrease in burden estimates up to 95%. Despite this, I found that during the period of 2011–2015 incidence remained high in southwestern China, including the Yunnan and Sichuan provinces, indicating that factors contributing to leptospirosis transmission are still present in these residual high-risk regions. To the best of my knowledge, this study is the only one of its kind to demonstrate province-specific DALY estimates for human leptospirosis, especially in China.

5.2 Introduction

Leptospirosis is a zoonotic disease of global public health importance caused by pathogenic spirochetes belong to the genus *Leptospira* (Vinetz, 2001). It has caused more than one million cases and 58,900 deaths per year (Costa et al., 2015), and it has been estimated approximately 2.90 million DALYs lost due to leptospirosis worldwide (Torgerson et al., 2015). Leptospirosis is acquired mainly through contact with contaminated water or soil containing *Leptospira*. In some cases, infections may also occur through direct contact with infected animals (Levett, 2001). Due to non-specific clinical characteristics, leptospirosis is often challenging to diagnose leading to underreported incidence which in turn may limit the effectiveness of control programs (Bharti et al., 2003; Lau et al., 2010).

Leptospirosis is an important zoonotic disease in China. It was first reported in 1934 and it became a mandatory notifiable disease since 1955. To date, more than 2.5 million cases and 20,000 deaths have been reported; more than 80% of the total provinces (34 provinces) have

reported leptospirosis cases (Zhang et al., 2012; Shi et al., 2000). Leptospirosis remains a significant public health problem in the country where a broad range of potential reservoirs and serovars are still circulating in the country. Furthermore, rapid population growth, poverty, and industrialisation have led to excessive urbanisation and environmental changes, such as deforestation and urban expansion (Yeh et al., 2011; Hu et al., 2014; Siciliano et al., 2012; Liu et al., 2008; Claudio et al. 2015), which might influence disease nidality through direct impacts on the natural habitat of reservoirs and affects the spillover of infection between wildlife animals, domestic animals, and humans. Also, extreme weather events, such as flooding following typhoons, may significantly impact impoverished communities with lack of access to safe water, sanitation, and health services (Lau et al., 2010), leading to an increased risk of *Leptospira* exposures.

Using notified leptospirosis morbidity and mortality data from the 1970s, a study has estimated that there were approximately 301,688 DALYs lost annually due to leptospirosis in China (Torgerson et al., 2015). Nevertheless, in the last two decades, leptospirosis incidence has reduced from 10.73 cases per 100,000 people in the 1960s to 0.59 cases per 100,000 people in the 2000s (Shi et al., 2000; Hu et al., 2014). In the light of changes in socioeconomic and environmental conditions that have undergone in China for the last two decades, there is a need to re-estimate the burden of leptospirosis and to identify residual pockets of transmission. To date, there is no single study that has estimated the changes in burden in terms of DALYs across China over time.

Using available passive surveillance data on human leptospirosis in China, we aimed to investigate the changes on notified morbidity and mortality of leptospirosis and to quantify the demographical, temporal and geographical heterogeneity of the burden during 2005–2015. The findings of this study provide evidence to inform policy to allocate effective targeted intervention strategies for better leptospirosis control programs in China.

5.3 Methods

5.3.1 Data sources

In China, leptospirosis is one of 39 notifiable infectious diseases that must be reported within 24 hours (Category B disease) (Zhang et al., 2012). To illustrate, infectious diseases

surveillance data, including leptospirosis, is analysed by the Center for Disease Control and Prevention (CDC) at various level: county, prefecture, provincial, and national level. Case information is entered by all healthcare providers at all levels via a nationally standard form into a web-based Notifiable Infectious Diseases Reporting Information System (NIDRIS). In addition, a national system called China Infectious Disease Automated-alert and Response System (CIDARS) has been developed since 2005 to provide real-time outbreak notifications (Vileg et al., 2017; Yang et al., 2011). In term of diagnosis, the provincial branches are responsible for testing suspected human patient and animal sera, collecting infected animals and identifying infectious isolates by culture and microscopic agglutination test (MAT), according to the national diagnostic criteria for leptospirosis issued by the National Health and Family Planning Commission (NHFPC) (Ministry of Health of China, 2008). Results are then verified by the national-level CDC and finally reported to NHFPC.

In this study, we used reported leptospirosis case data from 1 January 2005 to 31 December 2015. These data included information about age, gender, occupation, date of onset of illness, diagnosis and death, place of residence (i.e. county and province) and case classification (suspect, clinical, and confirmed). Yearly demographic data including population data by age, sex, and occupation were collected from the National Bureau of Statistics of China for each province from 2005 to 2015 (NBSC, 2016).

5.3.2 Human leptospirosis case definition

Based on China Ministry of Health diagnostic criteria for leptospirosis (Ministry of Health of China, 2008), leptospirosis cases are defined into three categories: suspected, clinical, and confirmed. Suspected cases are defined as an individual with: a) a clinical symptom such as acute fever (up to 39°C), which may be accompanied by chills, myalgia, or malaise and; b) history of exposure within a month prior to the onset of illness to the following risk factors: epidemic season, reside in epidemic area, either direct or indirect contact with suspected animals and their urine or faeces or contaminated water and soil. Clinical (probable) cases are defined as suspected cases with at least one of the following clinical manifestations: conjunctival hyperemia, gastrocnemius tenderness, or enlargement of the lymph nodes. Confirmed cases are defined as suspected cases with one or more any of the following laboratory criteria: 1) positive culture of *Leptospires* from blood, urine, tissues, or cerebrospinal fluid (CSF); 2) Microscopic Agglutination Test (MAT) titre of ≥ 400 in single or

paired serum samples; 3) a fourfold or greater rise in MAT titres between acute and convalescent-phase samples; 4) presence of pathogenic *Leptospira* spp. detected by polymerase chain reaction (PCR); 5) presence of IgM antibodies by enzyme-linked immunosorbent assay (ELISA). Indeed, the IgM ELISA is not a 'gold-standard' serological test. While it has limited sensitivity and specificity, it has been useful especially in resource-poor areas in China. Additionally, as MAT is not sensitive for early infection and is not available in hospitals in remote areas, IgM ELISA has been used routinely in general laboratories.

5.3.3 Data analysis

Morbidity and mortality calculation

Gender, age and occupation-specific incidence rate per year was calculated. Annual number of laboratory-confirmed cases, total counties reported leptospirosis, incidence and case fatality rate (CFR) at province level were also calculated. We used yearly national and province-level population data obtained from National Bureau of Statistics as the denominator to calculate incidence and mortality rates over time.

In the analysis, occupational group was defined into three main categories based on the type of industry: primary, secondary, and tertiary workforces. Farmers, plant growers, herdsman, seaman, and fishers were categorized as primary (agricultural-related) workforces. The secondary industry was defined as manufacture-related work. The tertiary workforce was defined for those individuals who work in services (e.g., teachers, doctors, nurses, students). The occupation classified as 'others' include individuals who retired/not working, including children and undefined profession.

Exploration of seasonal patterns

A multiplicative seasonal decomposition analysis was conducted using SPSS version 24 (IBM Corp., Armonk, NY, USA) to decompose the leptospirosis monthly incidence (Yt) into a combined trend (Tt), a seasonal component (St), and an error or residual component (Et) (Cleveland et al., 1990). The relationship between the different decomposition terms and leptospirosis incidence is:

$$Yt = Tt + St + Et$$

DALYs estimation

Based on total cases, we estimated the burden in terms of age-, sex- and province-specific DALYs during the period of study. We estimated the DALYs for each year by adding the number of Years of Life Lost due to death in the population (YLLs) and the number of Years Lived with Disability (YLDs) due to the disease (Murray 1994). The estimate of YLLs was obtained by multiplying number of cases per year and the standard life expectancy and age of death in years. To estimate life expectancy at the age of death, we used a standard life table used for the estimation of Global Burden of Disease 2010 (Murray et al. 2012). YLDs were calculated by multiplying incidence, disability weight (DW), and duration of the illness. The disability weight used for the estimation of YLDs was the same that was used in a study elsewhere (Torgerson et al., 2015). In brief, all death cases were defined as fatal cases. Thus, we were given a DW of 0.573 for one month as it was assumed that they had dialysis before death. For non-fatal cases, we assumed that there were 70% acute cases and 30% had chronic sequelae. Of those acute cases, 50% were mild (given a DW 0.053 for 2 months), 40% were moderate (DW 0.21–2 months), and 10% severe (DW 0.562 for 2 weeks, 0.51 for 2 weeks, and 0.21 for 1 month). Of those chronic cases, a DW of 0.245 for two months to three years was given (Torgerson et al., 2015). In our DALYs calculation, we did not consider age-weighting and discounting.

Statistical analysis

A simple linear regression model was used to examine annual trend in reported incidence, mortality, and burden estimates during 2005–2015, with the independent variable being the year and the dependent variable being leptospirosis incidence rate. As we observed that there were different trends during 2005–2015, we then divided the dataset into two blocks of years (2005–2010 and 2011–2015) to investigate epidemiological changes between these two periods. A chi-square ($\chi 2$) test was performed to determine the difference in the proportion of cases, deaths and burden by age, sex, and occupation in between time periods. *P* values of < 0.05 were considered statistically significant. All other statistical analysis was conducted using STATA version 13.0 (Stata Corp., College Station, TX, USA).

Mapping incidence and burden

For the purpose of our analyses, we used province as spatial unit of analysis. Map of cumulative incidence of leptospirosis (2005-2015) at province level was created. Changes in

the spatial distribution of incidence and burden during two periods (2005-2010 and 2011-2015) were mapped using ArcGIS 10.5 (ESRI Inc., Redlands, CA, USA). To allow comparison with the previous study by Zhang et al. (2012), we grouped provinces into four regions (Region A, B, C, and D).

5.4 Results

5.4.1 Descriptive analysis

A total of 7763 leptospirosis cases were reported during 2005–2015 (Table 5-1). Of these, 2403 cases (31%) were recorded as confirmed cases, 4588 (59%) as clinical cases, and 772 (10%) as suspected cases. The proportion of confirmed cases towards the total cases increased over time from 8.2% (120/1465) in 2005 to 56.7% (233/411) in 2015. The proportion of reported laboratory-confirmed cases during 2005–2015 varied across the 26 provinces in China (Appendix C: Table C-1).

By gender, a total of 5356 (69%) males and 2407 (31%) females were observed. The annual incidence rate (IR) was higher in males (0.08 cases per 100,000 people) compared with females (0.03/100,000 people) (χ^2 = 22.50, P = 0.013, Table 5-1). Our results indicate that incidence differed significantly by age group (χ^2 = 624.57, P < 0.001) with most of the cases (21%) reported in the 40–49 years-old age group. The higher incidence rate was identified in the older age groups of 50–59 years (0.09/100,000 people) and 60–69 years (0.08/100,000 people). However, leptospirosis in younger individuals aged under 20 years was also reported, which accounted for a total of 1075 cases (14%), with reported incidence rates ranging from 0.01–0.05/100,000 people. Based on patients' occupation, we could only identify two main occupational types: primary (agriculture) and tertiary (services). A total of 761 records were classified as 'other' including those who did not work, children, and retired people. The leptospirosis incidence rate was higher in the primary sector (0.18/100,000 people) compared with the group of tertiary workforces (0.04/100,000 people) (χ^2 = 47.15; P < 0.001). Furthermore, among the primary workforces, 298 (5%) cases were attributed to young farmers aged under 20 years old. Whereas, among the tertiary workforces, most cases (43%) were predominantly attributed to students aged under 20 years.

A more detailed leptospirosis cases by type of occupation was provided in Appendix C: Table C-2. Table C-2 indicates that, in general, most cases were reported among farmers (76.5%), followed by teacher/student (10.6%). Additionally, in the past 2-years (2014-2015), a relatively small number of leptospirosis cases have also been reported in cadre, commercial service workers, herdsman, seaman, fisherman and medical workers.

Leptospirosis was reported from all four regions in China; the highest reported incidence rate was primarily observed in the Region A and B (Figure 5-1). Based on the decomposition analysis, the incidence of leptospirosis showed a clear seasonal pattern. The incidence increased from April to September and reached a peak in August/September and then diminished from October thereafter. The lowest incidence was consistently observed in February (Figure 5-2).

Table 5-1 Annual number of notified leptospirosis and incidence rate by sex, age and occupation and the proportion of case in China, 2005–2015**.**

Characteristics		Number of cases (per 100,000 people)											Total	IR*
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015		
Sex	Female	439 (0.07)	217 (0.04)	300 (0.05)	254 (0.04)	197 (0.03)	218 (0.04)	134 (0.02)	154 (0.03)	156 (0.03)	207 (0.04)	131 (0.02)	2407	0.03
	Male	1026 (0.16)	500 (0.08)	658 (0.10)	675 (0.11)	462 (0.08)	500 (0.08)	289 (0.05)	337 (0.06)	280 (0.05)	349 (0.06)	280 (0.04)	5356	0.08
Age	0–9	41 (0.03)	28 (0.02)	34 (0.03)	20 (0.02)	18 (0.01)	10 (0.00)	8 (0.01)	4 (0.00)	5 (0.00)	6 (0.00)	3 (0.00)	177	0.01
	10–19	283 (0.13)	116 (0.06)	137 (0.07)	99 (0.06)	83 (0.05)	52 (0.03)	33 (0.02)	34 (0.03)	15 (0.01)	24 (0.02)	22 (0.01)	898	0.05
	20–29	236 (0.14)	86 (0.06)	107 (0.07)	120 (0.08)	70 (0.04)	62 (0.04)	40 (0.02)	47 (0.02)	48 (0.03)	71 (0.04)	45 (0.02)	932	0.05
	30–39	347 (0.14)	140 (0.07)	174 (0.09)	174 (0.09)	112 (0.06)	131 (0.07)	66 (0.04)	67 (0.04)	53 (0.03)	89 (0.05)	63 (0.03)	1416	0.07
	40–49	228 (0.12)	140 (0.07)	202 (0.10)	180 (0.09)	126 (0.06)	159 (0.08)	99 (0.05)	126 (0.06)	106 (0.05)	142 (0.07)	83 (0.03)	1591	0.07
	50–59	217 (0.15)	130 (0.08)	205 (0.12)	210 (0.12)	137 (0.08)	167 (0.10)	101 (0.08)	97 (0.07)	92 (0.07)	111 (0.08)	95 (0.05)	1562	0.09
	60–69	87 (0.09)	53 (0.06)	75 (0.08)	93 (0.10)	92 (0.09)	112 (0.12)	55 (0.06)	84 (0.09)	83 (0.09)	84 (0.09)	83 (0.06)	901	0.08
	70–79	16 (0.03)	15 (0.03)	23 (0.04)	30 (0.05)	20 (0.04)	27 (0.05)	20 (0.04)	32 (0.06)	23 (0.05)	22 (0.04)	25 (0.04)	253	0.04
	80–89	1 (0.00)	0.00	6 (0.04)	4 (0.02)	1 (0.00)	0.00	3 (0.02)	3 (0.02)	4 (0.02)	5 (0.03)	3 (0.01)	30	0.02
	90+	0.00	0.00	1 (0.07)	0.00	0.00	0.00	0.00	0.00	1 (0.05)	0.00	1 (0.05)	3	0.02
Occupation	Agriculture	1119 (0.32)	500 (0.15)	721 (0.22)	726 (0.24)	526 (0.18)	571 (0.22)	312 (0.11)	387 (0.14)	312 (0.12)	466 (0.19)	305 (0.13)	5944	0.18
	Services	263 (0.11)	125 (0.05)	148 (0.06)	110 (0.03)	90 (0.02)	63 (0.02)	54 (0.02)	39 (0.01)	54 (0.02)	56 (0.02)	56 (0.02)	1058	0.04
Case classification	Confirmed (n, %)	120 (8.2)	227 (31.7)	267 (27.9)	249 (26.7)	159 (24.1)	229 (31.9)	178 (42.1)	184 (37.5)	237 (54.4)	321 (57.7)	233 (56.7)	2403 (31)	
	Clinical (n, %)	1271 (86.8)	415 (57.9)	594 (62)	600 (64.7)	405 (61.5)	436 (61.5)	212 (50.1)	248 (50.5)	122 (28)	171 (30.8)	113 (27.5)	4588 (59.1)	
	Suspected (n, %)	74 (5.1)	75 (10.5)	97 (10.1)	80 (8.6)	95 (8.6)	53 (14.4)	33 (7.8)	59 (12)	77 (17.7)	64 (11.5)	65 (15.8)	772 (9.9)	
TOTAL		1465 (0.11)	717 (0.05)	958 (0.07)	929 (0.07)	659 (0.05)	718 (0.05)	423 (0.03)	491 (0.04)	436 (0.03)	556 (0.04)	411 (0.03)	7763	
No. counties reported		307	265	299	278	222	239	182	180	165	173	163	782	
CFR		3.29	2.66	3.86	2.04	1.82	1.53	1.17	1.02	1.16	1.07	0.24		

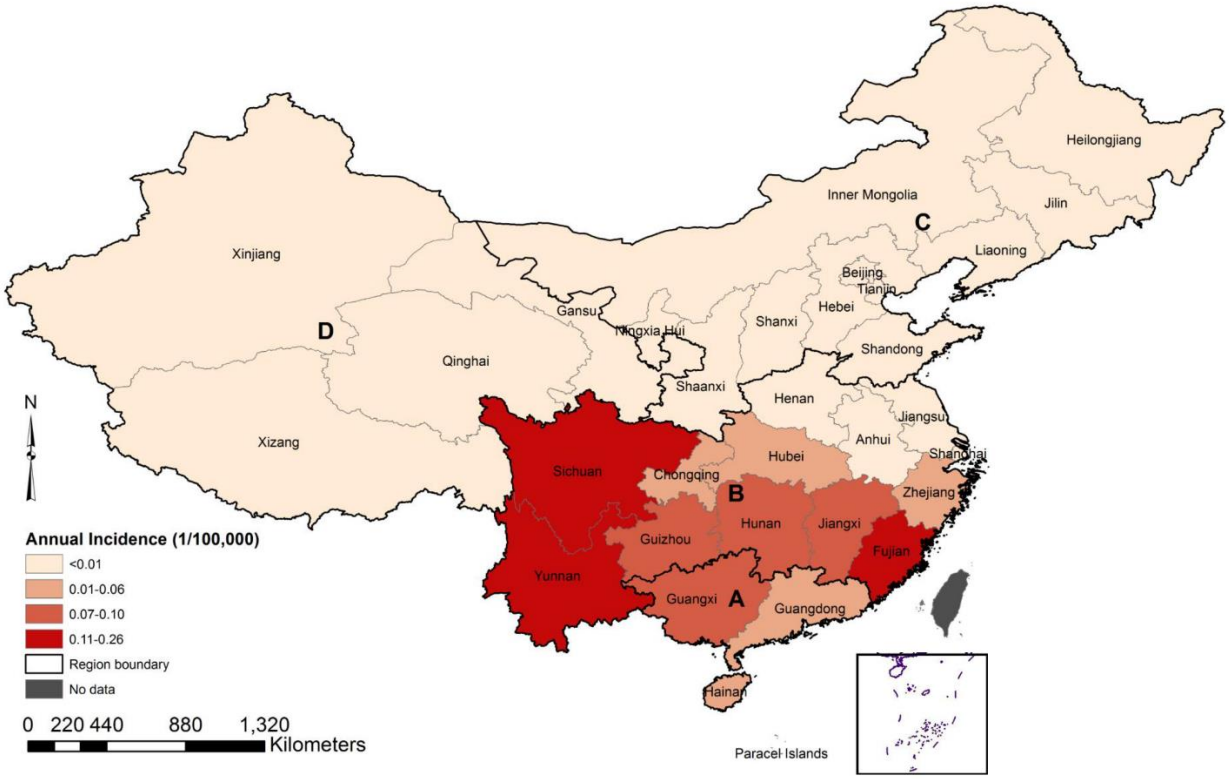

Figure 5-1 Annual average incidence of leptospirosis at province level, China, 2005–2015. Province was grouped into four regions (Region A, B, C, D) as identified by Zhang et al (2012).

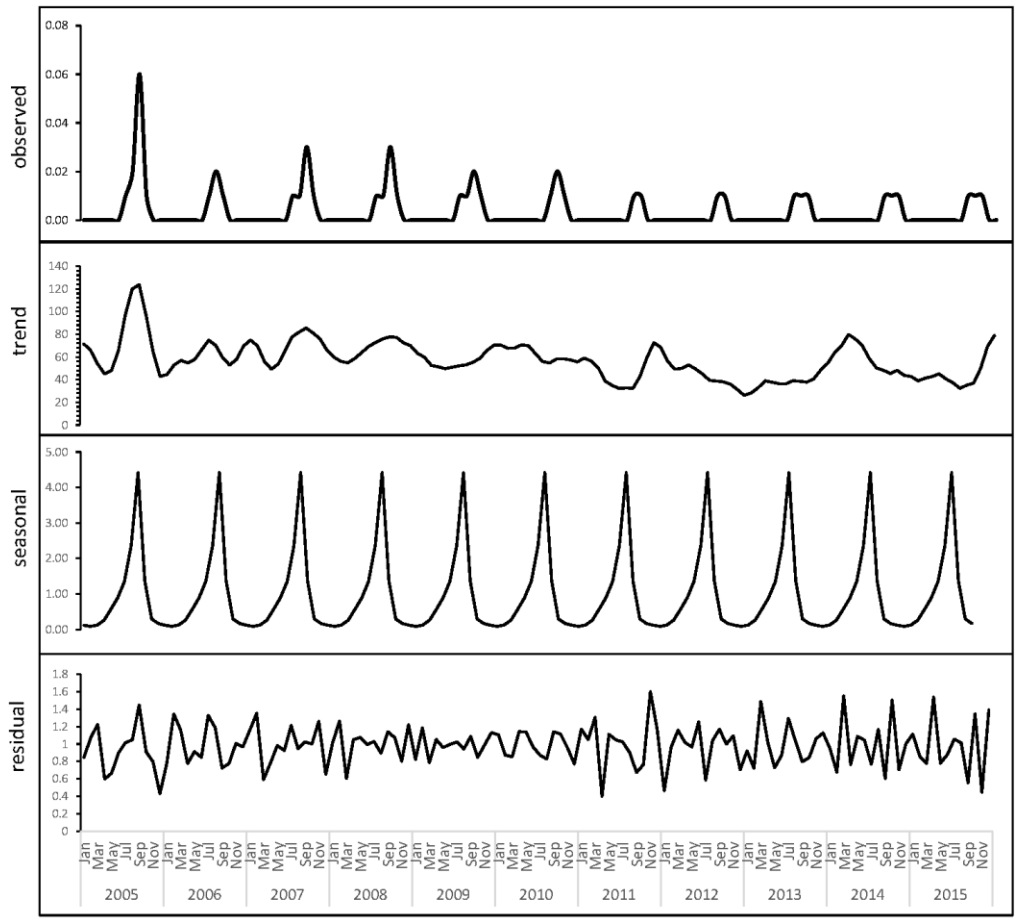

Figure 5-2 Decomposed monthly leptospirosis incidence in China

In total, leptospirosis cases were reported from 782 counties in 26 provinces in China (Table 5-2). Most leptospirosis cases were reported from Region B, where 6514 cases (84%) were reported during 2005–2015. The number of counties that reported cases demonstrated a significant reduction in 2005–2015 ($P < 0.001$). Overall, there was a significant declining trend in leptospirosis incidence from 0.11/100,000 people in 2005 to 0.03/100,000 people in 2015 ($R^2 = 0.646$; $P < 0.05$). Among provinces, both Sichuan and Yunnan had the highest reported incidence rate (0.26/100,000 people) in the country. Similarly, the case-fatality rates (CFR) also showed a downturn trend from 3.29% in 2005 to 0.24% in 2015 ($R^2 = 0.815$, $P < 0.001$). The highest CFR was recorded in Guizhou (13.41%) compared with other provinces. Detailed temporal distribution of leptospirosis incidence and CFR for each province during 2005–2015 is provided (Appendix C: Table C-1, Table C-3).

In addition, during 2005–2015, a total of 168 deaths attributed to leptospirosis reported in China. Of which, 71% (120/168) of reported deaths were attributed to males. A high mortality rate was observed in the 50–59 age group (0.20 per 100,000 people), followed by the 10–19 age group (0.18 per 100,000 people). A high number of deaths (125 out of 168) were attributed to patients who worked in the primary sector as a farmer. A high number of deaths were reported from Region B (74%), particularly in Guizhou, Sichuan, Hunan, Hubei, and Jiangxi (Appendix C: Table C-4). There was a decrease in the reported mortality rate since 2005 and it reached a very low level from 2011 thereafter. Reported deaths by case classifications were given in Appendix C: Table C-5.

Table 5-2 Reported cases, proportion of confirmed case, counties, incidence and fatality rate of leptospirosis at province level in China, 2005–2015.

	No. of cases reported (*n*=7763)	**% confirmed case (*n*=2403)**	**No. of counties reported (*n*=782)**	**Incidence per 100,000**	**CFR (%)**
Region A					
Guangdong	619	53.3	100	0.06	2.28
Guangxi	543	40.1	92	0.10	1.16
Hainan	47	10.6	15	0.05	0.00
Region B					
Jiangsu	37	54.1	25	0.00	1.30
Zhejiang	138	42.8	28	0.02	1.31
Anhui	310	8.4	31	0.05	1.03
Fujian	502	47	62	0.12	0.74
Jiangxi	421	5.5	52	0.09	1.62
Henan	3	0	3	0.00	0.00
Hubei	296	10.8	31	0.05	2.96
Hunan	656	15.9	98	0.09	3.10
Chongqing	200	10	33	0.06	0.49
Sichuan	2352	6.3	97	0.26	1.10
Guizhou	291	11.7	45	0.07	13.41
Yunnan	1308	86.2	36	0.26	0.15
Region C					
Beijing	2	50	2	0.00	0.00
Shandong	20	65	14	0.00	0.00
Hebei	3	33.3	3	0.00	0.00
Shanxi	3	33.3	3	0.00	0.00
Inner Mongolia	1	100	1	0.00	0.00
Liaoning	1	0	1	0.00	0.00

	No. of cases reported (*n*=7763)	% confirmed case (*n*=2403)	No. of counties reported (*n*=782)	Incidence per 100,000	CFR (%)
Jilin	2	100	2	0.00	0.00
Shaanxi	4	25	4	0.00	0.00
Region D					
Gansu	1	100	1	0.00	0.00
Qinghai	1	0	1	0.00	0.00
Xinjiang	2	0	2	0.00	0.00

5.4.2 Demographic and geographical changes in morbidity and mortality between 2005–2010 and 2011–2015

The trend in reported incidence and mortality was different between 2005–2010 and 2011–2015 (Figure 5-3). A total of 5439 cases were reported in 2005–2010. Subsequently, there were only 2324 cases reported in 2011–2015 (annual IR = 0.03/100,000 people), which was more than 50% lower than the preceding period ($P < 0.001$, Table 5.3). A slight decreasing trend in reported incidence was identified from 2005–2010 ($R^2 = 0.480$), while no trend in reported incidence has been observed during 2011–2015 ($P > 0.05$). Statistically, there was a significant difference in reported incidence between age groups during the period 2005–2010 ($z = 258.51$; $P < 0.001$) and the period 2011–2015 ($z = 50.83$; $P = 0.052$). The highest reported incidence rate was observed in the 50–59 age group (0.11/100,000 people). Moreover, there was no significant changes in gender and occupation-specific incidence from 2005 to 2015; the notified incidence remained high in males and primary workforces, especially farmers, during both periods ($P < 0.001$).

Of a total 168 deaths reported, most deaths (87%, 146/168) were observed during 2005–2010 (Table 5-3). Few deaths (22 deaths) were recorded during 2011–2015. However, we noted a significant difference in the mortality rate ($P < 0.001$) between 2005–2010 and 2011–2015. The mortality rate fluctuated during 2005–2010; where two peaks were observed in 2005 and 2007. In contrast, a relatively stable and low mortality rate was observed during 2011–2015.

Despite the significant drop in notified incidence and number of counties that reported leptospirosis, our analysis indicates 112 new counties notified leptospirosis infections in 2011–2015 (Appendix C: Table C-6). During this second period, we observed that leptospirosis infection had been reported in four new provinces: Hebei, Inner Mongolia, Jilin, and Gansu (Region C and D).

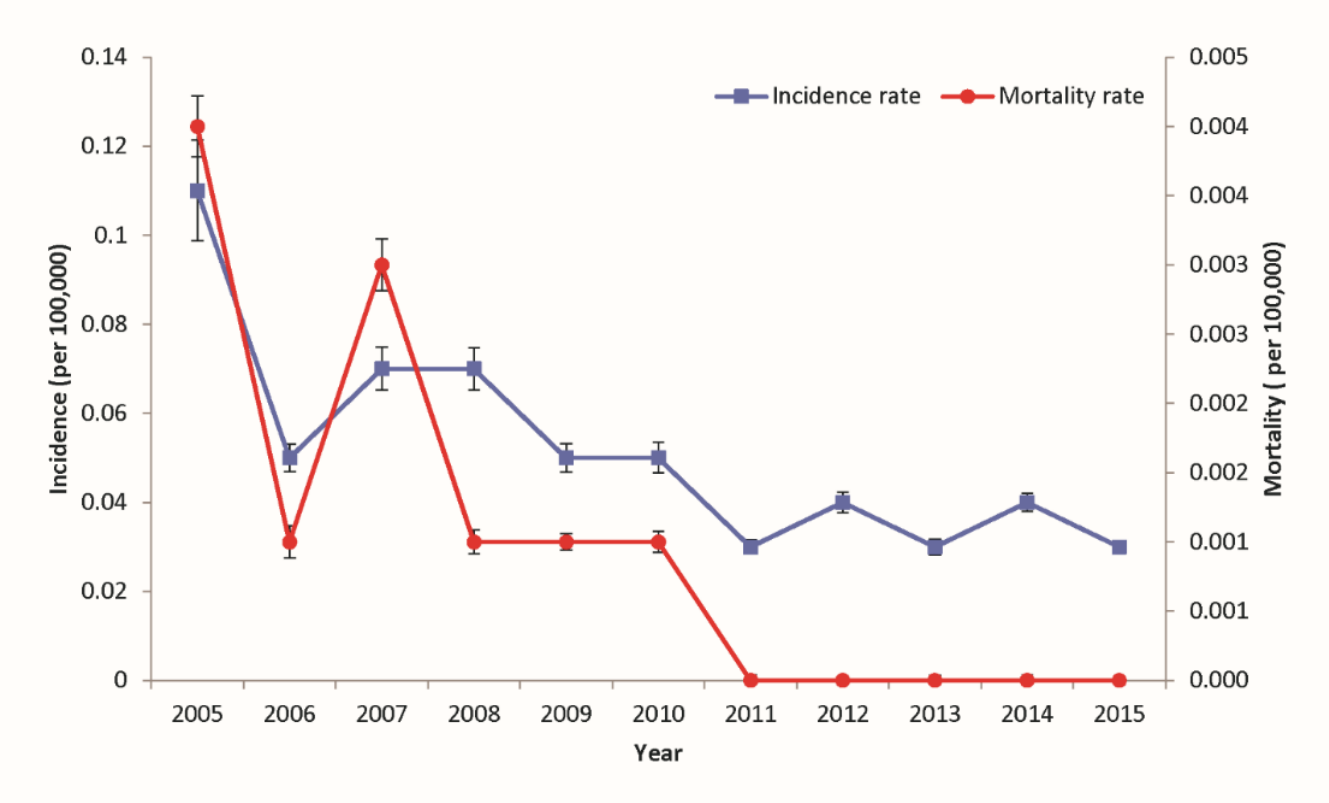

Figure 5-3 Annual reported incidence and mortality (per 100,000 people) of leptospirosis in China, 2005–2015

Table 5-3 Changes in notified incidence and mortality (per 100,000 people) due to leptospirosis in four regions in China during 2005–2010 and 2011–2015

Region	2005–2010				2011–2015			
	No. of cases[a]	Incidence	Deaths	Mortality	No. of cases	Incidence rate	Deaths	Mortality rate
A	835	0.05–0.14	39	0.00–0.01	374	0.04–0.06	4	< 0.01
B	4593	0.00–0.38	107	0.00–0.01	1941	0.00–0.28	18	< 0.01
C	9	< 0.01	0	0	7	< 0.00	0	0
D	2	< 0.00	0	0	2	< 0.00	0	0
Total	**5439**	**0.07**	**146**	**0.002**	**2324**	**0.03**	**22**	**< 0.01**

[a] included all cases (confirmed, clinical, and suspected)

5.4.3 Impact of changes in incidence and mortality on the burden of leptospirosis during 2005–2015

It is estimated that during 2005–2015 a total of 10,313 DALYs were lost due to leptospirosis or approximately 937 DALYs per annum (Table 5-4). Males are the most affected group with an estimated 7149 DALYs or approximately 70% of the total burden. The highest burden estimate was attributed to a group aged 10–19 years, both males and females, which accounted for around 30% of the total DALYs. The highest burden estimate was identified in Region B (7990 DALYs), followed by Region A (2312 DALYs) (Table 5-5).

Table 5-4 Age and gender-specific YLLs, YLDs, and DALYs estimates based on reported leptospirosis in China, 2005–2015.

Age	YLLs			YLDs			DALYs		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0–9	79.31	237.92	317.23	9.50	31.59	41.09	88.81	269.51	358.32
10–19	1077.14	1796.61	2873.75	40.37	163.4	203.77	1117.51	1960.01	3077.52
20–29	566.89	1281.47	1848.36	62.94	151.28	214.22	629.83	1432.75	2062.58
30–39	256.71	824.46	1081.17	117.32	213.98	331.31	374.03	1038.44	1412.48
40–49	255.03	620.29	875.32	132.52	240.34	372.87	387.55	860.63	1248.19
50–59	277.2	695.33	972.53	119.70	244.38	364.08	396.9	939.71	1336.61
60–69	73.73	397.18	470.91	58.90	150.57	209.47	132.63	547.75	680.38
70–79	17.28	52.81	70.09	16.15	42.99	59.14	33.43	95.8	129.23
80–89	0	0	0	2.37	4.75	7.12	2.37	4.75	7.12
90+	0	0	0	0.47	0.24	0.71	0.47	0.24	0.71
TOTAL	**2603.29**	**5906.07**	**8509.36**	**560.25**	**1243.52**	**1803.77**	**3163.54**	**7149.59**	**10,313.13**

Table 5-5 Temporal and geographical distribution of YLLs, YLDs, and DALYs of leptospirosis in China, 2005–2015.

	Years of Life lost (YLLs)	Years lived with disability (YLDs)	Disability-adjusted life years (DALYs)	DALYs/100,000 people
Year				
2005	2631.51	334.39	2965.90	0.22
2006	1066.17	163.63	1229.80	0.09
2007	1991.61	220.16	2211.77	0.16
2008	813.55	216.36	1029.91	0.08
2009	530.56	153.66	684.22	0.05
2010	345.99	168.38	514.37	0.04
2011	249.07	99.75	348.82	0.03
2012	303.1	116.14	419.24	0.03
2013	245.77	100.94	346.71	0.03
2014	287.34	130.15	417.49	0.03
2015	44.69	100.22	144.91	0.01
Region				
A	2035.89	276.92	2312.81	1.44
B	6473.47	1517.36	7990.83	1.11
C	0	8.55	8.55	<0.01
D	0	0.95	0.95	<0.01

Our results indicate a 95% decline in DALYs due to leptospirosis from 2005 to 2015 ($P < 0.001$, Table 5.5). The highest burden was estimated in 2005 (2966 DALYs), including 2632 YLLs and 334 YLDs; whereas the lowest burden estimates were identified during 2015 (144 DALYs). During 2005–2010, the total burden of leptospirosis was estimated at approximately 8636 DALYs (1439 DALYs per annum). This consisted of 7379 YLLs and 1257 YLDs. It was much higher than the period of 2011–2015, which accounted for approximately 1600 DALYs or a decrease of 80% from the previous period (Appendix C: Table C-7).

Between 2005–2010 and 2011–2015, a decline in DALY estimate was observed in almost all provinces (Figure 5-4). In 2005–2010, high DALYs estimates were observed in Sichuan (1337 DALYs), Guizhou (1936 DALYs), Hunan (1374 DALYs), and Guangxi (1293 DALYs). These four provinces had contributed to approximately 70% of the total DALYs during the period. However, a substantial reduction (on average at 53%) in DALYs occurred in many areas, including in those four provinces during 2011–2015 ($P < 0.05$). Although there was a significant reduction in DALYs, we identify that higher estimates of the burden remain observed in young individuals of both sexes, aged 10–19 years ($P < 0.05$, Figure 5-5). The burden estimates remained high among males (1316.8 DALYs) compared with females (360.3 DALYs) during 2011–2015 ($P < 0.05$).

A larger quantity of annual YLLs estimates were lost during 2005–2010 (1229 YLLs) than in 2011–2015 (225 YLLs) ($P < 0.05$). Leptospirosis resulted in approximately 5689 YLLs during 2005–2007, and it has contributed 55% of the total DALYs. A three-fold reduction in the number of YLLs was observed in 2005–2006, but a slight increase was observed in 2007. Moreover, we found higher YLLs estimates were contributed by economically less-developed provinces, such as Sichuan, Guizhou, Hunan, and Guangxi. The highest YLLs estimate was attributed to younger individuals aged 10–19 years. Similarly, YLDs estimates declined over time ($P < 0.001$) and a significant difference with annual YLDs was observed between the two periods ($P < 0.001$). An extended analysis was provided (Appendix C: Table C-8 to Table C-11).

In terms of YLLs, Guizhou had the highest estimates on YLLs, which account for 2300 YLLs or 27% of the total YLLs during 2005–2015, followed by Hunan, Guangxi, and Sichuan (Figure 5-6). In Guizhou, the highest YLLs estimates were observed during 2005–2010 (1800 YLLs). During 2011–2015, a dramatic change in YLLs estimates was observed in most provinces. However, the YLLs consistently remained relatively high in Guizhou. In terms of YLDs, Sichuan and Yunnan had higher estimates during both periods.

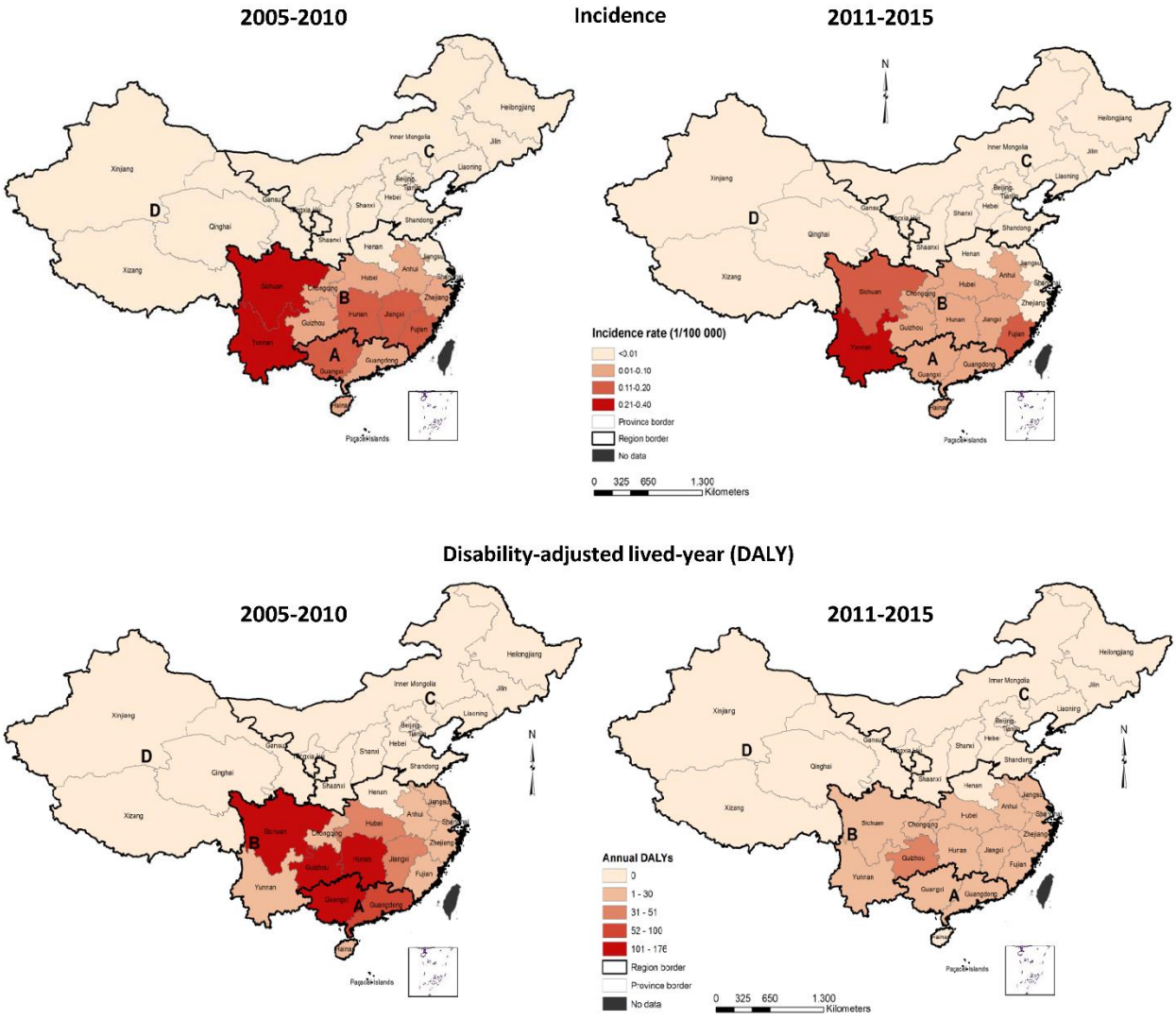

Figure 5-4 Changes on notified incidence (top) and geographical distribution of the burden (bottom) of leptospirosis in China over two periods, 2005–2010 and 2011–2015.

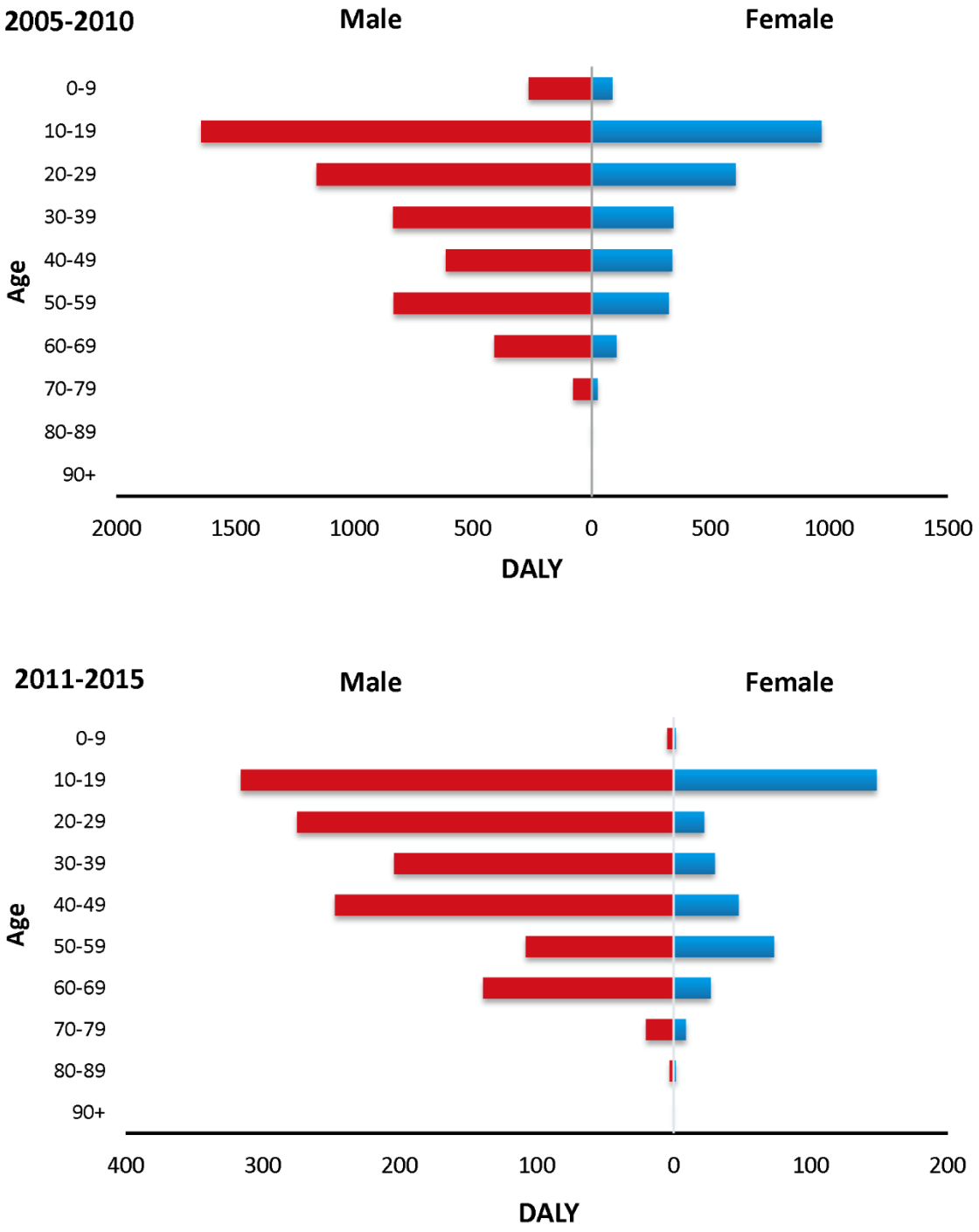

Figure 5-5 Temporal distribution of the burden estimates of leptospirosis by gender and age groups in China during 2005–2010 and 2010–2015.

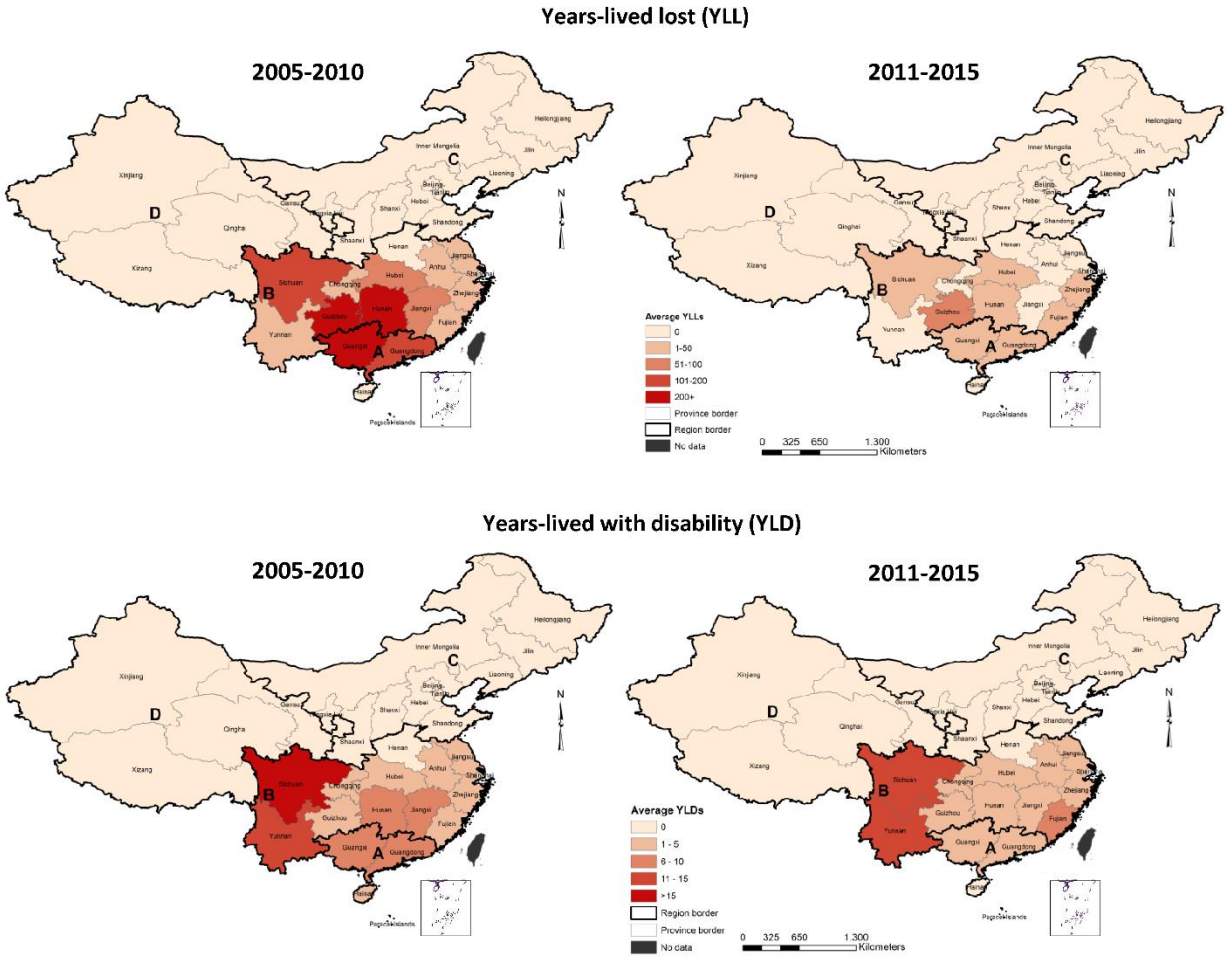

Figure 5-6 Changes in geographical distribution of years of life lost (YLL) and years-lived with disability (YLD) due to leptospirosis in China during 2005–2015.

5.5 Discussion

Our study quantified the remarkable decrease in leptospirosis incidence and mortality in China during 2005–2015, which was accompanied by substantial changes in the demographic and geographic pattern in disease burden estimates. We observed a remarkable decline in reported incidence and mortality in all provinces especially in region A and B where leptospirosis is principally most prevalent, such as Sichuan and Yunnan. These findings are in line with previous county-level studies which also reported a reduction in notified incidence while local outbreaks were still frequently reported in some areas (Li et al., 2013; Fan et al., 2014; Wang et al., 2014; Wu et al., 2015; Xu et al., 2016a; Tang et al., 2017)

Our analysis indicates that following a steep downward trend during 2005–2010, the reported incidence of leptospirosis in China remained quite low during the last five years. This finding suggests that China might have reached a low-level leptospirosis transmission similar to other developed countries (Gsell, 1990); although this might not indicate a real epidemiological situation as evidenced by the existence of persistent geographical foci of infection that can potentially lead to future outbreaks in the country. Also, we observed marked variation in fatality-rates across regions over time, which may be explained by the heterogeneity of the level of awareness and knowledge among populations towards leptospirosis—inadequate measures for early diagnosis and treatment especially during outbreaks, delay in seeking treatment, and severity of illness due to variation to *Leptospira* exposure and localised risk factors. Hence, more targeted control efforts are needed, especially in those high-risk areas and economically less developed areas, by enhancing awareness, improving access to safe water and sanitation facilities, and strengthening healthcare and local surveillance systems.

Our study demonstrates updated burden estimates in terms of DALYs for leptospirosis in China. To the best of our knowledge, this is the first study that attempted to quantify the spatiotemporal heterogeneity in the burden of leptospirosis using time-series historical notification data, especially in China. From 2005 to 2015, it was estimated that more than 10,000 DALYs were lost due to infections where the burden was predominantly contributed by high YLLs. However, our estimates are in stark contrast with those reported by a study elsewhere (Torgerson et al., 2015). Our smaller DALYs estimates may reflect the sharp reduction in both reported incidence and mortality that occurred during 2005–2015.

The burden estimates provided by Torgerson et al. (2015) were mainly generated based on the morbidity and mortality estimates developed by another study elsewhere (Costa et al., 2015) that involved modelling on the morbidity and mortality data by incorporating several variables, adjustments, and uncertainties. Their study was a global study and applied a global model to each country. It is important to consider that epidemiological conditions for leptospirosis transmission and notifications are geographically non-stationary and this approach might be inadequate to capture small-scale heterogeneities. Importantly, that study used published data from the 1970s, a period when leptospirosis was highly endemic and when China’s surveillance systems might be different than in the 2000s. This study extends Torgersen’s (2015) study in that we used high-resolution, contemporaneous data based on

recent national Chinese disease surveillance systems that have relatively good coverage across the country. This study successfully demonstrated spatiotemporal heterogeneity in the burden within China that was not captured by previous studies. We also identified variation in the surveillance system or diagnostic capacity, as evidenced by the difference in laboratory-confirmed cases among provinces (*see* Appendix C Table C.1), which means that adjustments should be cautiously applied for the whole country. Applying adjustments to the whole country could be over/underestimating the actual incidence and mortality rates.

It should also be noted that our burden estimate was based on passive surveillance and all cases reported during the period. One of the major limitations in using surveillance data is that could be over or underestimate the actual incidence/burden. The number of reported cases, the proportion of laboratory-confirmed cases, and fatality-rates have shown to be markedly varied during the period of study and across provinces, indicating a variation in diagnostic techniques capacity across the provinces and, therefore, may bias our analysis. It should be noted that the surveillance system in China is mainly hospital-based, but their laboratory capacity to undertake diagnosis through MAT, ELISA, or PCR also varies across hospitals. Also, since leptospirosis often presents as a broad spectrum of clinical manifestations, more untreated cases or false-negative cases (misclassification) might have occurred and lead to a high number of underreported and misdiagnosed cases, especially in resource-limited endemic areas. The recent findings indicated the presence of leptospiral infection among patients with undifferentiated fever in Hainan province (Wu et al., 2017), suggesting that the incidence and burden may be underestimated. Thus, enhanced-surveillance prospective population-based studies may better help to determine existing leptospirosis cases in China.

Another drawback is that there was no detailed data available on patient's clinical presentations in our dataset, so that it was not possible to determine the severity of disease that may help to assess disability weight for DALY estimation as well as to explain the variation of fatality-rates across China. In addition, in this study, we used all categories of cases including suspect, clinical, and confirmed leptospirosis cases as defined by China health authority. It is necessary to acknowledge that there may also be a reporting bias that affects our analysis as leptospirosis have overlapping clinical presentations with another disease (e.g., dengue) (Bharti et al., 2003).

Changes in incidence and burden can be partly associated with improvement in prevention and control measures including health promotion activities, sanitation, and the application of leptospirosis vaccination program in both human and livestock animals (e.g., pigs) (Yang et al., 2011; Hu et al., 2014; Wang et al., 2014; Zhou et al., 2015; Xu and Ye, 2018). In terms of the surveillance system, the development of NIDRIS and CIDARS following outbreaks of the severe acute respiratory syndrome (SARS) in 2003 has helped to efficiently improve the timeliness, completeness, and coverage of the data across China as well as facilitating early detection of diseases outbreaks (Yang et al., 2011). However, it has been confirmed that during 2005–2015, there was no significant change in the surveillance systems as well as diagnostic tests, specifically for leptospirosis. While, in terms of the vaccination program, human leptospirosis vaccine has been developed since 1958 and until now it has been administered to high-risk populations in China during the epidemic seasons. A multivalent inactivated vaccine is currently the only one available in China (Xu and Ye, 2018). However, there is no available evidence that provide a detailed information regarding vaccination coverage for the same period (2005-2015). Despite these improvements, however, few outbreaks remain occur in some localities in China.

Changes in ecological and social conditions that have been underway in China in the past 20 years may have also played an essential role in leptospirosis epidemiology. Changes in the landscape, agricultural practices, and livestock husbandry—for instance, restriction on livestock herding, farming modernisation, and pigs or livestock vaccination (Dai, 2010; Hu et al., 2014)—could have impacted the transmission rate of leptospirosis in China. Industrialisation, for example, has led to significant epidemiological shifts in rural areas through the introduction of agricultural technology and mechanisation which might reduce the rate of human exposure to the *Leptospira*-contaminated environment. Also, we noticed that there were significant anthropogenic ecological changes following the development of the Three Gorges Dam and the nationwide reforestation program called “Grain for Green”, which probably had an effect on leptospirosis transmission. Water impoundment in many endemic areas has been known to have an impact on rodents’ habitat and population dynamics of the pathogen in those regions (Kittinger et al., 2009; Wang, 2010). These projects have also been reported to have had a substantial impact on other rodent- and water-borne diseases, such as

hemorrhagic fever with renal syndrome and schistosomiasis (Xie et al., 2015; Chang et al., 2016; Zhou et al., 2016). However, the role of environmental changes on space-time variation on leptospirosis incidence and burden still needs to be explored. Also, a substantial change in the quality of livestock husbandry in China (e.g., improved waste management and farm biosecurity) might also have contributed to a decrease in transmission rate in livestock (Hu et al., 2014). A review of significant changes in the epidemiology of infectious diseases in China, including leptospirosis, has also been described elsewhere (Wang et al., 2008; Zhang and Wilson, 2012).

A detail differentiation of occupation (provided in Appendix C: Table C-2) indicates a reduction in cases in common high-risk occupation (e.g., farmer). Indeed, there was an increased number of cases in commercial service workers and cadres in the past 2-years (2014-2015), however, the number remained relatively low compared to farmers. This is clear that the most affected populations by leptospirosis is still farmer relative to other occupation. This finding shows that the change in leptospirosis trends did not associated with occupation.

Our results demonstrate that the highest DALY was attributed to younger individuals aged 10–19 years due to higher mortality (YLLs) observed in this group. It is important to note that about 10% of the leptospirosis cases was reported among students (Appendix C: Table C-2); of these, about 98% were aged below 20 years and most them were lived in the Southwest China (63%), in particular, Sichuan province (38%) (data not shown). Interestingly, higher DALYs estimates were identified in economically less-developed provinces in China including Guangxi in Region A and Guizhou and Sichuan in Region B. Guangxi and Guizhou are known to have a low gross regional product among provinces in China (NBSC, 2016).

High burden estimates in school-aged children may probably be associated with lack of parental supervision because of parental migration from rural areas to the cities that happened during the last three decades. Lack of parental supervision in preventing children from engaging in unhealthy behaviors and being in unhealthy environments may likely increase the risk of pathogenic exposure and children's ill health (Li et al., 2015). Additionally, rural migration has shifted labor allocation and participation in families in farming activities, where children, women, and elderly become more active in farming (Chang et al., 2011; Mu and van de Walle, 2011) and, therefore, they are more likely to be exposed to *Leptospira*-contaminated environments. It has been indicated in our findings that 5% of the total cases

among farmers were attributed to young farmers (aged under 20 years). Health education and awareness amongst this population group, especially in rural communities is, therefore, essential to further reduce the risk in this demographic group. These findings highlight the importance of improving current local surveillance for leptospirosis and healthcare services for the high-risk populations living in the high-risk areas identified in our study.

We also found that disease transmission might have emerged in some counties located in temperate regions to the north of the country although at the very low rate. This may partly be due to change in environmental conditions (i.e., climate variation and changes in land use/land cover) or the translocation of potential reservoirs from adjoining endemic regions. Climate variation notably the increase in temperatures may have driven the spread of *Leptospira* towards temperate regions in China through its impact on rodent population growth in these areas (Desai et al., 2009). Several outbreaks in China have been thought to be associated with high rainfall intensity (Wang et al., 2014). However, we suggest that further investigation should be performed to determine whether the emerging incidence may correlate with changes in climate and other environmental and social conditions (e.g., human migration).

However, our study has several limitations that need to be considered, which are mainly associated with the data. First, as there was no information regarding serovars in our data, we were not able to analyse further whether the observed change the distribution in incidence, mortality, and burden might also linked with a dynamic change in circulating serovars in the country during the period of study, which may reflect the distribution of potential animal reservoirs. A recent study by Zhang et al (2019) demonstrates the genetic diversity across China, suggesting the variation in animal reservoirs responsible for human leptospirosis in a region. Second, the observed reduction in reported incidence and mortality from 2005 to 2015 may also be a result of the changes in social and environmental conditions in endemic areas as has been discussed above. In a subsequent study we, therefore, will aim to understand the drivers of such reduction by focusing on high-risk areas and will quantify the attributable fraction of determinants, such as socioeconomic development, farming practices, and environmental changes. Third, in this study, I defined “Occupation” into groups, including primary (raw-based industry, commonly known as agriculture and fisheries), secondary (manufacturing) and tertiary (service) sector according to national standard of job

classification in China rather than using a single or detail occupation. Indeed, every single occupation may have differences in terms of leptospirosis epidemiology, behaviour and risk exposure. However, due to the small number/sparse distribution of cases by occupation (e.g., farmer vs Seaman/fisherman) (see Appendix C, Table C-2) in the available dataset, I did not able to explore the trends/effects of every single occupation on leptospirosis incidence. Therefore, for that reason I combined categories according to available standard occupation classification.

5.6 Conclusion

In the last eleven years, the disease burden estimates of leptospirosis indicated a declining trend across the country, suggesting the opportunity to control and eliminate leptospirosis. Leptospirosis should not be neglected as it remains an important zoonotic disease and disproportionately affects farmers and young populations, especially in that remote rural areas where basic sanitation and disease awareness are lacking. Enhanced intervention strategies will be needed in the residual high burden regions identified in this study, including promoting the importance of personal protective equipment (PPE) and livestock vaccination among farmers also improving awareness on risk of leptospirosis towards general population. Active surveillance is urgently required to update disease burden estimates of leptospirosis to help define necessary public health interventions. Finally, these findings will help design targeted intervention strategies in China to reduce the burden of human leptospirosis. An evaluation of the role of environment and socioeconomic factors on the changing leptospirosis epidemiology and burden should be considered in future work. Moreover, this study highlights a number of gaps in knowledge which will be directly addressed in the subsequent Chapters of this Thesis.

Chapter 6 Geographical and temporal distribution of the residual clusters of human leptospirosis in China, 2005–2016

This chapter has been published in *Scientific Reports* as an original peer-reviewed research paper. The concept and design of the study presented in this Chapter 6 was formulated by PWD (85%) with the assistance of RJSM (15%). WYZ provided the data. PWD was responsible for data management (100%), data analyses (100%) and the interpretation of results (85%) was discussed in consultation with RJSM (10%) and all co-authors (5%). PWD was responsible for drafting the manuscript (100%). PWD was responsible for revision of the final version of the manuscript (90%), taking into account the comments and suggestions of RJSM (5%) and all co-supervisors (5%).

6.1 Context

The results of Chapter 5 revealed that despite the significant reduction in leptospirosis morbidity and burden in the past two decades, leptospirosis transmission remains high in some regions across China. Importantly, the study detailed in Chapter 5 identified significant spatial heterogeneity in leptospirosis DALYs that could be strongly correlated with local demographical, environmental, and socioeconomic conditions. However, such evidence is lacking, leading to inefficient resource allocation and difficulty in applying control programs. Exploration of the spatial patterns of leptospirosis incidence, as well as the spatial variation of its drivers at finer spatial resolution, is important to better inform local health authorities in effectively designing and implementing targeted public health interventions, towards the elimination of leptospirosis in the residual high-risk areas.

In Chapter 6, using similar leptospirosis data as that in Chapter 5, I sought to explore whether the distribution of leptospirosis incidence was spatially clustered in particular areas of China, to what extent geographical patterns at county level changed over time, and to identify demographic, ecologic, and socioeconomic characteristics in the identified high-risk counties. To address these objectives, I employed a set of spatial analyses, including Moran’s I and local indicator of spatial association (LISA), to investigate global spatial clustering and to

locate high-risk counties, respectively. In addition, I compared the demographic, ecological, and socioeconomic conditions of the identified high-risk counties relative to low-risk counties. In this Chapter, I demonstrate that leptospirosis incidence was spatially clustered, but the propensity of clustering significantly declined during the period studied (i.e., became more randomly distributed). I identified a discrete number of high-risk counties in the provinces situated in tropical and sub-tropical regions of China (i.e. Yunnan, Sichuan, Chongqing, Guizhou, Guangdong, Guangxi, Fujian). Moreover, I found that in high-risk counties, leptospirosis disproportionally affected people aged 21–47 years, males, and farmers. In addition, compared with low-risk areas, I demonstrated that high-risk counties for leptospirosis appear to have higher precipitation rates, to be located at higher altitude, to be more rural, and to have lower livestock density, lower crop production and lower gross domestic product (GDP). This evidence is vital as it will help design effective local specific interventions to high-risk leptospirosis areas in China.

6.2 Introduction

Leptospirosis, an emerging yet neglected zoonotic disease caused by the pathogenic spirochetes belonging to the genus *Leptospira,* has been a significant global public health hazard (Levett, 2001). Infection can be asymptomatic or can manifest as a life-threatening disease due to acute renal failure, liver injury, or pulmonary haemorrhage syndrome (McBride et al. 2005). Annually worldwide, leptospirosis is estimated to cause more than one million cases, 58,900 deaths, and the loss of more than 2.90 million DALYs (Costa et al., 2015; Torgerson et al., 2015). The high incidence occurs during wet seasons and flooding reaching to more than 100 per 100,000 (World Health Organization, 2003). Human infection occurs via direct contact between injured skin or mucous membrane with the urine or blood containing the bacteria of the infected animals or due to exposure to bacterial-contaminated soil or water. At present, a total of 10 pathogenic *Leptospira* and five intermediate species have been identified so far and it is likely that novel species will be continuously discovered (Xu et al., 2016; Puche et al., 2018). *Leptospira* could be carried by wide-range animals such as pigs, cattle, and dogs, but rodents act as an eminent role in shedding the bacteria into the environment (Ellis et al., 1981; Backhans and Fellström, 2012). The spatial variation of leptospirosis incidence has been known to be driven by ecological (e.g., precipitation,

elevation, animal hosts, land use types) and anthropogenic factors (e.g., farming activities, poverty) (Lau et al., 2012a; Bacallao et al., 2014; Suwanpakdee et al., 2015; Zhao et al., 2016; Rood et al., 2017).

In China, since the 1950s there were more than 2.5 million cases and approximately 20,000 deaths reported to the national disease notification system (Yan et al., 2006). Within the last two decades, it was estimated that at least 10,000 DALYs were lost because of leptospirosis and it disproportionately affected males, young populations, and farmers (Dhewantara et al., 2018a). *Leptospira interrogans* serogroup Icterohaemorrhagiae serovar Lai has been responsible for most human infections in China and *Apodemus agrarius* is the most important animal host among other animals, such as pigs, cattle, and dogs (Shi et al. 2000; Zhang et al. 2012; Liu Y. et al. 2016). Leptospirosis cases have been notified in almost all provinces in China except the provinces of Ningxia and Xizang (Shi et al., 1995; Liu, 2012; Dhewantara et al., 2018). The geographical distribution of leptospirosis in China has been associated with climatic factors where the majority of incidences occurs in tropical and sub-tropical regions in the southwest, central, south, and southeast of China (Shi et al. 1995; Zhang et al., 2012; Zhao et al., 2016). A recent study suggested that physical environmental and socioeconomic characteristics could also play an important role in preserving leptospirosis transmission in China (Zhao et al., 2016). However, further investigation is required to improve our understanding of the characteristics of high-risk areas of leptospirosis throughout the country. A better understanding of such characteristics would help guide health authorities in identifying potential areas for leptospirosis transmission as well as in targeting vulnerable populations.

During the last two decades, there was a decline in the number of notified leptospirosis cases and mortality in China, which might be partly due to the effectiveness of control programs deployed by Chinese authorities, including rodent control, improvement in sanitation conditions, and vaccination during epidemic season, especially in high-risk communities (Hu et al., 2014; Xu and Ye, 2018). However, local leptospirosis outbreaks are still occurring in certain parts of the country (Ma et al., 2010; Li et al., 2013; Wang et al., 2014; Tang et al., 2017) indicating that leptospirosis remains an important zoonotic disease in the country. However, changes in the geographical distribution of leptospirosis incidence in China during the last decades, has not been adequately explored. More importantly, little is known about

the location of residual high-risk foci of leptospirosis and key demographic, ecological and socioeconomic characteristics that could explain residual disease transmission in those areas. This knowledge gap hinders the design and implementation of targeted interventions towards reducing risk and eliminating leptospirosis in China.

Geographic information systems (GIS)-based technologies have now been widely used in numerous infectious disease studies including in the field of leptospirosis (Barcellos and Sabroza, 2000; Suwanpakdee et al., 2015; Rood et al., 2017). It allows researchers and health authorities to better explore and understand the disease pattern and its underlying determinants. GIS can be used to map disease rates and help locate and characterize high-risk areas where interventions should be conducted. By combining GIS and spatial statistics, social and environmental risk factors associated with high-risk areas could be determined.

The aims of this study are i) to investigate whether or not the spatial pattern of leptospirosis incidence was clustered over China during the study period, ii) to identify the location of high- and low-risk counties for leptospirosis and iii) to characterise high-risk counties by identifying differences between them and other type of counties in terms of their demographical, ecological, and socioeconomic conditions. These research aims fit with the current gap in knowledge in terms of modifiable factors that distinguish high-risk from low risk areas that could be targeted for the design of local interventions. Findings from the present study would have much value for policymaking, especially at county level, to strengthen disease surveillance programs and intervention strategies for leptospirosis.

6.3 Methods

6.3.1 Data collection

Leptospirosis infection data

We utilised notified human leptospirosis data that had been used in our previous study elsewhere (Dhewantara et al., 2018a). Briefly, in China, leptospirosis has been classified as Class B Notifiable Disease since 1955. All diagnosed cases of leptospirosis must be reported by all healthcare providers at county-level to the Center for Disease Control and Prevention through the China Information System for Diseases Control and Prevention (CISDCP). Notified leptospirosis cases include information about sex, age, occupation, date of onset of

illness, date of diagnosis, date of death, case classification (suspected, clinical, and laboratory-confirmed), and address. Leptospirosis cases are defined into three categories: suspected, clinical, and confirmed case (Ministry of Health of China, 2008). Suspected cases are defined as an individual with: a) a clinical symptom such as acute fever (up to 39°C), which may be accompanied by chills, myalgia, or malaise and; b) history of exposure within a month prior to the onset of illness to the following risk factors: epidemic season, reside in epidemic area, either direct or indirectly contacted with suspected animals and their urine or faeces or contaminated water and soil. Clinical (probable) cases are defined as suspected cases with at least one of the following clinical manifestations: conjunctival hyperemia, gastrocnemius tenderness, or enlargement of the lymph nodes. A confirmed case is defined as a suspected case with one or more any of the following laboratory criteria: 1) positive culture of *Leptospira* from blood, urine, tissues, or cerebrospinal fluid (CSF); 2) microscopic agglutination test (MAT) titre of ≥ 400 in single or paired serum samples; 3) a fourfold or greater rise in MAT titres between acute and convalescent-phase samples; 4) presence of pathogenic *Leptospira* spp detected by polymerase chain reaction (PCR); 5) presence of IgM antibodies by enzyme-linked immunosorbent assay (ELISA). All cases reported from 1January 2005 to 31 December 2016 were included in our analyses.

For the purpose of spatial analyses, all individual leptospirosis cases were linked to respective county-level polygons based on county code, using the GIS software (ArcGIS version 10.5.1, ESRI Inc., Redlands, CA, USA). Mainland China comprises 31 provinces/autonomous region/municipalities and more than 2,900 counties, with populations ranging from 7123 to 5,044,430 people and geographic areas ranging from 5.4 to 197,346 square kilometers.

Ecological and socio-economic characteristics data

Leptospirosis risk is perceived to be multifactorial in nature involving complex interactions between ecological and socioeconomic conditions (Lau et al., 2012a; Rood et al., 2017). Elevation data and monthly precipitation data with 30 arc-seconds (~ 1-km) spatial resolution was extracted from WorldClim (v.2) (available at www.worldclim.org), which was based on the average meteorological data for 1970-2000 (Hijmans et al., 2005; Fick and Hijmans, 2017). An urban extent grid (v.1) raster dataset was obtained from the Global Rural-Urban Mapping

Project (GRUMP v.1) (Center for International Earth Science Information Network - CIESIN - Columbia University et al. 2011) and used to determine the proportion of urbanized or rural areas of each county (http://sedac.ciesin.columbia.edu/data/set/grump-v1-urban-extents). Data for pig and cattle density for each county was sampled from Gridded Livestock of the World version 2.01 with 1-km spatial resolution retrieved from FAO-GeoNetwork (http://www.fao.org/geonetwork/srv/en/main.home) (Robinson et al., 2014). Farmland productivity raster map were obtained from the Resource and Environmental Science Data Center of the Chinese Academy of Sciences (http://www.resdc.cn) (Xu et al., 2017). Socioeconomic condition of each county was indicated by the gross domestic product (GDP). A raster map of 2010 Gross Domestic Product (GDP) of China with 1-km resolution was used (http://www.geodoi.ac.cn/weben/doi.aspx?Id=125) (Huang et al., 2014). Zonal mean values for each raster datasets were sampled at each county polygon using Zonal Statistics module in the Spatial Analyst toolbox in ArcGIS software.

6.3.2 Data analysis

Descriptive analysis and disease mapping

A county-level notified human leptospirosis cases were analysed descriptively and overall yearly notified leptospirosis and number of county reported leptospirosis were plotted. Number of leptospirosis cases of each county was then utilized to explore the spatial distribution of the leptospirosis in China. A county-level crude standardized morbidity ratio (SMR) was estimated by dividing the observed number of cases by the expected number of cases in the study population (overall incidence rate of human leptospirosis for the whole country from 2005 to 2016 multiplied by the population of each county) (Lawson and Williams, 2001). County-level population data for 2005–2016 were obtained from the National Bureau of Statistics of China. To reduce random variation resulting from a small number of observations and to produce statistically more precise risk estimates, spatial smoothing based on empirical Bayes method was applied (defined as smoothed SMRs), so that the effect of different population sizes in corresponding county can be adjusted (Marshall, 1991; Meza, 2003). The empirical Bayes smoothing procedure was implemented using *R* software package '*DCluster'.*

Global and local spatial autocorrelation statistics

To determine the presence of spatial dependence in the smoothed SMRs across counties during the period studied, global Moran's *I* statistics was calculated. As proposed by Assunção and Reis (Assunção and Reis, 1999; Bivand et al., 2013), Moran's *I* statistics were adjusted based on the Empirical Bayes Index. Moran's *I* value ranging from -1 to 1 with a value close to 0 indicates no spatial clustering (random). A positive value indicates positive autocorrelation and a negative value means negative autocorrelation (Moran, 1950). A spatial weight matrix was constructed based on *k*-nearest neighbour approach (Bivand et al., 2013). The significance of Moran's *I* of smoothed rates was assessed using Monte-Carlo randomization with 999 permutations. Significance ($P < 0.05$) of the test statistic indicates that incidence is spatially clustered or dispersed. Moran's I population was performed under R environment on package '*spdep*' (Bivand 2017; R Core Team 2015).

Local indicators of spatial association (LISA) analysis was performed as the global pattern was not random. LISA was calculated to detect the presence of clusters of counties with high (high-high, HH) and low rates (low-low, LL), as well as spatial outliers (high-low, HL and low-high, LH). HH clusters are defined when a county with a high value of leptospirosis incidence is surrounded by other counties also with high values leptospirosis incidence (later classified as a high-risk county) (Anselin, 1995). While LL clusters represent counties with low values of leptospirosis incidence surrounded by neighbouring counties with low values of leptospirosis incidence (classified as low-risk county). The HL or LH clusters indicate counties with high or low incidence surrounded by counties with low or high incidence. From a spatial epidemiology point of view, the spatial outliers can explain whether the area defined as receptive area (L-H) or endemic area (HL. LH areas are expected to be vulnerable to disease introduction as they are surrounded by high-risk areas. In contrast, HL areas may play an important role in spreading the disease to their low-risk neighbours and the probability of transmission is a function of both sharing similar underlying epidemiological conditions that may favour infection spread. LISA analysis was carried out by using GeoDA ver. 1.8 software (Anselin et al. 2005). Maps were created using ArcGIS v10.5 (ESRI, Redlands, CA, USA).

Statistical analysis

Descriptive analyses were performed to profile and compare demographical, ecological, and socioeconomic conditions of all cluster categories (e.g., HH, LL, LH, HL) as identified by LISA analysis during the 12-year period studied. Continuous variables (e.g., age, elevation, precipitation, pig density, cattle density, farmland production and GDP) were described using their mean and 95% confidence interval (CI) or median and interquartile range (IQR). Categorical variables (e.g., sex, occupation type, type of county) were described as count and proportions and 95%CI. Differences in case demographic information, ecological and socioeconomic conditions between clusters were tested either using χ^2 tests (for categorical variables) or one-way ANOVA or Kruskal-Wallis test with post hoc Tukey's honestly significant difference (HSD) test (for continuous variables). Levels of significance were set at 5%. All statistical analyses were performed using SPSS 24 (IBM Corp, Armonk, NY, USA).

6.4 Results

6.4.1 Descriptive analysis

A total of 8158 human leptospirosis cases were notified during 2005–2016 in 794 counties from a total of 2922 counties. Of which, 2,633 cases (32.27%) were laboratory confirmed cases. During 2005–2016, the notified incidence decreased as well as the number of counties with leptospirosis (Figure 6-1). Incidence dropped after 2005, but there was a slight increase in rates during 2007–2008 before incidence continued to decrease until 2016. The number of counties with leptospirosis appears to have a similar pattern to that of the number of reported cases. The number of counties decreased over time but was relatively stable during 2011–2016 ranging from 163 to 182 counties (Appendix D: Table D-1).

Our results indicate geographical and temporal variation in the crude standardized morbidity ratios (SMRs) of notified human leptospirosis in China at county level (Figure 6-2). The smoothed SMRs maps reveal a clear distribution of counties with relatively high leptospirosis rates also gradual changes in rates at the county level in China during 2005–2016 (Figure 6-3). Two counties in the south of Yunnan province, Xishuangbanna Prefecture City (Mengla County) and Pu'er Prefecture City (Menglian County), consistently had the highest rate during 2005–2016. High smoothed rates were also observed in counties situated in the southeast of

Sichuan, in the southeast Guizhou border to Hunan and Guangxi, north Fujian and southern Anhui.

Figure 6-1 Annual notified incidence rate (per 100,000 people) and number of counties with human leptospirosis in China, 2005–2016. The graph was created by in R environment using ‘ggplot2’ package.

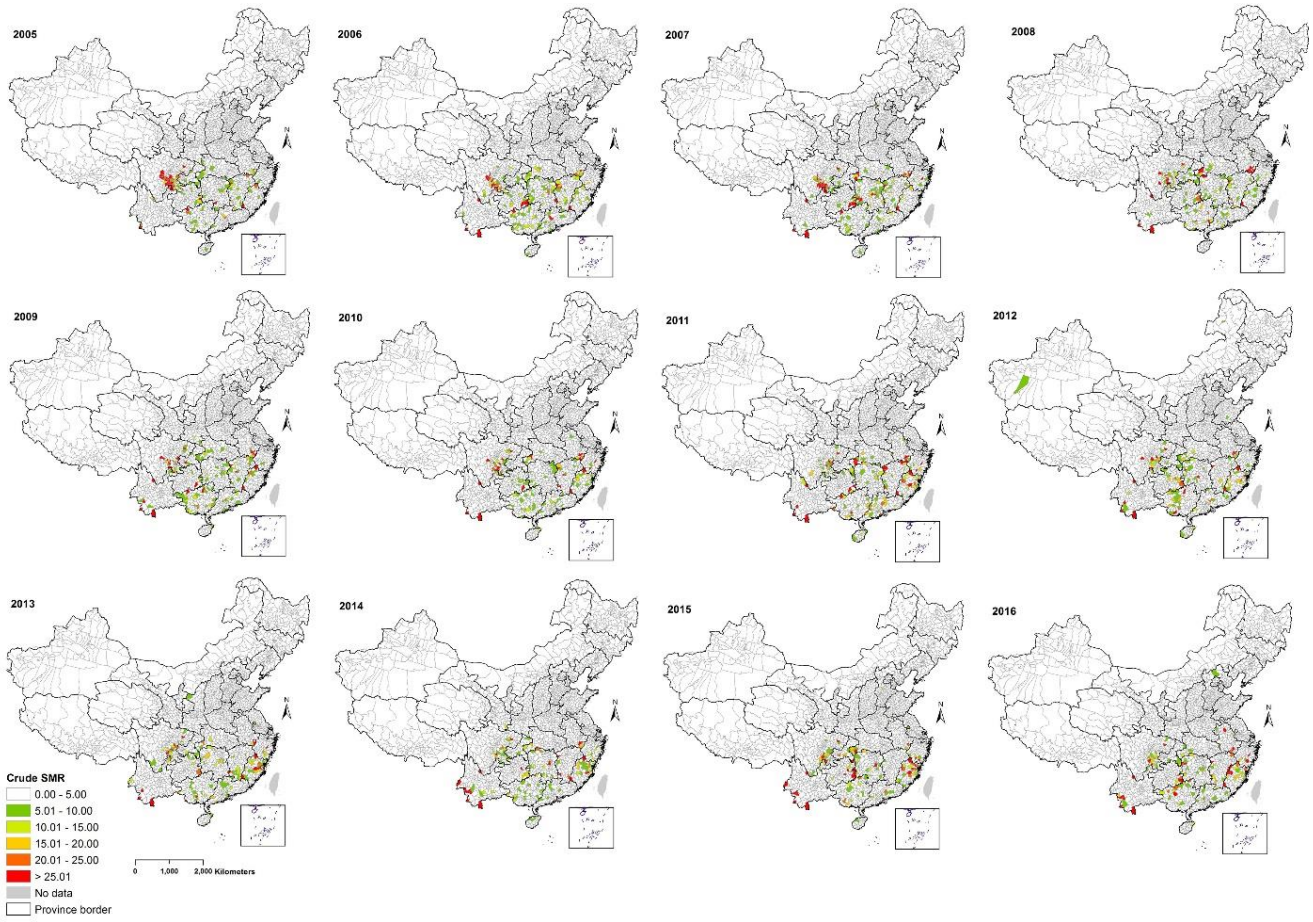

Figure 6-2 Crude standardized morbidity ratios (SMRs) for human leptospirosis by counties in China, 2005–2016. The map was created in ArcGIS 10.5.1 software, ESRI Inc., Redlands, CA, USA, (https://www.arcgis.com/features/index.html).

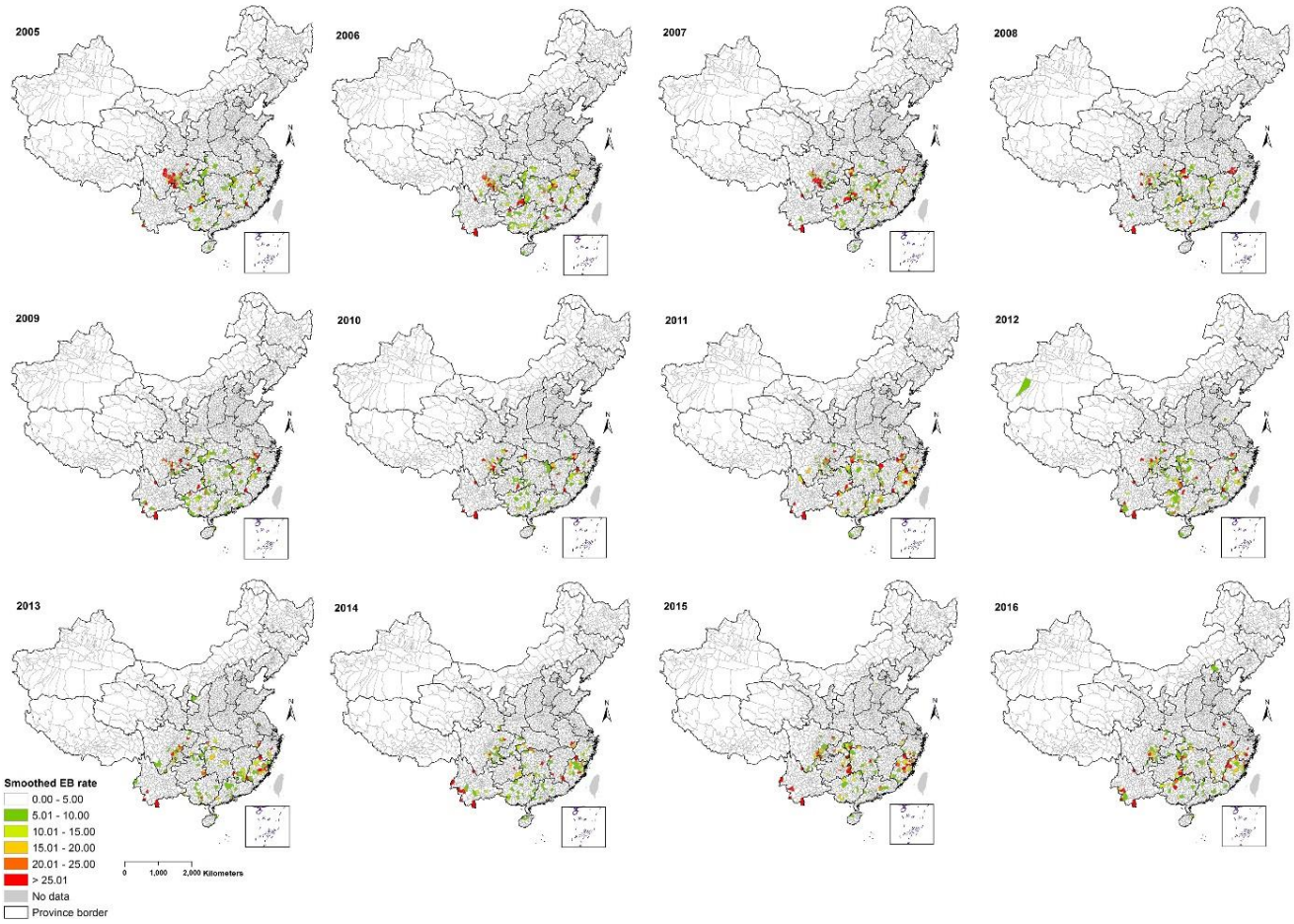

Figure 6-3 County-level smoothed rates maps of human leptospirosis using empirical Bayesian estimates, China, 2005–2016. The map was created in ArcGIS 10.5.1 software, ESRI Inc., Redlands, CA, USA, (https://www.arcgis.com/features/index.html).

6.4.2 Spatial autocorrelation analysis

The Moran's *I* analysis demonstrates a significant positive spatial autocorrelation in rates throughout the period studied, indicating that leptospirosis incidence was spatially clustered. Yet, there was a decreasing trend in the Moran's value over time and reached the lowest value in 2013 (I = 0.009, P value = 0.03) (Table 6-1).

The local indicator spatial association (LISA) test identified high-risk counties (classified HH clusters; red color) in southwestern provinces (e.g., Sichuan, Guizhou, Yunnan), central province (e.g., Hunan), southeastern provinces (e.g., Fujian, Anhui, Jiangxi, Zhejiang) and southern provinces (e.g., Guangxi and Guangdong) (Figure 6-4). Low-risk counties (LL

clusters; green color) were predominantly detected in provinces in the east towards northeast China.

Table 6-1 Spatial autocorrelation (Global Moran's *I*) of human leptospirosis in China from 2005-2016.

Year	Moran's *I*	*P* value
2005	0.3167	0.001
2006	0.0390	0.011
2007	0.0711	0.004
2008	0.0841	0.001
2009	0.0404	0.013
2010	0.0308	0.011
2011	0.0376	0.003
2012	0.0373	0.016
2013	0.0102	0.032
2014	0.0097	0.033
2015	0.0232	0.012
2016	0.0198	0.015

The annual incidence rate in high-risk clusters fluctuated during the study period, ranging from 0.28 to 2.67 per 100,000 people with the highest rates observed in 2005. The number of high-risk counties was reduced 25% from 64 in 2005 to 48 counties in 2016 (Table 6-2). In total, there were 265 (10.35%) counties in 12 provinces classified as high-risk clusters during 2005–2016 (Table 6-3). A high proportion of high-risk counties relative to their total counties observed in Fujian (41%), Guangxi (32%), and Sichuan (31%). From 2005 to 2016, high-risk counties were consistently observed in the provinces of Yunnan, Sichuan, Guizhou, Fujian, and Anhui. Four counties including Yanjin (Yunnan province), Yibin and Qianwei (Sichuan province), and Shexian (Anhui province) were high-risk counties for 10 years of the period studied.

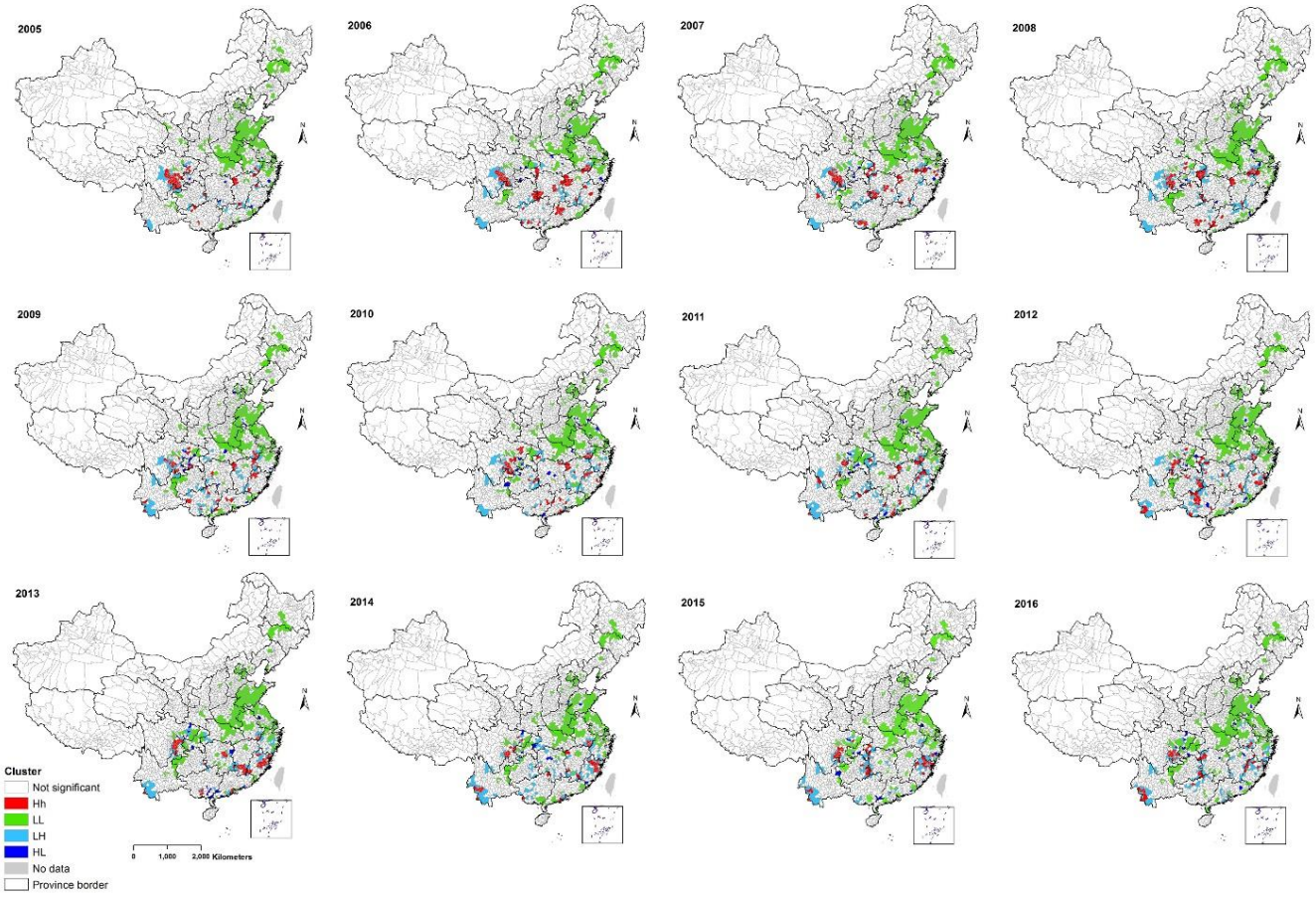

Figure 6-4 Annual spatial cluster patterns of human leptospirosis as determined by local indicator spatial autocorrelation (LISA), China, 2005–2016. The HH (later stated as high-risk, red) cluster was defined when high values were surrounded by high values. LL (low-risk, green) clusters represented a cluster of low rates surrounded by counties with low rates. LH (light blue) or HL (dark blue) was defined if a cluster of low or high rate values were surrounded by high or low rates. The map was created in ArcGIS 10.5.1 software, ESRI Inc., Redlands, CA, USA, (https://www.arcgis.com/features/index.html).

Table 6-2 Descriptive statistics of human leptospirosis clusters, China, 2005–2016.

Year	Cluster[a]	No. of cases	Rates per 100,000	No. of counties	Type of the counties[b]		Population at risk
					Rural	Urban	
2005	H-H	757	2.67	64	62	2	28,477,361
	H-L	32	0.70	9	8	1	4,582,405
	L-H	12	0.07	45	45	0	17,408,650
2006	H-H	237	0.78	72	71	1	30,219,755
	H-L	9	0.09	11	11	0	9,878,203
	L-H	29	0.12	75	69	6	24,206,070
2007	H-H	290	1.04	64	60	4	27,915,298
	H-L	17	0.37	8	8	0	4,545,932
	L-H	68	0.32	64	59	5	21,000,362
2008	H-H	267	0.94	58	56	2	28,431,877
	H-L	18	0.34	9	9	0	5,263,666
	L-H	13	0.05	71	67	4	25,248,350
2009	H-H	113	0.48	53	51	2	23,175,690
	H-L	20	0.13	18	18	0	15,972,238
	L-H	68	0.19	89	83	6	35,524,615
2010	H-H	302	0.93	59	57	2	32,040,701
	H-L	11	0.07	17	16	1	14,364,705
	L-H	26	0.07	95	87	8	35,361,925
2011	H-H	110	0.48	45	37	8	22,927,200
	H-L	15	0.14	15	14	1	10,563,439
	L-H	29	0.07	107	96	11	41,261,003
2012	H-H	75	0.28	56	51	5	25,891,146
	H-L	1	0.01	10	10	0	8,416,354
	L-H	32	0.08	104	97	7	38,346,349
2013	H-H	133	0.40	60	52	8	32,470,676
	H-L	41	0.34	16	16	0	11,987,768
	L-H	33	0.09	86	79	7	38,621,772
2014	H-H	207	0.98	47	44	3	21,169,075
	H-L	3	0.04	11	10	1	7,821,347
	L-H	44	0.10	113	104	9	45,010,020
2015	H-H	86	0.49	45	45	0	17,341,826
	H-L	7	0.06	12	11	1	10,492,490
	L-H	66	0.19	98	89	9	33,872,308
2016	H-H	147	0.72	48	46	2	20,300,837
	H-L	23	0.16	16	14	2	14,518,982
	L-H	1	0.00	112	104	8	46,584,188

[a] H-H, high-high (high-risk); H-L, high-low; L-H, low-high. The High-High (HH) (later stated as high-risk) cluster defined when they have high values surrounded by high values. Low-low (LL) (low-risk) clusters represented cluster of low rates surrounded low rates counties. Low-high (LH) or high-low (HL) was defined if a cluster of low or high rates values surrounded by high or low rates. [b]Type of counties defined based on the predominant proportion of area calculated from mean values of pixels of gridded raster urban-rural maps (CIESIN, 2012).

Table 6-3 Yearly number of high-risk counties (n = 265) in each province as identified by local indicator spatial association (LISA), China, 2005–2016.

Province	Total counties (% of high-risk counties)	Number of high-risk counties												No. of cases (% total cases)
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	
Guangdong	24 (20.2)	0	6	1	2	4	7	10	2	4	1	0	2	661 (8.10)
Guangxi	35 (31.8)	4	8	6	11	7	3	3	10	4	2	0	2	569 (6.97)
Zhejiang	7 (7.8)	0	0	4	1	0	1	0	0	0	1	2	1	149 (1.83)
Anhui	10 (9.5)	2	6	4	6	6	5	5	5	3	6	1	3	358 (4.39)
Fujian	35 (41.2)	1	2	0	0	5	5	7	7	18	14	14	7	535 (6.56)
Jiangxi	25 (25)	6	11	5	6	7	5	5	2	7	3	0	2	442 (5.42)
Hubei	7 (6.8)	0	2	4	6	0	1	1	2	0	0	2	0	299 (3.67)
Hunan	35 (28.7)	0	10	12	1	1	2	5	5	5	2	4	4	683 (8.37)
Chongqing	5 (13.2)	2	0	0	0	2	0	0	0	0	0	0	1	208 (2.55)
Sichuan	57 (31.1)	43	20	22	19	17	23	5	13	15	13	13	18	2410 (29.54)
Guizhou	11 (12.5)	1	4	2	3	0	3	1	6	1	0	5	2	297 (3.64)
Yunnan	14 (10.9)	5	3	4	3	4	4	3	4	3	5	4	6	1415 (17.34)

6.4.3 Comparative analysis of spatial clusters profile

In general, the demographical, ecological and socioeconomic characteristics among clusters differed significantly ($P < 0.001$) (Table 6-4). The characteristics of age, gender, and occupation were statistically significantly different ($P < 0.001$) between clusters. Leptospirosis infections in high-risk clusters were observed in relatively younger groups (median 35; interquartile range, IQR: 21–47, $P < 0.001$) compared with cases reported in other types of clusters. In contrast, more leptospirosis cases were observed among older population in low-risk clusters (48, IQR: 34–57). Overall, a high number of leptospirosis case was observed in males than in females ($P < 0.001$) in all clusters, but high-risk clusters had a relatively higher proportion of male cases than low-risk clusters. Additionally, the high-risk clusters had more farmers (80.20%, $P < 0.001$) compared with other cluster types.

Elevation, precipitation, type of county, livestock density, farmland production, and gross domestic product (GDP) significantly differed between clusters ($P < 0.001$). The high-risk clusters were situated in areas at higher elevation (576.01 m; 95% CI: 451.17–700.25, $P < 0.001$) and higher precipitation rate (136.86 mm per month; 95% CI: 123.61–150.12, $P < 0.001$) compared with low-risk clusters. High-risk clusters were more rural (100%) than the other types of clusters ($P < 0.001$). Pig density did not differ among high-risk (212.20 head/km^2, 95%CI: 146.40–278.00) and low-risk clusters (190.50, 95%CI: 176.43–204.58), but it was still higher than the other clusters. Cattle density in high-risk clusters was much lower (7.88 head/km^2, 95%CI: 4.14–11.62) than that low-risk clusters (36.36 head/km^2, $P < 0.001$). Both receptive clusters (HL and LH clusters) had moderate livestock density. The high-risk clusters had lower farmland production (2,949.67 kg/ha; 95% CI: 1,953.41–3,945.93 $P< 0.001$) compared with low-risk clusters (4,148.50 kg/ha 95% CI: 3,951.64–4,345.36). Additionally, the GDP of high-risk clusters was much lower (440.80 Yuan, 95% CI: 236.61-644.98, $p<0.001$) than that in low-risk clusters (4,448.88 Yuan, 95% CI: 1025.29-1830.60).

Table 6-4 Comparative analysis of demographic, ecological and socioeconomic variables stratified by four types of spatial clusters as determined by LISA, China, 2005–2016.

Characteristics	Cluster					F / χ^2	*P*-value
	High-High* (n=22)	High-Low (n=94)	Low-High (n=199)	Low-Low (n=634)	Other** (n=1733)		
Demographical							
Age (years)							
Median (IQR)	35 (21-47) [a]	45 (32-56) [b]	44 (30-57) [b]	48 (34-57) [c]	41 (30-53) [b]	F=185.38	<0.001 [#]
Sex, n (%)							
Male	985 (69.60)[a]	270 (71.42)	229 (76.84)	215 (63.23)	1001 (63.27)[b]	χ^2 = 33.10	<0.001
Female	431 (30.40)[a]	108 (28.58)	69 (23.16)	125 (36.77)	581 (36.73)[b]		
Occupation, n (%)							
Farmer	1136 (80.20)[a]	265 (70.10)[a]	212 (71.14)[a]	247 (72.64)[a]	1080 (68.27)[b]	χ^2 = 57.79	<0.001
Non-farmer	280 (19.80)[a]	113 (29.90)[a]	86 (28.86)[a]	93 (27.36)[a]	502 (31.73)[b]		
Ecological and Socioeconomic							
Mean elevation (m)	576.01 [ab] (451.17-700.25)	250.94 [a] (190.66-311.21)	675.15 [b] (577.41-772.90)	207.49 [a] (177-45-237.52)	1020.36 [c] (963.39-1077.34)	F=82.50	<0.001
Mean monthly precipitation (mm)	106.82 [a] (97.45-116.19)	101.40 [a] (95.26-107.55)	120.67 [b] (117.40-123.93)	76.88 [c] (74.57-79.19)	62.79 [d] (61.08-64.49)	F=167.25	<0.001
Rural-type counties[†] (%)	100.00	93.61 (86.45-97.11)	91.45 (86.66-94.63)	76.02 (72.54-79.19)	86.60 (84.9-88.1)	χ^2 =58.43	<0.001
Mean pig density (head/km2)	212.20 [a] (146.40-278.00)	212.49 [a] (181.57-243.41)	134.28 [b] (114.48-154.09)	190.50 [a] (176.43-204.58)	88.68 [b] (83.25-94.11)	F=78.40	<0.001
Mean cattle density (head/km^2)	7.88 [a] (4.14-11.62)	24.18 [ab] (18.06-30.29)	23.54 [ab] (19.73-27.35)	36.36 [b] (31.26-41.46)	19.62 [ab] (17.55-21.70)	F=14.41	<0.001
Mean farmland production (kg/ha)	2949.67 [ab] (1953.41-3945.93)	3372.04 [b] (2854.01-3890.06)	1457.58 [c] (1267.94-1647.22)	4296.41 [c] (4080.49-4512.33)	2315.05 [a] (2208.14-2421.97)	F=99.84	<0.001
GDP[‡]	440.80 [a] (236.61-644.98)	3070.73 [b] (2042.65-4098.83)	1427.95 [c] (1025.29-1830.60)	4448.88 [d] (4006.23-4891.54)	1974.07 [c] (1787.85-2160.30)	F=41.99	<0.001

Note: * High-High (High-risk counties): a county identified if only as HH based on LISA for more than 50% of the period of study; ** Other: not statistically significant cluster as determined by LISA.
Results expressed as mean (95% CI) unless otherwise noted;
[#] Kruskal-Wallis test
[†] Type of each county (rural or urban) was defined based on the predominant proportion of area. The proportion of area was calculated from mean values of pixels of raster maps of each county polygon (CIESIN, 2012)
[‡] Unit: RMB 10,000 (Chinese Yuan)
[a,b,c,d] Different letter denotes significant difference after post hoc Tukey's HSD adjustment between value between clusters at level ≤ 0.05
IQR, interquartile range; GDP, gross domestic product

6.5 Discussion

We analysed notified human leptospirosis data from 2005 to 2016 in China to determine the spatiotemporal geographical distribution in incidence rates, to identify residual high-risk counties for leptospirosis and most importantly to profile the demographical, ecological and socioeconomic characteristics between high-risk and low-risk counties. Overall, although there was a gradual decline in the notified leptospirosis incidence and a reduction in the number of counties reporting leptospirosis during the period studied, our analysis has revealed residual counties with high leptospirosis incidence in the southwestern, central, and southeastern China. Additionally, our study demonstrates important demographical, ecological and socioeconomic differences between high-risk and low-risk counties which could form the basis of future disease elimination strategies. These findings highlight the need for targeted interventions that account for local determinants to further reduce the burden of leptospirosis in China.

Our analysis reveals persistently high incidence in a limited set of counties in the south Yunnan, namely, Mengla County in Xishuangbanna prefecture and Menglian County in Pu'er prefecture, which border with Myanmar and Lao P.D.R (Luang Namtha province). These findings also have regional significance since leptospirosis is also highly prevalent in Myanmar and Lao P.D.R (Laras et al., 2002; Kawaguchi et al., 2008; Dittrich et al., 2015). The high incidence of leptospirosis in this area may be linked to shared climatic and local socioecological characteristics. For example, Xishuangbanna prefecture is characterised by a tropical and monsoonal climate, which provides favorable conditions for *Leptospira* environmental survival. In addition to paddy fields, approximately 30% of the total land area of Xishuangbanna prefecture is covered by rubber plantations (Senf et al., 2013). Most people are involved in cash crops plantations (e.g., rubber, tea, corn, rice) as well as small-scale pig farming (Riedel et al., 2012). Rural communities in this area are known as the poorest populations with the annual GDP per capita less than US$100. Uncontrolled cross-border live animal trade, such as pigs, cattle and buffalo, have potential to spread some zoonotic diseases including leptospirosis since these species are known to be important reservoirs for particular pathogenic *Leptospira* serovars (Ellis et al., 1981; Shi et al.,1997).Hence, targeted intervention should be implemented in these high-risk areas and the communities living along the Mekong river basin. Transboundary disease monitoring programs both in humans and livestock animals should be prioritised to control leptospirosis, especially in the border

between Yunnan, Lao P.D.R, and Myanmar. Further research will be carried out to better understand key factors that drive leptospirosis transmission in these high-risk counties at local level.

Despite a remarkable decrease in leptospirosis rates in the last decade (Zhang et al., 2012; Dhewantara et al., 2018a), our analyses demonstrated significant annual spatial clustering of leptospirosis cases. Yet, our annual estimates of clustering (as measured by Moran'*I* statistics) indicate apparent reduction in the tendency for leptospirosis clustering with time. This may partly be explained by considerable control efforts as well as ecological and social changes that occurred during the last few decades in China (Liu et al., 2018) which bring endemic areas to a lower endemicity level and *on par* with low endemicity areas surrounding them. Substantial preventive and control actions have been promoted, including rodent control programs and vaccination especially in endemic areas (Hu et al., 2014; Xu & Ye, 2018). Also, significant investment to improve hygiene and sanitation infrastructure (Ministry of Environmental Protection, 2000; Li et al., 2015) throughout the country might also have helped at reducing the geographical extent of leptospirosis risk in China.

The observed changes in the geographical distribution of leptospirosis risk could be also linked with landscape changes that have been undergoing in China (Lambin et al., 2010). Of note, over the past three decades, China experienced a large-scale modification in landscape due to industrialisation and urbanisation (Deng et al., 2015; Zhang et al., 2017; Long et al., 2018), which may have impacted directly or indirectly the spatial distribution of leptospirosis. China's land cover has been substantially impacted by the national-scale reforestation policy known as Grain for Green Program (Delang & Yuan, 2015) which to some extent might have changed vegetation structure and the diversity and population dynamics of host animals, including rodents, leading to changes in the distribution of leptospirosis risk. In addition, ecological impact due to the development of Three Gorges Dam might have also altered rodent abundance (Chang et al., 2016) and this might reduce the transmission risks in those affected areas. It was evidenced in this study by low-level incidence in Hubei and Chongqing, which is consistent with an existing local study (Long et al., 2007). Moreover, a recent seroprevalence survey in the Three Gorges Dam region has also indicated that *Leptospira* prevalence in host animals, especially in rodents, was low (Wang et al., 2017). The geographical changes in leptospirosis risk could be also due to changes in human

behaviours. In China's rural areas, where leptospirosis is endemic, modernisation had triggered substantial changes in farming practices via mechanisation. This change might have reduced the level of exposure to leptospiral contaminated water or soil. Further local investigation is essentially required in the high-risk counties identified in this study to assess the impact of landscape and social changes on the spatial variation of risk of leptospirosis.

Our analysis identified consistent spatiotemporal clusters of local leptospirosis in China during 2005 to 2016. Most of the high-risk counties were spatially clustered in the tropical and sub-tropical region in south China comprising 12 provinces: Guangdong, Guangxi, Zhejiang, Anhui, Fujian, Jiangxi, Hubei, Hunan, Chongqing, Sichuan, Yunnan, and Guizhou. Those provinces are situated along China's major river basin of the Yangtze, Lancang (upper Mekong) River and Pearl River. Based on our findings, the persistent leptospirosis hotspots that exist over time in southwestern, central, and southeastern counties highly suggest that most leptospirosis incidence in these high-risk areas could be primarily driven by the interplay between agricultural activities, low socioeconomic conditions, rodent proliferation, and climate. Our study indicates that in high-risk counties, leptospirosis was observed in the younger population and among males and farmers compared with low-risk counties; suggesting that intervention in the residual high-risk counties should be more focused on this active population group that engage with agricultural activities. Our findings also indicated that high-risk counties had ecological and socioeconomic characteristics that are also common in areas where leptospirosis is endemic. High-risk counties were economically less-developed and were more rural, situated in moderate elevation with higher precipitation compared with low-risk counties. Interestingly, livestock population density and farmland production in high-risk counties was much lower than that of low-risk areas, which suggests that small-scale farming may partly play in the epidemiology of leptospirosis in those high-risk counties. These high-risk counties were much more concentrated in the southwest China (Sichuan and Yunnan) where most people here engaged primarily in subsistence farming (e.g., paddy rice, rubber plantation, shifting cultivation, small scale animal farming) (Chen et al. 2016; Xu et al., 2017). However, the role of rodent and livestock density on leptospirosis occurrence deserves further local investigations. To illustrate, in Guizhou, it was identified that *L. interrogans* serogroup Icterohaemorrhagiae serovar Lai was predominantly identified in rodent *A. agrarius* (Liu et al., 2016). In Pan'an county in Zhejiang, *Rattus confucianus* and *R. flavipectus* were found to be dominant and potential source of leptospiral infection (Ying and Zhang, 2011). In

addition, several major outbreaks in high-risk counties identified in this study following heavy rainfall leading to flooding have been reported, including in Sichuan (Wang et al. 2014) and Anhui (Ren et al. 2005), highlighting the importance of rainfall and flooding on leptospirosis risk.

While the evidence presented in this study can be beneficial to help identify areas where surveillance and interventions should be directed, there are some study limitations that need to be considered. We incorporated all cases (i.e. suspect, clinically diagnosed and laboratory confirmed leptospirosis cases) in our analyses to allow comparison with Chinese government reports and local studies. However, as this study used leptospirosis notification data collected from a passive surveillance system, it has the potential to greatly underestimate the actual incidence rates as our dataset merely captures individuals who seek medical treatment. There could be some individuals who represent subclinical, mild influenza-like symptoms and were not aware and/or unable to look for treatment immediately, especially in remote and poor rural areas in China. In addition, there might also be variation in awareness and diagnostic capacity among doctors and hospitals over time and space, which could misrepresent the spatial extent of the disease.

6.6 Conclusions

In summary, our study reveals for the first time the dynamic pattern of leptospirosis distribution in China and identified consistent high-risk counties in China, suggesting that improved intervention strategies should be more targeted towards communities living in these high-risk counties.

Chapter 7 Spatial distribution of leptospirosis incidence in the Upper Yangtze and Pearl River Basin, China: tools to support intervention and elimination

This chapter will be presented as a paper. The manuscript is submitted to the Science of The Total Environment. The concept and design of the methodology was formulated by PWD (85%) with the assistance of RJSM (15%). WYZ provided the data. PWD was responsible for data management (100%), data analyses (100%) and the interpretation of results (85%) was discussed in consultation with RJSM (10%) and all co-authors (5%). PWD was responsible for drafting the manuscript (100%). PWD was responsible for revision of the final version of the manuscript (90%), taking into account the comments and suggestions of RJSM (5%) and all co-supervisors (5%).

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7.1 Context

The studies in Chapter 5 demonstrated that the high burden of leptospirosis was observed in broad regions across the Chinese landscape. In particular, Chapter 6 revealed that small pockets of high-risk counties are situated in tropical and sub-tropical provinces in the southwest and south of China, especially in the provinces along China's two major rivers—Yangtze River and Pearl River. Prior research detailed in Chapter 5 suggested that leptospirosis incidence is highly seasonal but its annual pattern tended to be different between the southwest and south region, suggesting that risk factors are likely heterogeneous between regions. From these findings, it is hypothesised that the role of climate, and environmental and socioeconomic factors in leptospirosis transmission in southwest (Upper Yangtze River Basin, UYRB) and south (Pearl River Basin, PRB) regions of China may be geographic-specific as leptospirosis transmission is occurring at local level.

Before commencing the research set out in this chapter, there were no studies in the literature that had investigated the spatial heterogeneity of drivers of incidence of leptospirosis in these two high-risk regions. To guide effective targeted disease control and public health interventions, local health authorities and policy makers require detailed information regarding areas where disease is prevalent, how it spreads geographically and what are potential risk factors that drive its patterns (Pfeiffer et al., 2008).

Taken together, findings from research detailed in Chapter 5 to Chapter 6 emphasised the need for quantifying the effect of local environmental and socioeconomic factors on the geographical variation of incidence of leptospirosis and to use this evidence to develop the predictive maps of incidence of leptospirosis in both regions. Such maps could provide useful evidence to inform policymakers in prioritising areas of interventions as well as in estimating the at-risk populations so that resources could be adequately delivered.

In this chapter, I set out my research into the geographical distribution of leptospirosis incidence in these two main river basins and the development of a predictive map of leptospirosis incidence, controlling for environmental and socioeconomic factors. In Chapter 7, I utilise comprehensive environmental and socioeconomic risk factor data including precipitation, NDVI, NDWI, LST, elevation, slope, land cover, crop production, livestock density, GDP and population density. Non-spatial and spatially explicit models of predicted incidence of leptospirosis were built. I built two zero-inflated Poisson (ZIP) Bayesian conditional autoregression (CAR) models to predict leptospirosis incidence in both UYRB and PRB and taken into account of those environmental and socioeconomic factors, time (quarter and period) as fixed-effect and a spatially structured random effect.

Results presented in this chapter demonstrate areas of priority for leptospirosis control in both the UYRB and the PRB. My predictive maps showed that the distribution of the high incidence areas in the UYRB are located in counties along the border of Chongqing, Hubei, and Guizhou towards the Sichuan basin and northwest Yunnan. In the PRB, the highest predicted incidence was identified in areas situated in the middle and lower reaches of the basin.

This Chapter indicates that surveillance and control strategies should be improved and extended towards the counties adjacent to the high-incidence counties. In addition, public health interventions should be targeted on the population at-risk on the areas where incidence is predicted to be high.

7.2 Introduction

Leptospirosis, a waterborne bacterial disease caused by the Gram-negative spirochete Leptospira, is a globally widespread life-threatening yet neglected zoonotic disease (Levett, 2001, Bharti et al., 2003). A recent report demonstrated that every year at least approximately 1 million leptospirosis cases and 58,900 deaths are reported across the globe, and it leads to the loss of roughly 2.9 million DALYs (Costa et al., 2015, Torgerson et al., 2015). However, the burden is considered to be higher due to inadequate surveillance and under-reporting, especially in developing countries where the capacity to diagnose leptospirosis is limited, and awareness of the disease is lacking (Bharti et al., 2003, Haake and Levett, 2015).

To our knowledge, there are currently 35 species belonging to the genus *Leptospira* with more than 250 serovars identified. Of which, 13 species have been recognised as pathogenic (Guernier et al., 2018; Vincent et al., 2019; Casanovas-Massana et al., 2020). Livestock and companion animals can host the bacteria, but rodents are considered as the important reservoir for maintaining *Leptospira* in the environment (Haake and Levett, 2015, Zhang et al., 2019, Krijger et al., 2019). Infection in human occurs due to direct exposure of injured skin or mucous membranes with the infected animal tissues or urine, or by indirect contact with mud or water containing pathogenic *Leptospira* (Levett, 2001). Though leptospirosis incidence is commonly high in tropical and subtropical rural areas especially infecting agricultural workers, leptospirosis outbreaks are now increasingly reported in major urban areas as a consequence of poor waste management and informal urban development, especially in developing countries (McBride et al., 2005, Felzemburgh et al., 2014, Sahimin et al., 2019). Moreover, incidence of exposure is expected to be higher in the future due to severe climate events and flooding driven by climate change (Lau et al., 2010).

In China, leptospirosis is also of public health importance, resulting in more than 2.4 million cases and 20,000 deaths since it has been reported in 1955 (Shi and Jiang, 2000). A recent study has estimated that approximately 10,000 DALYs were lost during the past decade (Dhewantara et al., 2018a). The leptospirosis outbreak is strongly seasonal with the highest incidence commonly reported during the wet season (Zhang et al., 2012). *Leptospira interrogans* serogroup Icterohaemorrhagiae serovar Lai has been responsible for most leptospirosis cases in China and *Apodemus agrarius* is known as the most important host among other animals, such as pigs, cattle and dogs (Li et al., 2013, Hu et al., 2014). To

address the problem of leptospirosis infection, China's health authorities have been implementing prevention and control measures including improvement in access to water and sanitation, reduction of leptospiral infection in animal hosts, and vaccination of high-risk populations (Xu and Ye, 2018). These strategies have successfully reduced leptospirosis incidence to a low-level in the past few decades, offering an opportunity for the elimination of leptospirosis transmission in the country (Zhang et al., 2012, Dhewantara et al., 2018a). However, recent evidence has shown that while such interventions have resulted in a significant reduction in incidence, persistent residual high-risk clusters of leptospirosis remain in the country, concentrating in tropical and sub-tropical regions along the Yangtze and Pearl River catchment areas (Dhewantara et al., 2018b). Previous studies suggested that the geographical distribution of leptospirosis incidence in China is influenced by the natural (climate) and anthropogenic landscape characteristics (Shi et al., 1995, Zhang et al., 2012, Zhao et al., 2016). Yet, there are limited studies examining the role of climate, environmental and socioeconomic factors on the geographical heterogeneity in leptospirosis incidence, especially in these two high-risk areas – i.e., Yangtze and Pearl River Basins.

Due to its high burden and its debilitating impacts especially on vulnerable populations in many developing countries, control of leptospirosis is now receiving much more attention. The World Health Organization – Leptospirosis Research Group (LERG) recommends the development of predictive tools to support the identification of geographic areas that are at highest risk and populations affected by leptospirosis as integral to effectively targeting interventions (WHO - Leptospirosis Burden Epidemiology Reference Group, 2010). Risk mapping is increasingly being used for planning, monitoring and evaluation, and resource allocation in various disease control programs (Soares Magalhães et al., 2011, Owada et al., 2018). In recent years, a growing number of studies using spatial analytical tools have been carried out, aiming to develop predictive maps of leptospirosis incidence to assist leptospirosis control (Lau et al., 2012a, Zhao et al., 2016, Rood et al., 2017, Mayfield et al., 2018b, Baquero and Machado, 2018, Dhewantara et al., 2019b, Jagadesh et al., 2019). While leptospirosis is an important public health problem in China, similar risk prediction approaches have not been well-explored thus far. A previous country-level study in China used ecological niche modelling to predict the country-wide geographical distribution of leptospirosis, accounting for climate and environmental and socioeconomic variables (Zhao et al., 2016). However, this approach was unable to fully explain heterogeneity, spatial dependency, and

uncertainty. Fine-scale risk mapping that accounts for spatial dependency in the data and uncertainties is essential as it could help improve risk estimation and thus provide better guidance for effective spatially-targeted resource allocation and disease control for the attainment of elimination (Clements et al., 2006, Atkinson and Graham, 2006, Tchuem Tchuenté, et al., 2018).

Bayesian conditional auto-regressive (CAR) modelling allows accounting for both spatial dependency and uncertainties. This technique provides a flexible and rigorous approach for multilevel spatial analysis and disease mapping that allows for accounting risk heterogeneity and unmeasured factors in a coherent manner as well as reducing errors in the estimates where the denominator (population) is small through smoothing, using Markov chain Monte Carlo simulation (Best et al., 2005). Previous studies have demonstrated the value of such a spatial modelling approach to examine infectious disease risk (Yang et al., 2005, Hu et al., 2012, Gou et al., 2017, Jagadesh et al., 2019). Recently, Jagadesh et al. (2019) demonstrated the application of spatial Bayesian regression approach to predict geographic distribution of leptospirosis in French Guiana. However, the study only accounted for environmental and climatic factors (e.g., land cover, topography and meteorological variables) in the model. The relative importance of socioeconomic factors and animal reservoirs (e.g., livestock density, rodent abundance) in the geographical variation in leptospirosis incidence is poorly explored.

In this study we aimed to quantify the role of environmental and socioeconomic factors on the spatial distribution of leptospirosis within the two high risk areas of China—the Upper Yangtze River Basin (UYRB) and Pearl River Basin (PRB)—and to generate an adjusted incidence maps of human leptospirosis incidence for each region that account for the variation in climate, environmental and socioeconomic factors. The results of this study will be beneficial to health authorities and policymakers in identifying areas within the two high-risk areas where surveillance, case management, and interventions should be improved to ensure the effectiveness of control and elimination strategies of leptospirosis transmission in the UYRB and PRB.

7.3 Methods

7.3.1 Study sites

In this study, we limited our analyses to the two major river basins in China, Upper Yangtze River Basin (UYRB) and Pearl River Basin (PRB) where residual leptospirosis incidence has been recently identified (Dhewantara et al., 2018a, 2018b). The upper reaches of (UYRB stretch from Mt. Geladandong (6,621 m) in southwest Qinghai Province towards Chongqing municipality, crossing the Sichuan Plateau to Yichang. It extends more than 4511 km which accounts for 70% of the total length of the Yangtze River (6300 km) with a drainage area of approximately 1,000,000 km^2 (Fang et al., 2018) (Figure 7-1). The natural environment of UYRB is complex, and includes almost all geological, topographical, climatic, vegetation and soil types in China. The primary land use and land cover are mixed forest, bare land, and farmland. The UYRB is situated in the subtropical monsoon zone with an annual average temperature of approximately 16–20°C. The precipitation in the UYRB is primarily influenced by the Indian monsoon system with the annual precipitation less than 500 mm. The monsoon system brings abundant precipitation—approximately 70–80% of the basin's total annual precipitation during the summer (May to October)—and may cause persistent rainfall when the rain belt is suspended within the basin for several weeks. The heavy and long-lasting rainfall usually leads to frequent floods. Frequent floods and droughts have been known as a major environmental issue in this region (Yu et al., 2009, Guo et al., 2013, Fang et al., 2018).

In the south of China, The Pearl River is the third-longest river in China (2400 km) and covers an area of approximately 400,000 km^2, stretches from part of Yunnan towards Guangdong province. It is the third largest river in terms of drainage basin area (4.573 × 105 km^2) in China (Zhang et al., 2010). The PRB lies in the tropical and sub-tropical climate zones with annual mean temperature ranging from 14°C to 22°C and mean precipitation of approximately 1525 mm per year. Precipitation is high during April–September, accounting for 80% of the yearly total precipitation rate (Zhang et al., 2010). In addition, the PRB is one of the regions most affected by frequent weather-related events and floods, causing significant social and economic losses (Wen, 2006).

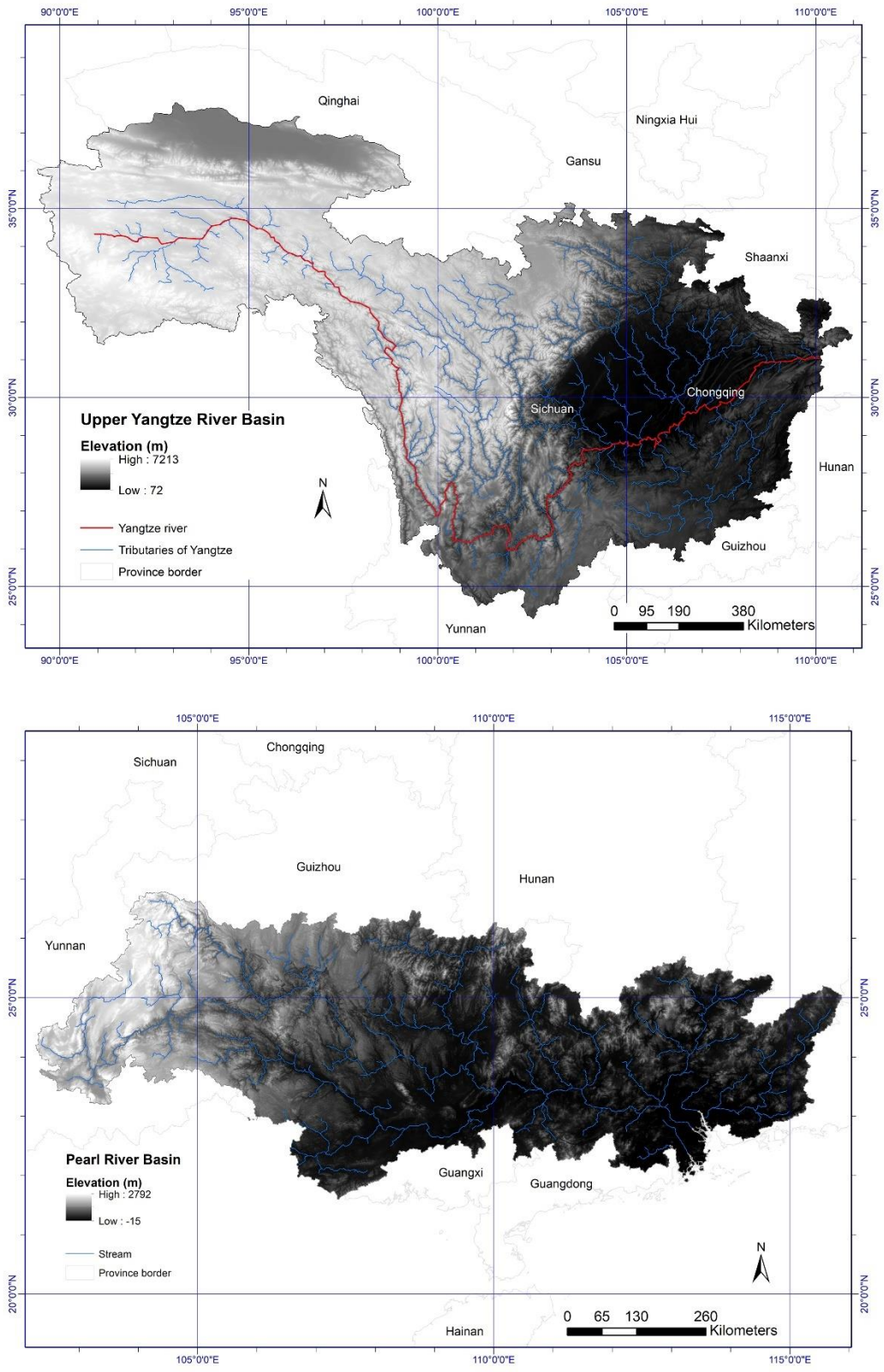

Figure 7-1 Study sites

7.3.2 Data collection

Data on human leptospirosis

In this study I used reported leptospirosis notification data from the period of 1 January 2005 to 31 December 2016, which has been described elsewhere (Dhewantara et al., 2018b). Briefly, in China, leptospirosis has been classified as a Class B Notifiable Disease since 1955. All diagnosed cases of leptospirosis must be reported by all healthcare providers at county-level to the Center for Disease Control and Prevention through the China Information System for Diseases Control and Prevention (CISDCP). Notified leptospirosis cases include information about sex, age, occupation, address, date of onset of illness, date of diagnosis, date of death, case classification (suspected, clinical, and laboratory-confirmed). Leptospirosis cases are defined into three categories: suspected, clinical, and confirmed (Ministry of Health of China, 2008). A suspected case is defined as an individual with: a) a clinical symptom such as acute fever (up to 39°C), which may be accompanied by chills, myalgia, or malaise and; b) history of exposure within a month prior to the onset of illness to the following risk factors: epidemic season, reside in epidemic area, either direct or indirectly contacted with suspected animals and their urine or faeces or contaminated water and soil. A clinical (probable) case is defined as a suspected case with at least one of the following clinical manifestations: conjunctival hyperemia, gastrocnemius tenderness, or enlargement of the lymph nodes. A confirmed case is defined as a probable case with one or more any of the following laboratory criteria: 1) positive culture of Leptospira from blood, urine, tissues, or cerebrospinal fluid (CSF); 2) microscopic agglutination test (MAT) titre of ≥ 400 in single or paired serum samples; 3) a fourfold or greater rise in MAT titres between acute and convalescent-phase samples; 4) the presence of pathogenic *Leptospira* spp detected by polymerase chain reaction (PCR); 5) the presence of IgM antibodies by enzyme-linked immunosorbent assay (ELISA).

In this study, analysis was limited to leptospirosis notification data reported from counties in the UYRB and PRB regions. For the purpose of our analyses, the data were divided into two temporal periods: 2005–2010 and 2011–2015 as our previous work (Dhewantara et al., 2018a) had identified different trends in leptospirosis morbidity during those two periods. Leptospirosis counts were aggregated at county-level by quarter and block of periods, adjusted by the population at risk in each county.

Environmental data

Several environmental data subsets known to be associated with leptospirosis transmission were incorporated in our spatial models, including climate (precipitation, temperature), flooding, topographic (elevation and slope), landscape (vegetation, land cover), residential setting (urban/rural) and livestock (pig and cattle density) (Lau et al., 2012a, Suwanpakdee et al., 2015, Hagan et al., 2016, Rood et al., 2017, Ledien et al., 2017, Baquero and Machado, 2018, Mayfield et al., 2018b). For both regions, data for monthly precipitation, normalized difference vegetation index (NDVI), modified normalized difference water index (MNDWI) and land surface temperature (LST) between 2005 and 2016 were collected from different publicly available sources. Monthly precipitation data with 30 arc-seconds (~ 1-km) spatial resolution was downloaded from WorldClim (v.2) (available at www.worldclim.org) (Hijmans et al., 2005). Data for NDVI, which serves as a proxy of vegetation (biomass productivity) were obtained from the United States Geological Survey (USGS) moderate-resolution imaging spectroradiometer (MODIS) product (MODIS 13Q1 v006/Terra Vegetation Indices 16-Day L3 Global) with 250-meter spatial resolution. NDVI could be also used to reflect abundance of food in the ecosystem which may correlated with rodent abundance (Lumbierres et al., 2017, Yu et al., 2017). Data for MNDWI, which was used as a proxy of waterbodies or floods were obtained from MODIS 09A1 (500-meter spatial resolution). In the absence of an RS product to indicate flooding, MNDWI was be as a proxy of the propensity for a location to flood; MNDWI is an index for water on the ground which has large values in areas with long term or permanent high soil moisture. The assessment of MNDWI as a flooding indicator associated with risk of leptospirosis has been documented in a study by Ledien et al (2017). Values for MNDWI were calculated based on the surface reflectance of green (545-565 nm) and short-wave infrared (SWIR) (1628-1652 nm). Land surface temperature (LST) data were obtained from MODIS 11A2 v006 (1-km x 1-km grid cell resolution). These monthly precipitation, NDVI, MNDWI and LST data were averaged into quarters.

Land cover raster data for two time points (2005 and 2010) were retrieved from the Data Center for Resources and Environmental Sciences, Chinese Academy of Sciences (RESDC) (http://www.resdc.cn) and reclassified into five categories: cultivated land, forested land, grassland, waterbodies and artificial surfaces. Elevation and slope data at 1-km spatial resolution were derived from a GTOPO30 digital elevation model obtained from the USGS archive. A 5 × 5 km resolution rural/urban surface derived from the Global Rural-Urban

Mapping Project (GRUMP, v1, 1995) product was obtained from the Center for International Earth Science Information Network of the Earth Institute at Columbia University (http://sedac.ciesin.columbia.edu/data/set/grump-v1-urban-extents). To best of my knowledge, this was the only best available raster data for urban/rural classification. Livestock data, including gridded pig and cattle density for the reference year 2005 and 2010, were obtained from Gridded Livestock of the World with 1-km spatial resolution (http://www.fao.org/geonetwork/srv/en/main.home) (Robinson et al., 2014, Gilbert et al., 2018). I used two time points for land cover and livestock data (2005 as reference year for period of 2005-2010 and 2010 as reference year for 2011-2016) as there were no yearly data for both land cover and livestock density available. Additionally, I assumed that changes in landscape and livestock density appeared to be less significant over short-time period (yearly).

Socioeconomic data

Socioeconomic risk factors known to be associated with leptospirosis incidence were included in the geographical models, including agricultural practices (surrogated by crop productivity), gross domestic product (GDP) and population (Bacallao et al., 2014, Mayfield et al., 2018b). Since annual raster data for crop productivity, GDP and population density from year 2005-2016 were not available, we used best available datasets that could reflect for each period studied as follow: i) raster data for crop productivity (in kilograms per hectare) for 2000 (as reference for period 2005-2010) and 2010 (as reference for period 2011-2016) were obtained from the Resource and Environmental Science Data Center of the Chinese Academy of Sciences (http://www.resdc.cn) (Xu Xinliang et al., 2017); ii) data for GDP in 2005 and 2010 (as reference for period 2005-2010 and 2011-2016, respectively) with 1-km resolution was obtained from (http://www.geodoi.ac.cn/weben/doi.aspx?Id=125) (Huang Y et al., 2014). Raster data on China population density estimates (in people per hectare) for 2000 and 2010 (as reference for period 2005-2010 and 2011-2016, respectively) with the resolution of 100 m were obtained from WorldPop database (https://www.worldpop.org/geodata/summary?id=1222). In addition, population at risk estimates for each year and county were obtained from the China National Bureau of Statistics.

Spatial data management

In this study, I used county as the geographical unit of analysis. A county-level shapefile of China was obtained from DIVA GIS (https://www.diva-gis.org/Data). The shapefile for both the UYRB and PRB boundaries were obtained from World Resources Institute (Gassert et al., 2013) and HydroSHEDS database (Lehner, 2013), respectively. For each basin, county's polygons that located within and intersected by the basin's boundary were selected, which was done by using selection tools in the GIS. Based on this GIS analysis, total of 386 counties were covered by UYRB with 170 million population. While in the PRB, total of 281 counties were selected with total of at least 150 million population. Values of environment and socioeconomic variables for each county in each basin were extracted using zonal statistics tools in the GIS software (ArcGIS version 10.5.1, ESRI Inc., Redlands, CA, USA). Each leptospirosis case, environmental and socioeconomic data then were linked to the county polygon ID using the GIS software. Environmental and socioeconomic variables included in this analysis are summarised in Appendix E: Table E-1.

7.3.3 Data analysis

Non-spatial models: variable selection and analysis of residual spatial autocorrelation

To examine the presence of collinearity between environmental and socioeconomic variables, a Spearman's correlation coefficient for all pairs of variables was estimated. If the correlation coefficient (Spearman's rho) between a pair of variables was $|\geq 0.7|$ (Dormann et al., 2013), the variable was excluded from the analysis. Poisson generalized linear models (GLMs) were then constructed to test statistical associations between individual, environmental, and socioeconomic variables and leptospirosis counts. All univariable models included the individual-level variables (age, sex, and occupation), environmental (precipitation, NDVI, NDWI, LST, elevation, slope, or livestock density), socioeconomic variables (crop production, population, or GDP) and time (quarters and block of year) as fixed effects. Female, non-farmer, Quarter-1 (Q1) and 1st block of year (2005–2010) were set as reference. In the univariable analysis, variables with a *P*-value of 0.20 in the likelihood-ratio test were considered for inclusion through a manual backward stepwise variable selection process in a multivariable analysis. Using a backward stepwise process of variable selection, variables with a *P*-value more than 0.05 were excluded from the final multivariable model. All statistical

analyses were carried out using the statistical software STATA 15 (Stata Corp., College Station, TX). Spatial autocorrelation in the residuals of the final GLM models were examined using Moran's *I* statistics. Prior to the analysis, a Queen-based spatial adjacency weight matrix was constructed using GIS software. Moran's *I* analysis was performed using GeoDA software (Anselin, 2005). Moran's *I* value ranging from -1 to 1 with a value close to 0 indicates no spatial clustering (random). A positive value indicates positive autocorrelation and a negative value means negative autocorrelation (Moran, 1950). The significance of Moran's *I* was assessed using Monte-Carlo randomization with 999 permutations. Significance (*P* value < 0.05) of the test statistic indicates that residual is spatially clustered or randomly distributed.

Spatial-temporal models

Zero-inflated Poisson (ZIP) Bayesian spatial conditional autoregressive (CAR) models of leptospirosis counts were developed for each region (i.e. UYRB and PRB) and fitted in OpenBUGS version 3.2.3 rev 1012 statistical software (Medical Research Council Biostatistics Unit, Cambridge, United Kingdom and Imperial College London, United Kingdom). ZIP models were selected to account for the excess zero counts in quarterly leptospirosis notifications (Lambert, 1992, Agarwal et al., 2002). ZIP models have been used previously in mapping risk of several diseases including schistosomiasis (Vounatsou et al., 2009) and hand foot and mouth disease (HFMD)(Song et al., 2018). The ZIP distribution consists of two components: a Poisson count stage with parameter λ and a Bernoulli zero-inflation stage with parameter *p.* We denote the ZIP distribution as O ~ ZIP (λ, *p*), where λ is the Poisson mean parameter conditional on the observed value not being an inflated zero. The *p* is the probability of being an inflated zero. The zero values in the ZIP distribution can be viewed as comprising two components: 'structural zero' and 'sampling zero'. One portion of the zeros arises from the Bernoulli distribution with parameter *p* indicating the probability of inflated zeros ('structural zeros'), whereas the other portion ('sampling zeros') comes from what would be expected given a Poisson distribution with parameter *λ* (Hu et al., 2011, Torabi, 2017).

The mathematical notation of ZIP model is provided below. We denote the observed counts of leptospirosis (O) for i^{th} county (i=1, …, n) in the j^{th} quarter and k^{th} block of year.

$$\Pr(O_{ijk}|\,\lambda_{ijk},p_{ijk}) = \begin{cases} p_{ijk} + (1-p_{ijk})e^{-\lambda_{ijk}} & \text{if } O_{ijk} = 0, \\ (1-p_{ijk})e^{-\lambda_{ijk}}\dfrac{\lambda_{ijk}{}^{O_{ijk}}}{O_{ijk}!} & \text{if } O_{ijk} > 0, \end{cases}$$

$$O_{ijk} \sim Poisson\,(\eta_{ijk})$$

$$\eta_{ijk} = p_{ijk}.\lambda_{ijk}$$

$$logit\,(p_{ijk}) = \alpha + \sum_{z=1}^{Z} \beta_z\,.\,x_{ijk} + s_i$$

$$log\,(\lambda_{ijk}) = \alpha + \sum_{z=1}^{Z} \beta_z\,.\,x_{ijk} + s_i$$

Where p_{ijk} is the probability of non-zero count, λ_{ijk} is the mean count of leptospirosis without taking overdispersion into account in i^{th} county, j^{th} quarter and k^{th} block of year, α is the intercept, β is a matrix of z^{th} coefficient, x is a matrix of z^{th} covariate and s_i is the spatially structured random effect for i^{th} county. The OpenBUGS code for the ZIP-CAR model was provided in the Appendix E.

To improve convergence, all environmental variables values were centred by subtracting the mean and dividing by the standard deviation. Non-informative priors were used for the intercept (α), and the effect sizes of covariates beta (β) (normal distribution prior with mean zero and precision 0.01). The spatial structured random effects (s) were assumed to follow a normal distribution, with a mean of zero and a variance of $1/s_i$, where the precision of s_i was given a non-informative gamma prior distribution with shape and scale parameters = 2, 0.05. The prior distribution of Φ was also given a non-informative gamma prior distribution with shape and scale parameters = 2, 0.05.

For each model, a burn-in of 5,000 iterations was used followed by 5,000 iteration intervals. Convergence was assessed using visualisation of history and density plots of the series of posterior values. A further 10,000 iterations were run when model parameters were successfully converged. These ten thousand values from the posterior distributions of each model parameter were stored and summarised for the analysis using the posterior mean and

95% credible intervals (95% CrI). Coefficient was considered as significant at an α-level of 0.05 which indicated by 95% CrI that excludes zero. The mean, standard deviation, and spatial-structured random effects were extracted from the posterior distributions. The county level predicted incidence was calculated by dividing the predicted mean count of leptospirosis by the county level population and visualised in the GIS software.

To evaluate the predictive accuracy, mean absolute percentage error (MAPE) was calculated (Hyndman and Koehler, 2006). MAPE is a measure how large the differences between observed (O_i) and expected leptospirosis incidence (P_i) for i^{th} county (i=1, …, n). The MAPE is calculated by using formula:

$$MAPE = \frac{1}{n}\sum_{i=1}^{n}\frac{|P_i - O_i|}{O_i}\ x\ 100$$

In this study we used a cut-off of 50%; which MAPE < 50% indicated a model have good performance on predicting incidence.

7.4 Results

7.4.1 Descriptive statistics

In total, 4690 leptospirosis cases were reported from both UYRB and PRB between 2005 and 2016, accounting for 57.48% of the total reported leptospirosis for that period. Of these leptospirosis cases, 3217 were reported from 185 (48.55%) counties within the UYRB region. In the UYRB region, leptospirosis was predominantly reported among farmers (n = 2704, 84.05%), males (n = 2221, 69.03%), and the population group with a median age of 41 years (interquartile range, IQR = 27-55) (Appendix E: Table E-2). The high incidence was observed in counties in Sichuan, including Yilong and Huaping, and in some counties in Leshan and Yibin. Some high incidence counties were also observed in the Hubei province (e.g., Jianshi and Enshi County) (Figure 7-2). The incidence reached a peak in the third quarter (Juli-September) of a year (Appendix E: Figure E-1).

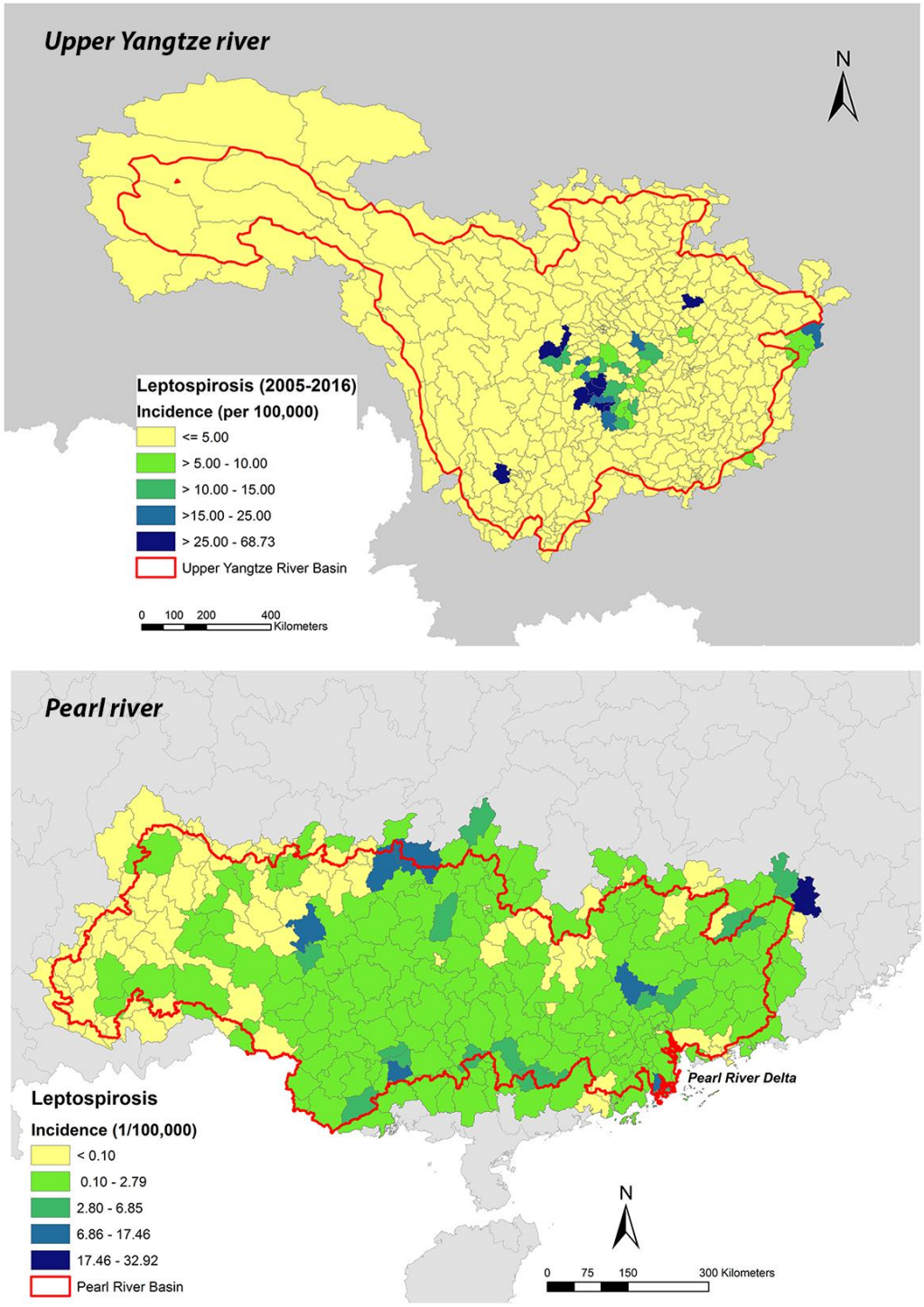

Figure 7-2 Distribution of observed cumulative leptospirosis incidence (2005–2016) in the Upper Yangtze River Basin (UYRB) (top) and the Pearl River Basin (PRB) (bottom), China.

In the PRB region, during the same period, a total of 1473 leptospirosis cases were reported from 199 (70.82%) counties. Leptospirosis infection was attributed to farmers (n = 913, 61.98%), males (n = 1053, 71.48%) and the population group with a median age of 44 years (IQR = 30–57). A high cumulative incidence of leptospirosis cases was observed in counties in Guangxi (Liping, Rongjiang and Tian'e County), Guangdong (Qingxing County) and southwest Fujian (Wuping County). Annually, the incidence was at its highest in the third quarter (Juli-September) (Appendix E: Figure E-2).

7.4.2 Variable selection: univariable and multivariable analysis

Univariate analyses showed that type of residence (urban/rural) and population density had significantly strong correlation in the UYRB (Spearman's coefficient = 0.81, $P < 0.05$). In addition, strong correlation was also identified between slope *vs* elevation (Spearman's coefficient = 0.88, $P < 0.05$) and slope *vs* pig density (Spearman's coefficient = 0.81, $P < 0.05$), respectively (Appendix E: Table E-3). Thus, both population density and slope were not included into the multivariable model of UYRB. In the PRB, strong association was only found between urban/rural and GDP (Spearman's coefficient = 0.94, $P < 0.05$) (Appendix E: Table E-3) and therefore we did not include the urban/rural variable in the multivariable analysis. Non-spatial multivariate analysis showed that all variables were found to be significantly associated with leptospirosis counts (Appendix E: Table E-4; Table E-5) and therefore we considered all these significant environmental and socioeconomic covariates in our spatial predictive models. Spatial autocorrelation in the residuals of the final multivariable models were detected ($p<0.05$), thus the spatial models were built.

7.4.3 Spatial-temporal model

Based on the Poisson part of the ZIP model, in the UYRB, precipitation and MNDWI was significantly and positively associated with the leptospirosis counts (Table 7-1). Elevation was significantly and negatively associated with leptospirosis counts. The mean of leptospirosis counts was significantly lower in the second quarter relative to the first quarter and was significantly lower in the period 2011–2016 compared with 2005–2010.

Based on the Poisson part of the ZIP model, In the PRB, precipitation, NDVI, pig density and cattle density and land cover were found to be significantly and positively associated with leptospirosis counts (Table 7-2). The expected mean of leptospirosis counts was significantly lower in the second and third quarter compared with the first quarter, and significantly lower in the period 2011–2016 relative to 2005–2010.

Table 7-1 Model effect sizes for leptospirosis cases in the UYRB, China

Covariate	Logit component Mean (95% CrI)[a]	Poisson part Mean (95% CrI) [a]
Environmental		
Precipitation	6.84 (-11.88, 22.44)	3.28 (0.70, 9.71)
LST	-5.32 (-22.17, 9.27)	-1.14 (-7.71, 2.09)
NDVI	8.36 (-7.97, 22.84)	2.16 (-1.87, 12.81)
MNDWI	-8.61 (-21.91, 2.532)	4.12 (0.38, 14.24)
Cattle density	1.29 (-12.98, 15.02)	-0.09 (-4.30, 3.73)
Pig density	2.22 (-19.02, 22.56)	-6.25 (-27.17, 7.75)
Elevation	0.92 (-19.52, 15.62)	-8.04 (-22.57, -1.98)
Land cover		
Cultivated land	Reference	Reference
Forested land	-0.04 (-26.46, 17.71)	-0.22 (-23.09, 3.28)
Grassland	2.01 (-16.1, 20.36)	-1.96 (-25.35, 6.82)
Waterbodies	-0.25 (-20.04, 19.61)	-0.95 (-20.1, 18.03)
Artificial surfaces	1.25 (-18.37, 20.9)	11.27 (-11.3, 51.51)
Socioeconomic		
Crop production	-5.90 (-23.45, 12.32)	10.12 (-1.60, 53.52)
Urban *vs* rural	3.16 (-13.73, 24.04)	4.17 (-1.01, 18.02)
GDP	3.63 (-13.01, 18.62)	-23.47 (-127.7, 0.49)
Time		
Q2 *vs* Q1	6.22 (-9.029, 22.59)	-16.7 (-41.95, -5.352)
Q3 *vs* Q1	-2.62 (-20.24, 16.29)	-5.94 (-11.14, 5.131)
Q4 *vs* Q1	0.07 (-19.41, 19.64)	-0.13 (-19.17, 19.01)
2011-2016 *vs* 2005–2010	3.02 (-16.87, 20.61)	-8.34 (-31.18, -1.73)
Intercept	1.94 (-17.58, 20.86)	-1.55 (-25.46, 5.33)
Tau, precision		38.28 (4.95, 102.2
Sigma		0.05 (0.01, 0.20)

[a]CrI, Bayesian Credible Interval (The posterior distributions are summarised by the posterior mean and 95% CrI. A variable was considered as significant if it excluded 0).

Table 7-2 Model effect sizes for leptospirosis cases in the PRB, China

Covariate	Logit component Mean (95% CrI)[a]	Poisson part Mean (95% CrI) [a]
Environment		
Precipitation	-5.87 (-15.49, 3.25)	0.79 (0.12, 1.58)
LST	12.18 (1.45, 24.69)	-0.28 (-0.94, 0.32)
NDVI	5.53 (-13.91, 23.04)	7.22 (3.46, 9.89)
MNDWI	-2.14 (-21.36, 16.84)	2.10 (-7.30, 10.25)
Pig density	-9.99 (-19.10, -3.26)	0.92 (0.48, 1.33)
Cattle density	-3.41 (-11.92, 1.83)	0.62 (0.24, 0.99)
Elevation	2.63 (-9.01, 15.02)	-0.47 (-1.47, 0.50)
Land cover		
Cultivated land	Reference	Reference
Forested land	8.75 (-8.08, 26.81)	1.65 (-1.54, 4.15)
Grassland	-1.58 (-22.48, 18.65)	2.22 (-2.87, 6.66)
Waterbodies	4.18 (-14.43, 22.21)	4.98 (0.03, 9.30)
Artificial surfaces	-0.87 (-21.00, 19.37)	-6.94 (-22.18, 5.60)
Socioeconomic		
GDP	-3.44 (-14.14, 9.03)	0.34 (-0.31, 0.94)
Time		
Q2 *vs* Q1	-0.01 (-16.74, 14.38)	5.98 (7.97, 4.10)
Q3 *vs* Q1	9.09 (-6.25, 25.21)	-5.91 (-8.12, -4.19)
Q4 *vs* Q1	-0.03 (-19.60, 19.62)	-0.12 (-20.43, 20.06)
2011-2016 *vs* 2005-2010	8.96 (-8.64, 26.82)	-3.46 (-5.12, -1.21)
Intercept	6.54 (-11.35, 23.04)	1.99 (0.66, 3.50)
Tau, precision		0.23 (0.11, 0.42)
Sigma		4.79 (2.38, 8.66)

[a]CrI, Bayesian Credible Interval (The posterior distributions are summarized by the posterior mean and 95% CrI. A variable was considered as significant if it excluded 0).

7.4.4 Smoothed incidence maps of leptospirosis in the UYRB and PRB

Our smoothed incidence map of leptospirosis incidence in the UYRB (Figure 7-3) indicates that the distribution of leptospirosis was spread out from east towards south of the region, with the highest predicted incidence identified in a cluster of counties in the eastern part (Chongqing, west Hubei and Guizhou), central part (the southern part of Sichuan basin) and southern part (northeast Yunnan). The predicted population at risk of leptospirosis is 103,907,069 people in a total of 179 counties. The mean absolute percentage error (MAPE)

of the model was 18.91%, indicating that the model showed good predictive performance (< 50%).

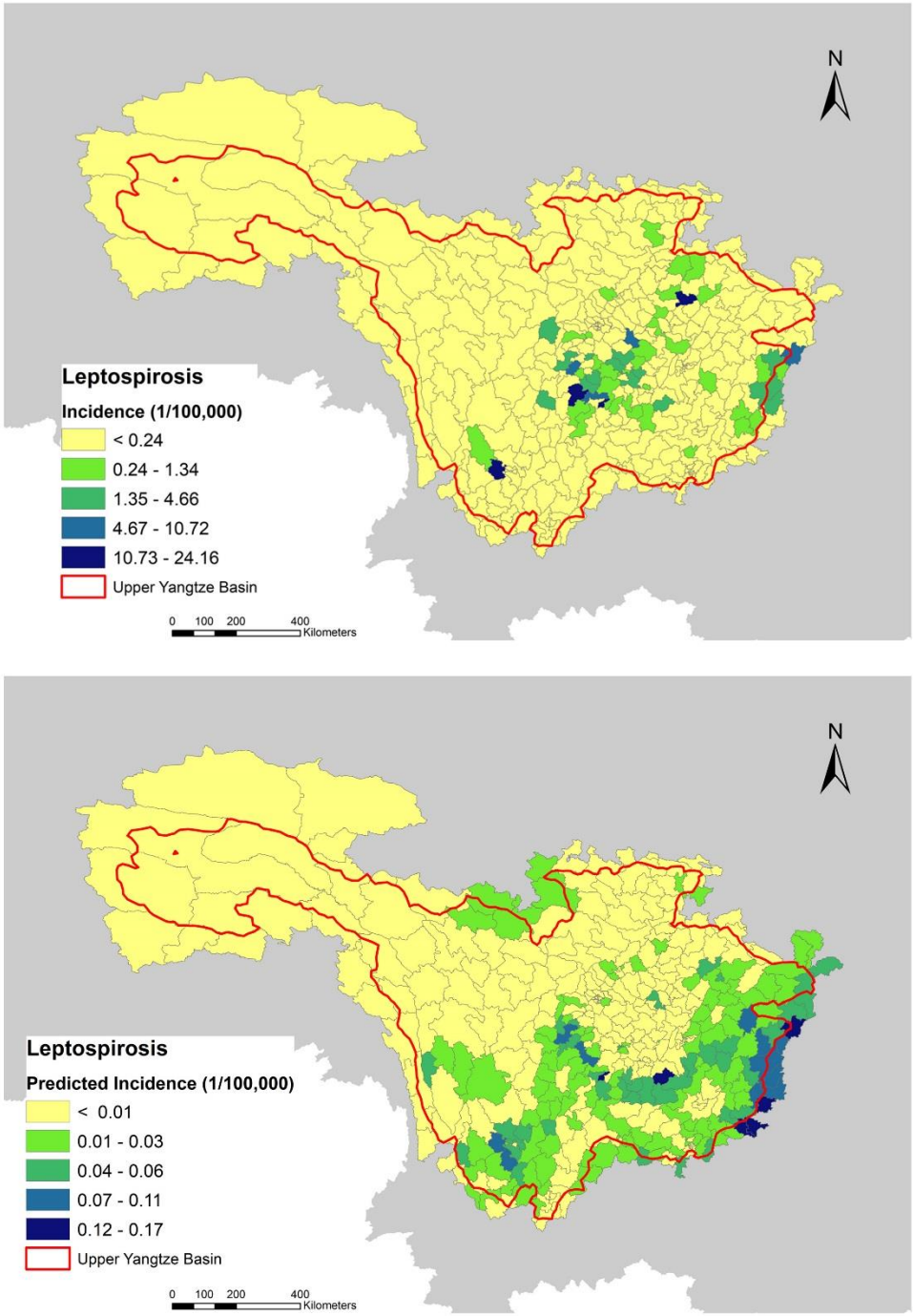

Figure 7-3 Spatial distribution of the observed leptospirosis incidence during 2011–2016 (top), predicted leptospirosis incidence for respective period (bottom) for the same period in the UYRB after controlling the effects of environmental and socioeconomic factors.

The geographical distribution of leptospirosis incidence in the PRB (Figure 7-4) appeared to be consistent with the observed incidence; although, it was more expanded and some high incidence counties appeared in the southern part of the basin. The incidence of leptospirosis was predicted to be higher in Hengxian (Nanning), Yongfu (Guangxi), Guangdong (e.g. Gaoming, Sihui, Longmen, Doumen, Xinyi), Fujian (Wuping) and Huichang (Jiangxi). In the PRB, the predicted population at risk was 50,681,249 people located in 105 counties. The MAPE of the model was 33.22%, suggesting that the model showed good predictive performance (< 50%). Maps of predicted standard deviation (SD) of incidence of leptospirosis, the posterior mean of spatially structured random effects and the probability of non-zero count is available in Appendix E: Figure E-1 and Figure E-2.

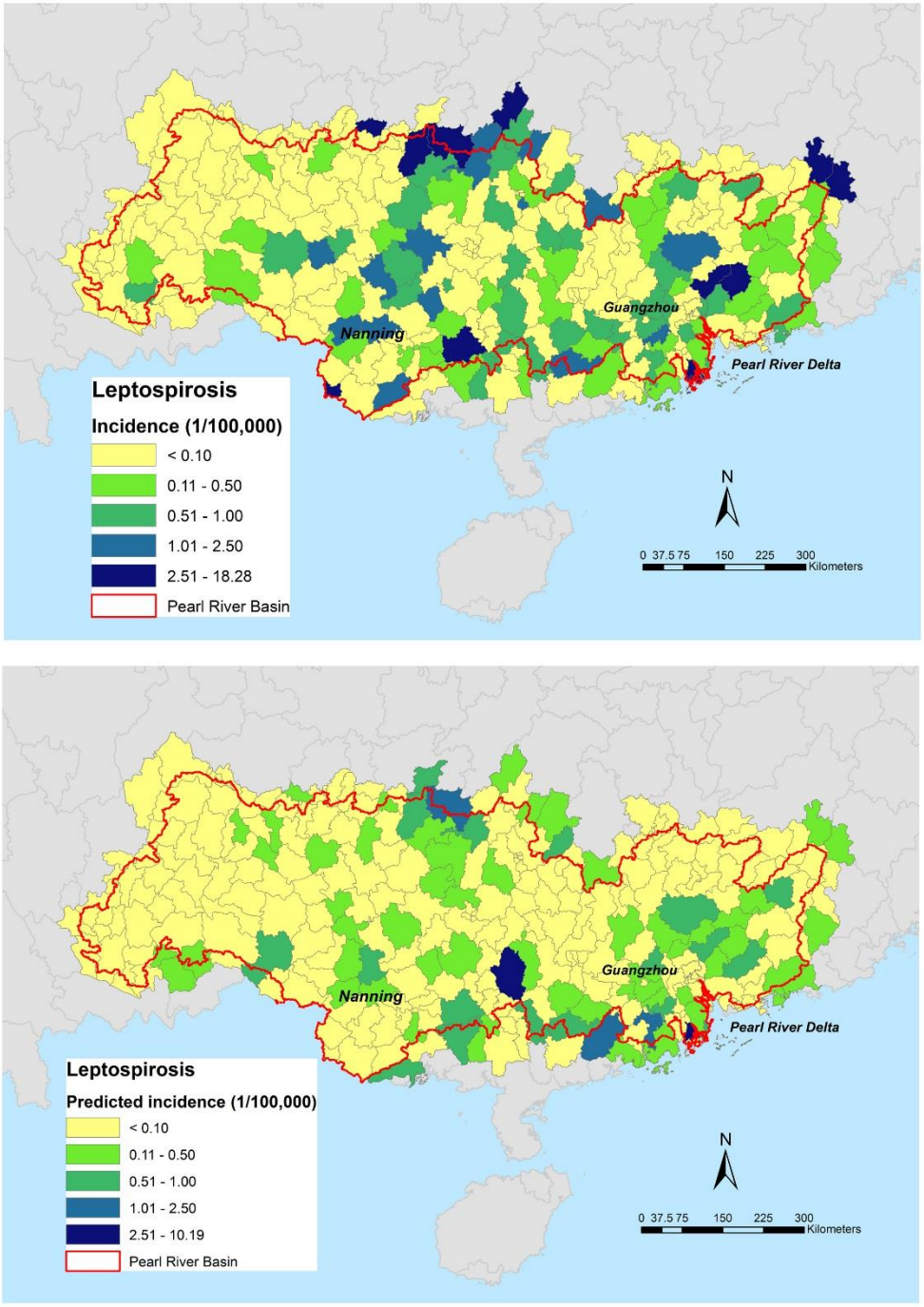

Figure 7-4 Spatial distribution of the observed leptospirosis incidence during 2011–2016 (top), predicted leptospirosis incidence for respective period (bottom) in PRB region after controlling the effects of environmental and socioeconomic factors.

7.5 Discussion

Using recent notified leptospirosis data and a state-of-the-art approach for spatial modelling, our study investigated the small-scale geographical heterogeneity of leptospirosis incidence within the two residual high-risk areas in China, the UYRB and PRB. This is the first study to provide projections of leptospiral infection incidence at county-level the UYRB and PRB. Our study provides further insights on the effects of environmental and socioeconomic on the distribution of risk of leptospirosis to those already gained in prior studies (Zhao et al., 2016, Jagadesh et al., 2019). Our spatial modelling approach demonstrated that the incidence of leptospirosis is highly variable even within the regions and is driven by different ecological drivers after controlling for environmental and socioeconomic factors. Our findings suggest that interventions within the two high risk areas need to be highly targeted and local-specific if elimination is to be reached. Our study contributes evidence for designing and implementing targeted preventive and leptospirosis control policies in these both regions. Summary of the findings of this study was given in Table 7-3.

In the present study, we demonstrate that seasonality in the incidence of leptospirosis notifications vary with geography in that for the UYRB, the incidence of leptospirosis was significantly lower in the second quarter (April–June) compared with the first quarter (January–March). In contrast, the incidence of leptospirosis notifications in the PRB was significantly higher in the second quarter relative to the first quarter. This finding reaffirms our previous study that recognised different temporal patterns of leptospirosis notifications between south coastal (Guangxi, Guangdong) and central inland (Sichuan, Chongqing, Guizhou, Hubei, Anhui) (Dhewantara et al., 2018a) areas. In addition, our findings also consistent with findings in other studies elsewhere. For instance, strong and different seasonality pattern of leptospirosis incidence has also been observed in elsewhere (Desvars et al., 2011, López et al., 2019). This seasonality patterns are greatly depending on climatic variability and the intensity of extreme weather events and flooding (Desvars et al., 2011). For instance, in northern Argentina, leptospirosis incidence increased during warm and temperate season, between December and May each year (López et al., 2019).

Table 7-3 Summary of the findings

	Upper Yangtze River Basin (UYRB)	**Pearl River Basin (PRB)**
Ecological feature	Stretch from Mt. Geladandong (6,621 m) in southwest Qinghai Province towards Chongqing municipality, crossing the Sichuan Plateau to Yichang. More than 4511 km which accounts for 70% of the total length of the Yangtze River (6300 km) with a drainage area of approximately 1,000,000 km^2 Diverse and complex vegetation, soil type, climate and topography. Featured by mixed forest, bare land and cropland. Indian monsoon system, subtropical zone, 70-80% of the annual rainfall fall during May-October (summer). Mean temperature from 16–20°C. Intense floods and droughts.	Stretch up to 2400 km (Yunnan to Guangdong), covers about 400,000 km^2. Affected by tropical and subtropical climate, with annual mean temperature ranging from 14°C to 22°C and mean precipitation of approximately 1525 mm per year. About 80% of the annual rainfall fall during April-September. Mean temperature ranging from 14-22°C. Frequent and severe climate-weather events (typhoons) leading to floods.
Counties and population[a]	386 counties, about 170 million people	281 counties, approximately 150 million people
Total reported leptospirosis cases (2005-2016)	3217 cases (185 counties)	1473 cases (199 counties)
Findings of the study[b]	The spatial variation in leptospirosis incidence was associated with precipitation, MNDWI (flood) and elevation	Precipitation, NDVI (vegetation/biomass), livestock density and land cover explained the geographical heterogeneity of leptospirosis incidence
Predicted population-at-risk estimate[b]	103,907,069 people in 179 counties	50,681,249 people in 105 counties
Suggested focus of intervention	Revitalize drainage systems, WASH and rodent control. Strengthen climate-based early warning systems for surveillance	Improve farm (small-scale) biosecurity measures (livestock vaccination, rodent control and waste management). Enhance disease awareness programs towards high-risk population

		(farmers) (e.g., promoting PPE, chemoprophylaxis and IEC)

[a] Based on GIS analysis. County level population data were obtained from China National Bureau of Statistics.
[b] Based on ZIP-CAR spatial model.

The difference in seasonality patterns between the two high risk areas may partly be driven by different climatic conditions that modulate exposure. The UYRB is situated in the subtropical monsoon area and is primarily influenced by the Indian monsoon system which brings abundant and long-lasting rainfall during May–October leading to severe floods. In contrast, the PRB lies in the tropical and sub-tropical climate zones with high precipitation during April–September. The findings provide important knowledge for anticipating leptospirosis outbreaks and for strengthening the surveillance and the capacity to diagnose acute undifferentiated illness in these regions.

In line with other studies our results indicate that in both regions, the incidence of leptospirosis was significantly lower in 2011–2016 compared with 2005–2010 (Dhewantara et al., 2018a, 2018b). Based on the model, a prominent predicted reduction was identified in the UYRB. In the past few decades, significant progress has been made in the control of leptospirosis including the provision of access to safe water, sanitation and hygiene, improvement in biosecurity by reducing of leptospiral infection in animal (livestock) hosts through vaccination, and vaccination of high-risk populations (Hu et al., 2014, Xu and Ye, 2018). In addition, this reduction could be linked with massive changes in land use along the Yangtze river (e.g., the development of Three Gorges Dam, land conversion due to urbanisation) and the introduction of agricultural mechanisation (Delang and Yuan, 2015, Chang et al., 2016), which may have directly or indirectly altered rodent/host diversity and reduced contact with a contaminated environment (Haake and Levett, 2015, Zhang et al., 2019).

Our study extended knowledge by that improving prior model developed by Jagadesh et al. (2019) through the addition of relative importance on socioeconomic and animal factors along with environmental variables. Our models accounted for various predictors and spatial autocorrelation in the data that improve the accuracy of the estimation. Most importantly, the

study provides uncertainty maps (e.g. maps of standard deviation) (Appendix E: Figure E-3 and Figure E-4) that may better inform the need for evaluating and scaling-up the coverage of interventions towards both high- and low-risk areas. For example, the uncertainty maps can be used to locate areas where diagnostic capacity needs to be improved or where more active population-based surveillance is needed, especially in that known low-risk areas to accurately estimate the burden of leptospirosis.

In both regions, we found that the leptospirosis incidence was significantly higher in areas with higher precipitation, which is consistent with previous studies elsewhere (Baquero and Machado, 2018, Gutierrez and Martinez-Vega, 2018, Dhewantara et al., 2019a). However, the effect size of rainfall was significantly higher in UYRB compared with PRB. In addition to rainfall in the UYRB, both elevation and MNDWI (a proxy for flooding) could adequately explain the geographical variation of the incidence of leptospirosis. Our results for UYRB indicate that lowland and flood-prone areas are at higher risk for leptospirosis transmission—a finding that is consistent with the known hydro-ecology of this region (Yu et al., 2009). This finding also supports previous studies that elevation and flooding play a role in the epidemiology of leptospirosis (Lau et al., 2012, Wang et al., 2014). The UYRB features a predominantly a low-flat landscape, with abundant rainfall and frequent flooding, especially in the areas of the Yangtze valley and Three Gorges Dam reservoir (Yu et al., 2009). These findings confirm that leptospirosis transmission in UYRB is likely to be driven by extreme climatic events. Specific interventions that could be done in this area are improving the drainage systems as well as especially in that areas with high-risk of flooding and providing better access safe water and better sanitation and hygiene (WASH). In addition, the development of outbreak early warning system may be necessary to improve leptospirosis surveillance for timely preparedness and response.

In PRB, the incidence was predicted to be higher in areas with a high greenness index (high biomass or vegetated areas) and a dense livestock (both pig and cattle) population, and in areas where waterbodies predominant. This could be due to a number of reasons. For example, higher greenness may be linked with an abundant rodent population and diverse animal reservoirs. This allow for the maintenance of *Leptospira* in the environment. This is supported by recent findings from a study in Jiangxi Province (Zhang et al., 2019)—which is adjacent to the PRB and shares typical climate and ecological characteristics—that revealed

high diversity of host animals and pathogenic *Leptospira* strains. Further, people living in areas with a dense livestock population have the potential to be exposed to infected animals or a contaminated environment. The finding in the PRB are also consistent with findings reported about American Samoa (Lau et al., 2012a) and Fiji (Mayfield et al., 2018b) that a significant effect of livestock density was an increased risk of leptospirosis infection. Further, higher incidence was found in areas with abundant waterbodies, such as lakes or in proximity to a river; this could be partly explained by behavioural factors (e.g., swimming, fishing, bathing), and such areas are prone to floods. Studies have reported that the presence of a river adjacent to human settlement increased the risk of leptospirosis (Lau et al., 2016, Mayfield et al., 2018a). Intervention programs in this region should be focused on preventing potential zoonotic transmission by improving biosecurity measures at farm level (e.g., livestock vaccination, rodent control and waste management). An integrated strategy to control leptospirosis in livestock by combining extensive biosecurity measures, vaccination, and chemoprophylaxis has successfully reduced the outbreak at farm level (Mughini-Gras et al., 2014; Pimenta et al., 2019). In addition, raising awareness among high-risk occupational groups (e.g., farmers, meat workers) through advocating protective wear for farmers (e.g. personal protective equipment) and chemoprophylaxis (doxycycline) and promoting awareness among populations at-risk (e.g. leaflets, educational packages) are also important.

Our results also indicated that broad socioeconomic variables (GDP, crop production, urban/rural) were not associated with the spatial variation in the incidence of leptospirosis in the both the UYRB and PRB. This finding contradicts other studies that reported the significant role of poverty indicators in the geographical variation in leptospirosis incidence (Mayfield et al., 2018b, Baquero and Machado, 2018). This finding is probably due to area-level socioeconomic status (SES) (as indicated by GDP) being a poor proxy of individual exposure risk and, thereby, unable to explain the spatial variation of leptospirosis incidence in the UYRB and PRB. Future models should incorporate individual/household-level socioeconomic factors (e.g., income, SES).

Here, our modelling identified high-incidence areas and they appear to be more widespread in both the UYRB and PRB. In the UYRB, the incidence is predicted to be high in counties that border Chongqing-Hubei-Guizhou and counties in the central and southern part of the Yangtze valley, affecting more than 100 million people in 179 counties. In the PRB, the high-

incidence counties are more scattered compared with the observed incidence counties. Higher incidence areas appear in the middle and lower reaches of the PRB. Our study estimated that approximately 50 million people in 105 counties are at high risk of contracting leptospirosis infection. In light of our study, the findings suggest there remain many areas that still have a high incidence of leptospirosis both in the UYRB and PRB, highlighting the importance of expanding the coverage of the intervention program towards larger areas within the region. It may also be necessary to evaluate and strengthen surveillance and diagnostic capacity in those predicted high-risk areas.

In this study, the model validation was based on MAPE. This study used CAR model, which is basically smoothing the observed rates across all known polygons (counties) of the study. This CAR method is not strictly a spatial prediction technique but rather a smoothing approach that accounting for correlated covariates. Thus, in this context, MAPE is a robust approach to look at differences between the observed counts in a area and the adjusted or smoothed counts under the model. MAPE could provide an assessment of the role of covariates at explaining area-based spatial autocorrelation.

Limitations

Some limitations in this study should be considered when interpreting the findings. First, the study utilised all reported leptospirosis cases from both regions, including those clinically diagnosed and laboratory confirmed cases. This approach was chosen as it would allow comparing with other local epidemiological studies and government reports. In addition, as the data used in the study were obtained from a passive surveillance system, the results presented here might be influenced by the under-reporting of leptospirosis due to poor awareness in the population towards the symptoms, availability or accessibility of health services, and diagnostic testing facilities—especially in remote areas. While leptospirosis is a notifiable disease in China its surveillance is primarily passive in nature. To date, there have been no studies reporting active surveillance (e.g., by means of serosurveys) to quantify the true burden of infection. However, the findings of the present study indicate the opportunities for health authorities in the identified high-risk areas to design and plan active surveillance activities to better understand the local conditions that contribute to the increase risk in those communities identified in our study. Second, the spatial (pixel size) and temporal resolution of

the covariates might be not perfect as some data were not available in finer spatial resolution (e.g., urban-rural raster data with 5 x 5 km spatial resolution) and matched with timeframe of the epidemiological data used in this study (e.g., GDP). This may influence the results as coarse spatial and temporal resolution might subject to measurement error. Additionally, we estimated and used the areal mean value of each remote-sensed covariates as a proxy for the actual exposures. However, this technique could lead to regression dilution bias due to imprecise exposure estimation, which may in turn underestimate the observed effects (Hutcheon et al., 2010). Fourth, although we accounted for several environmental and socioeconomic covariates in the development of prediction maps for leptospirosis, the observed effects may also be confounded by unmeasured factors (e.g., biosecurity improvement, rodent controls, and improvement in water supply, sanitation and hygiene (WASH) infrastructure in China). This is indicated by a relatively high standard deviation in some areas where leptospirosis is also predicted to be high (Appendix E: Figure E-1 and Figure E-2). Finally, in this study we did not identified any association between socioeconomic factors and leptospirosis incidence. We hypothesised that individual/household-level or community-level socioeconomic factors (e.g., behaviour, occupational exposure, presence of animal reservoirs in the household, access to safe drinking waste and sanitation, household income) could be more influential in explaining the spatial variation in the incidence of leptospirosis in both regions instead of broad socioeconomic factors. Unfortunately, in this study we did not include those variables as there was no such data available at county level. Further studies should include individual-, household-, and community-level socioeconomic factors in the prediction model to better understand the role of such factors on the spatial variation of leptospirosis in this region. In addition, future studies should attempt to look at the effect of climate change on the geographical distribution of the risk of leptospirosis in these regions, as the incidence of leptospirosis is likely to increase due to climate change and urbanisation (Lau et al., 2010). This could be achieved by incorporating various emission scenarios/representative concentration pathways (RCPs) into the models.

7.6 Conclusion

Our study demonstrated that drivers of leptospirosis incidence differ between high-risk areas of China, suggesting local-specific interventions. In UYRB, leptospirosis incidence was

strongly associated with flooding, while in PRB, it appeared to be strongly related with agricultural practices. The smoothed-predictive map of leptospirosis incidence developed in this study can aid health authorities and policymakers to identify areas within the two high-risk areas where surveillance and diagnostic capacity for leptospirosis control should be strengthened in order to achieve effective control and elimination.

Chapter 8 Climate variability, satellite-derived environmental data and human leptospirosis: a retrospective ecological study in China

This research chapter has been published in *Environmental Research* as an original peer-reviewed research paper. The concept and design of the study outlined in this Chapter 8 were formulated by PWD (80%) with the assistance of RJSM (10%) and WH (10%). WYZ provided the data. PWD was responsible for data management (100%), data analyses (100%) and the interpretation of results (85%) was discussed in consultation with WH (10%) and all co-authors (5%). PWD was responsible for drafting the manuscript (100%). PWD was responsible for revision of the final version of the manuscript (90%), taking into account the comments and suggestions of RJSM (5%) and all co-supervisors (5%).

Reprinted from Environmental Research, September 2019; Volume 176. **Dhewantara, P.W**., Hu, W., Zhang, W.Y., Yin, W.W., Ding, F., Mamun, A.A. and Soares Magalhães, R.J. Climate variability, satellite-derived physical environmental data and human leptospirosis: A retrospective ecological study in China.

8.1 Context

In my review detailed in Chapter 2 and Chapter 4, I indicated that climatic and environmental variables are important parameters when modelling leptospirosis transmission. Research detailed in Chapter 5 also highlighted that leptospirosis in China is highly seasonal, but I also found differences in the annual epidemic pattern across regions. This may be linked with climate variability. The research detailed in Chapter 6 demonstrated that weather is one of the important determinants of leptospirosis, which means areas differ in terms of their risk because of precipitation (i.e. areas with higher monthly precipitation are more likely to have higher leptospirosis incidence). The results presented in Chapter 7 further confirmed that the role of socioecological factors on leptospirosis incidence was significantly geographically varied at county level, emphasising that risk factors of leptospirosis incidence are highly local specific.

In order to effectively deliver intervention programs, health authorities also need adequate information on the best timeframe for conducting interventions. Localised risk forecasting tools are required to better improve prevention and preparedness for leptospirosis outbreaks as leptospirosis transmission is likely to operate at local level. So far, as indicated in the systematic review detailed in Chapter 4, studies have been conducted at various scales (national, sub-national, and local level) (Desvars et al., 2011; Chadsuthi et al., 2012; Suwanpakde et al., 2015; Matshushita et al., 2018) to look at the temporal associations between climate and leptospirosis. Few studies, however, have attempted to use remote sensed parameters to examine the associations between environmental variability and leptospirosis incidence and to develop temporal prediction models. The goal of this chapter is to provide temporal models, which account for climatic information and remote-sensed environmental indicators, as tools to anticipate leptospirosis outbreaks in high-risk counties identified in Chapter 6 and Chapter 7. Before the study outlined in this chapter was initiated, outbreak-prediction models for leptospirosis in China had not been developed. In light of the strong interplay between climate, environment, and leptospirosis emergence, it became important to be able to measure the temporal association between climate, physical environment, and the incidence of leptospirosis. Such evidence can be used to lay the foundation for developing an outbreak prediction system to better prepare and estimate the impact of leptospirosis outbreaks at county level.

In this chapter, I sought to assess the relationships between climate, environment and leptospirosis at local scale in selected high-risk counties in Yunnan and Sichuan province, namely, Mengla County and Yilong County, respectively. I selected these two counties due to several reasons. First, both counties were identified as high-risk counties as evidenced in Chapter 6 and Chapter 7. Second, both counties have different socioecological conditions in terms of climate, landscape, and sociocultural characteristics (Chen et al., 2016; Xu et al., 2017).

In this chapter, I used monthly laboratory-confirmed leptospirosis notification data from 1 January 2006 to 31 December 2016. I used ground weather data collected from the China Meteorological Data Sharing Service System. In addition, I used the moderate-resolution imaging spectroradiometer (MODIS) derived normalized difference vegetation index (NDVI), the modified normalized difference water index (MNDWI), and land surface temperature

(LST). I quantified the year-to-year associations between these weather and environmental parameters and leptospirosis incidence. This involved exploring the seasonality, investigating cross-correlation, and developing negative-binomial generalized linear regression models.

I demonstrated that seasonality of leptospirosis incidence is strong and site-specific. Results of generalized linear models demonstrated that in Mengla County, leptospirosis incidence was negatively associated with rainfall (lag of 6 months) and LST (lag 0 month). In Yilong County, the incidence of leptospirosis was positively associated with rainfall (lag 1 month), LST (lag 3 months) and MNDWI (lag 5 months). This study of the short-term effects of climate and environment on leptospirosis incidence have provided important evidence for improving our understanding regarding possible cycles of leptospirosis epidemics in both locations, which can be beneficial for strengthening surveillance programs at local level. In addition, in this chapter I indicated that local early warning systems for leptospirosis can be developed by putting altogether both local ground weather data and satellite-based environmental data.

8.2 Introduction

Leptospirosis is a water associated zoonotic disease caused by pathogenic Leptospira bacteria and is ubiquitously distributed in tropical and subtropical regions (Haake and Levett, 2015). Each year, about 1 million cases of human leptospirosis are reported globally and approximately 60,000 people lost their lives due to the infection (Costa et al., 2015). Leptospiral infection in humans presents a broad spectrum of symptoms ranging from flu-like illness, mild fever, headaches, jaundice, and myalgia to severe infection leading to pulmonary haemorrhage, renal failure, hepatic dysfunction even death (Levett, 2001). Given the non-specific clinical presentation, leptospirosis is often misdiagnosed especially in areas where surveillance and diagnostic capacity is limited. Infection in humans occurs due to the exposure to infected animals' tissues or urine or being exposed to water or soil containing the bacteria. The bacteria enter the human body through wound or mucosal membranes. A wide range of animals including domestic and livestock animals have been considered as carriers and are able to shed *Leptospira* spp serovars into the environment, though rodents are known as the key actor for leptospirosis transmission (McBride et al., 2005).

In China, leptospirosis was first reported in 1955 and since then it has become one of the infectious diseases that all health providers across China must give notification of (Shi et al.,

1995; Zhang et al., 2012). Most leptospirosis outbreaks are reported in rural areas where both rodents and livestock could be major sources of infections and where most people are intensively involved in subsistence agricultural activities (Zhang et al., 2012). Local outbreaks following heavy rainfall and flooding have been reported in some parts of China (Tang et al., 2017; Wang et al., 2014). Studies have shown that disease incidence and mortality has been declining since the 2000s, which is possibly due to demographical, ecological, and social changes (Dhewantara et al., 2018a; Zhang et al., 2012). Despite this dramatic reduction, residual high-risk areas for leptospirosis transmission still exist throughout the country (Dhewantara et al., 2018b), indicating that the drivers are still present. This has been evidenced by frequent annual local outbreaks, especially in resource-limited rural areas in southwest China (Zhou et al., 2015). A previous study demonstrated that during 2005–2015 high risk areas were identified in Yunnan and Sichuan Provinces in the southwest which contributed to 47% of the total reported cases (Dhewantara et al., 2018b). Yet, factors underlying local leptospirosis transmission in these two areas are far from clear. Hence, it is essential to assess and identify local key environmental drivers associated with continuous leptospirosis transmission in order to anticipate further localised outbreaks and bring the disease closer to being eliminated in China.

Indeed, leptospirosis transmission involves complex socioecological mechanisms. In tropical and sub-tropical regions, most leptospirosis outbreaks occur during humid and wet seasons or monsoons, which drive more water, moist soil, and flooding providing a favourable medium for *Leptospira* transmission. In such favourable environmental conditions, some pathogenic *Leptospira* strains can survive for days, even months (Andre-Fontaine et al., 2015; Baker and Baker, 1970). Further, in rural areas, the wet season coincides with intense farming activities (e.g. irrigating or planting paddy fields, harvesting and herding). At the same time, the rodent population becomes more abundant in the environment (Perez et al., 2011) as rainfall increases land and vegetation productivity and thus provides more food as well as suitable environment conditions for rodents to breed. Increases in the rodent population could boost *Leptospira* shedding into the environment as well as increase risk of transmission among reservoir animals. Moreover, lack of sanitation, poor waste management, and unsafe behaviours (e.g. walking barefoot) due to poor socioeconomic conditions increase the risk of human infection (Mwachui et al., 2015).

In the absence of adequate intervention strategies—such as routine surveillance, vaccination, social and environmental modifications (e.g., rodent control, water and sanitation improvements) and early-warning systems—leptospirosis transmission in residual high-risk areas is likely to continue. Climate change could potentially affect the seasonality and shift the geographical distribution of leptospirosis (Lau et al., 2010). The impact of meteorological factors on leptospirosis incidence has been widely investigated at various geographical settings and climatic zones (Chadsuthi et al., 2012; Coelho and Massad, 2012; Desvars et al., 2011; Ghizzo Filho et al., 2018; Gutiérrez and Martínez-Vega, 2018; Matsushita et al., 2018; Pappachan et al., 2004; Robertson et al., 2012; Soares et al., 2010; Suwanpakdee et al., 2015; Weinberger et al., 2014). Previous research demonstrated a strong association between leptospirosis incidence and climate, but its size and lagged effects varied between studies ranging from weeks to months. For instance, in New Caledonia, leptospirosis outbreaks were influenced by La-Niña periods which were responsible for heavy rainfall events in the island; it was found that rainfall at a lag of eight months was significantly associated with leptospirosis incidence at a given month (Weinberger et al., 2014). In addition, a recent study in Manila, Philippines, found an increase in leptospirosis hospital admissions was linked to rainfall at a lag of two weeks (Matsushita et al., 2018). Some studies have also demonstrated an association between leptospirosis occurrence and humidity and temperature (Joshi et al., 2017; Sumi et al., 2016). These studies used climatic data measured by ground stations. To date, few studies have investigated the role of climate on the leptospirosis outbreaks in China (Wang et al., 2014; Zhang et al., 2012). The association of climate variability on the incidence of leptospirosis in China, especially in residual high-risk counties remains unclear.

In addition to climate, the role of the physical environment on leptospirosis transmission is also important, such as the presence of waterbodies or flooding and variation in land cover (Della Rossa et al., 2016; Ledien et al., 2017; Matsushita et al., 2018). Currently, remote-sensing (RS) technologies provide a broad range of physical environment data at various spatial and temporal scales, which can help to better understand disease epidemiology (Hamm et al., 2015; Herbreteau et al., 2007). Such satellite-derived data have been widely used to identify environmental drivers of vector-borne disease such as malaria (Ebhuoma and Gebreslasie, 2016) or water-borne diseases such as cholera (Xu et al., 2015), but very few leptospirosis studies to date have used these RS data to quantify the role of environmental

risk factors in the temporal pattern of leptospirosis incidence. For instance, a moderate resolution imaging spectroradiometer (MODIS)-derived modified normalized difference water index (MNDWI) has been used as a flooding indicator and to help estimate risk for leptospirosis in Kampong Cham province, Cambodia (Ledien et al., 2017). This far, no studies have investigated the temporal relationships of both climatic and RS-based physical environmental indicators and leptospirosis in China. Combining both climatic and RS-based physical environment data can provide further insight into the local epidemiology of leptospirosis in China and it could be used to anticipate leptospirosis outbreaks in order to support local health authorities to better design timely and effective control strategies for leptospirosis, especially in residual high-risk areas.

In this present study, our primary objective was to examine the short-term associations between climatic and satellite-derived physical environmental data on human leptospirosis in high-risk areas in China.

8.3 Methods

8.3.1 Study area

This study was carried out in two counties, Mengla County in Yunnan Province and Yilong County in Sichuan Province (Figure 8-1). These two counties were selected because both were at the high-risk regions for leptospirosis in the country (Zhang et al., 2012; Dhewantara et al., 2018b). Moreover, both counties are situated in different climatic zones and exhibit unique socioecological features. Mengla County (21°27'33.24"N, 101°35'52.68"E) is located in Xishuangbanna and covers an area of 7093 km^2 with a predominantly mountainous landscape with elevation ranging from 480 m to 2023 m. Mengla county has a tropical monsoon climate with a wet season (May–October), dry and foggy season (November–December) and dry-hot season (January–April) and annual precipitation between 1200 and 2500 mm. It has a population of 200,000 people and is inhabited by about 11 ethnic groups of which, Dai and Hani are dominant. Each group has different types of agricultural activities. Most Dai people live in the lowland near the river and engage with wet paddy cultivation; while Hani people occupy the upland hills and are involved in shifting cultivation. This region has also been known as the second largest rubber plantation area in China (Chen et al., 2016).

Yilong County is under Nanchong city administration (31°16'17.62"N, 106°18'10.95"E) which lies in the typical subtropical humid zone characterised by high humidity, mild winter, and hot, humid summer. The city is also located in the Sichuan Basin where rainfall is abundant, with annual rainfall ranging from 900 to 1200 mm. Due to favourable climate and environmental conditions, most areas in the Sichuan Basin are suitable for agriculture, primarily rice plantation (Xu et al., 2017). The county covers an area of 1771 km^2 with a population of about 1.11 million people in 2009, and most people live in rural areas and engage in rice cultivation and animals farming. The county has a hilly landscape and is adjacent to the Jialing River, a tributary of the Yangtze River.

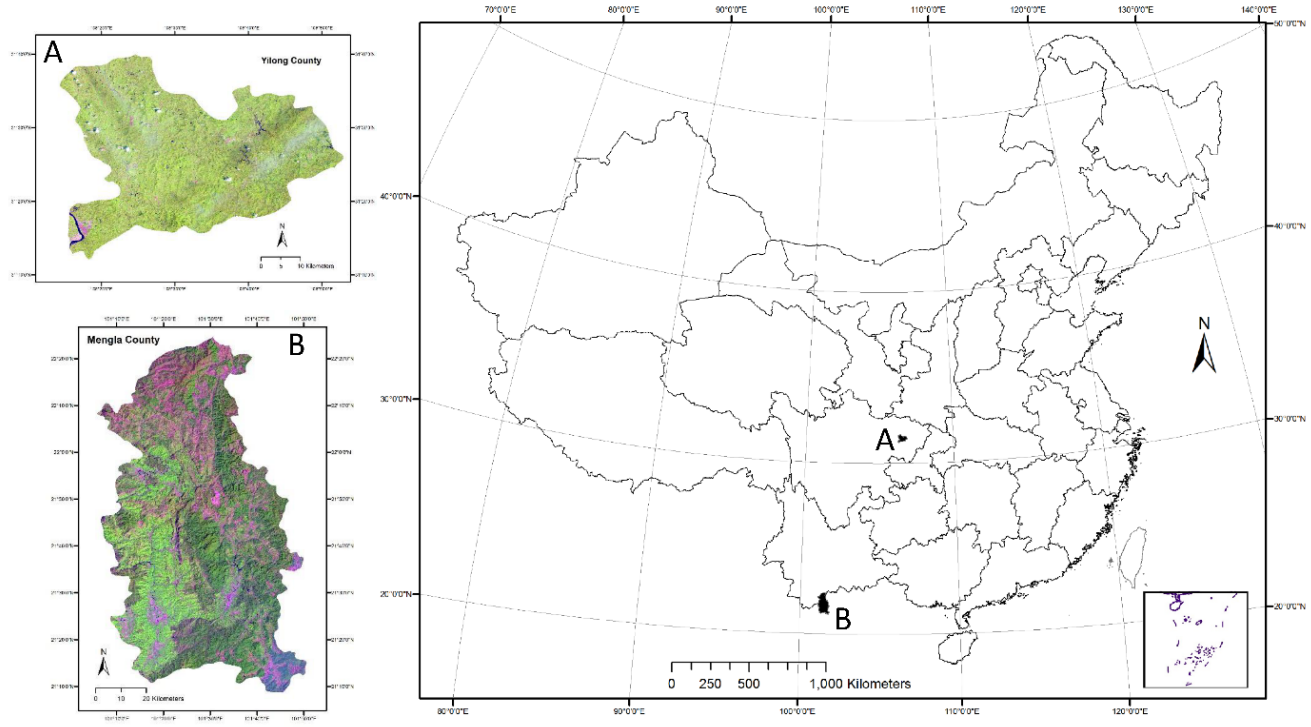

Figure 8-1 Map of study location: Yilong County, Nanchong, Sichuan (A) and Mengla County, Xishuangbanna, Yunnan (B), China. Image of Yilong County and Mengla County was retrieved from Landsat 8 OLI-TIRS (available online at https://landsatlook.usgs.gov/) and processed in ArcGIS 10.5.1 (ESRI Inc., Redlands, CA, USA).

8.3.2 Leptospirosis notification data

Monthly laboratory-confirmed leptospirosis cases in both counties for the period of 1 January 2006 to 31 December 2016 were collected from the Chinese Center for Disease Control and Prevention (China CDC) through the China Information System for Disease Control and Prevention (CISDCP). A total of 543 leptospirosis cases were reported during 2006–2016 from both counties. All cases included in the analysis were confirmed based on the standard diagnosis guidelines set by the National Health Commission of the People's Republic of China (Ministry of Health of China, 2008). In addition, yearly population data for both counties, obtained from the National Bureau of Statistics, were used to estimate the leptospirosis incidence. Ethics clearance for this project was approved by the Medical Research Ethics Committee of the University of Queensland (#2016001608) and the Ethics Committee of Beijing Institute of Disease Control and Prevention. All potentially identifiable information has been removed to protect the privacy of individuals.

8.3.3 Local meteorological data

Monthly data on rainfall and relative humidity (RH) for the same period were calculated from the daily meteorological records provided by the China Meteorological Data Sharing Service System (http://cdc.cma.gov.cn/). Weather data were reported from two local weather stations in both counties. Missing values were interpolated based on the nearby weather stations (Eischeid et al., 2000).

8.3.4 Remote-sensed environmental data

For each county, we obtained remote-sensed environmental data, including normalized difference vegetation index (NDVI), modified normalized water difference index (MNDWI) and land surface temperature (LST) from MODIS Terra satellite. Briefly, NDVI was calculated using red (wavelength: 620-670 nm) and near infrared (NIR) (841-876 nm) of MOD09A1 product with 8-day and 500-m resolution. The NDVI was used as a proxy of vegetation (biomass productivity linked with seasonal agricultural practices–rice harvesting cycle) that may also reflect abundance of food in the ecosystem and seasonal rodent abundance (Lumbierres et al., 2017, Yu et al., 2017). We used MNDWI as a proxy for the presence of standing waterbodies, floods or inundated water (Ledien et al., 2017). Values for MNDWI were calculated based on the surface reflectance of green (545-565 nm) and short-wave infrared (SWIR) (1628–1652 nm) (Xu, 2006). *Leptospira* survival and virulence depend on

temperature (Stoddard et al., 2014; Fraser and Brown 2017), hence we included data for land surface temperature (LST) (°C) extracted from MODIS Terra LST product (MOD11A2) with an 8-day composite and 1-km resolution. All MODIS products were downloaded from the United States Geological Survey (USGS) Earth Resources Observation and Science (EROS) Center (https://eros.usgs.gov/). To cover our two study areas, two MODIS tiles were required (h27v05, h27v06). All images were then mosaicked, re-projected, and resampled to 500 m to match with other products. The time-series monthly data of NDVI, MNDWI and LST for each county from January 2006 to December 2016 were extracted using ArcGIS v10.5. Values for NDVI and MNDWI range from -1 to 1. A detailed list of remote-sensing parameters included in the analyses are summarised in Appendix F: Table F-1.

8.3.5 Statistical analyses

Variable selection

Monthly leptospirosis counts were considered as a dependent variable in our analyses. Five independent climatic and RS variables were included in the analyses including rainfall, RH, NDVI, MNDWI and LST. Spearman's correlation coefficient was used to examine the bivariate association between independent variables. Strong correlated variables (Spearman's rho $\geq$ |0.8|) were analysed separately in the modelling stage to avoid collinearity issues. Associations were considered statistically significant at $P < 0.05$. Cross-correlation analysis was then performed to investigate significant temporal lags (in months) between leptospirosis incidence, climatic and environmental variables. The factors that did not show a significant temporal lag were not included in the final model. We included all variables that reached positive and negative significant lag values in the model selection processes with a maximum lag of eight months, according to previous findings (Chadsuthi et al., 2012; Weinberger et al., 2014) and also biological and epidemiological plausibility of leptospirosis transmission.

Exploration of seasonality

Decomposition analysis was applied to decompose the leptospirosis monthly notification time series data (Y_t) into a combined trend (T_t), a seasonal component (S_t), and an error or residual component (E_t) (Cleveland et al., 1990). The relationship between the different decomposition terms and leptospirosis incidence is:

$$Y_t = T_t + S_t + E_t$$

We included S_t into the model as a seasonal factor (SAF) to control the effect of seasonality in the regression model (Kumar, 2010).

Examining short-term associations

Since the residuals of the leptospirosis notification model are assumed to follow a Poisson distribution, we used a generalized linear model (GLM) to evaluate the effects of climatic and environmental factors on the incidence of leptospirosis, adjusted by seasonal components (SAF). To account for over-dispersion in the count data, a negative binomial distribution with a log link was used. The natural logarithm of the population was added as an offset term. The goodness-of-fit of the models was assessed based on Bayesian Information Criterion (BIC) and deviance. The model with the lowest BIC and deviance was chosen as the final model. The seasonality and autocorrelations of the deviance residuals of the final models were checked by visually examining the sequence charts and partial autocorrelation function over time lags. In addition, to test for collinearity among all explanatory variables in the final models, the variance inflation factor (VIF) was observed and variables with VIF ≥ 4 were removed (O'Brien, 2007). All statistical analyses were conducted using SPSS version 24 (IBM Corp, Armonk, NY, USA).

8.4 Results

8.4.1 Descriptive analysis

During the 11 years of the study period, there were a total of 573 and 459 leptospirosis cases reported in Mengla and Yilong counties, respectively. They account for 44.90% and 28.36% of total leptospirosis cases recorded in Yunnan and Sichuan Provinces, respectively. Table 8-1 summarises the mean, standard deviation (SD), minimum and maximum value, and 25th and 75th percentile of the distributions of leptospirosis cases, weather and remote sensed environmental parameters per month in the two counties studied during the entire study period.

On average, there were 4.34 (range 0–29) leptospirosis cases reported per month in Mengla County whereas, the monthly average number of leptospirosis in Yilong was 3.47 (ranging from 0 to 104 cases). Mean monthly rainfall (127.62 mm with range 0 to 555.9 mm) and humidity (80.33%, 69–91%) in Mengla County was relatively higher compared to Yilong

County. The monthly mean NDVI in both counties was not significantly different ranging from 0.06 to 0.84. The mean monthly MNDWI and LST in Mengla County was 0.1 and 6°C higher, respectively, compared with Yilong County. The wide range of monthly mean LST was observed in Yilong County (6.97°C to 37.79°C).

A strong seasonality pattern of leptospirosis incidence was identified in both counties with the highest incidence being attained in 2011–2012 (Figure 8-2). Bimodal annual seasonality was obviously observed in leptospirosis data from Mengla County; with two major peaks in May and September. In contrast, leptospirosis in Yilong County showed a single annual peak in September during the study period (Appendix F: Figure F-1).

Table 8-1 Summary statistics of monthly leptospirosis cases, climatic and environmental variables in Mengla and Yilong County, 2006–2016

Variables	Mengla County						Yilong County					
	Mean	**SD**	**Min.**	**Max.**	**P_{25}**	**P_{75}**	**Mean**	**SD**	**Min.**	**Max.**	**P_{25}**	**P_{75}**
Leptospirosis	4.34	6.07	0	29	0.00	7.00	3.47	13.68	0	104	0.00	0.75
Precipitation (mm)	127.62	121.47	0	555.9	32.22	194.35	33.60	38.00	0.66	230	6.43	49.30
RH (%)	80.33	4.75	69	91	77.00	83.00	74.60	5.44	58.30	85.77	70.53	78.76
NDVI	0.62	0.17	0.09	0.84	0.52	0.75	0.66	0.23	0.06	0.82	0.21	0.60
MNDWI	0.35	0.28	-0.28	0.93	0.17	0.57	0.24	0.17	-0.28	0.76	0.13	0.36
LST (°C)	29.72	3.93	20.97	37.53	26.38	32.82	23.50	8.47	6.97	37.79	15.03	31.42

Note: RH, NDVI, MNDWI and LST indicate relative humidity, normalized difference vegetation index, modified normalized difference water index and land surface temperature, respectively.

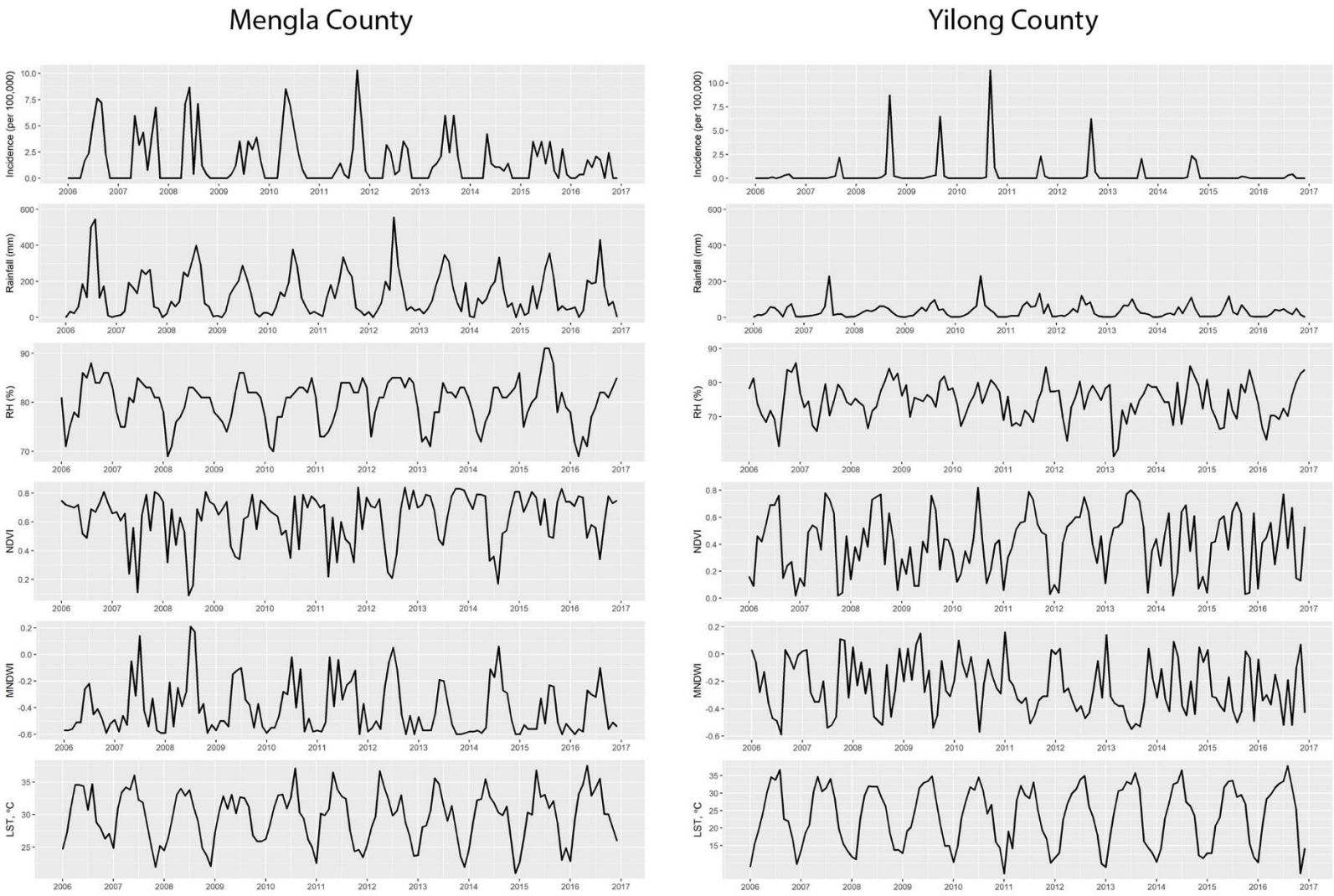

Figure 8-2 Monthly leptospirosis incidence, climatic and satellite-based environmental data in Mengla County, Xishuangbanna, Yunnan (left) and Yilong County, Nanchong, Sichuan (right), China, 2006-2016.

8.4.2 Correlation analyses

Results of the Spearman's correlation test indicated that all variables including rainfall, humidity, NDVI, MNDWI and LST were significantly correlated with leptospirosis incidence in Mengla County (Appendix F: Table F-2). However, NDVI was found to have an inverse association with leptospirosis incidence. In Yilong County, most variables showed significant correlation ($P < 0.001$) with leptospirosis incidence in the county, except humidity and MNDWI. No strong correlation ($r \geq |0.8|$) between leptospirosis and weather and environmental variables in both counties was observed.

8.4.3 Time series cross-correlation between leptospirosis incidence and lagged climate and environmental variables

In Mengla County, cross-correlation analysis identified significant maximum positive cross-correlation function (CCF) between leptospirosis incidence and rainfall was at a lag of one month (Figure 8-3; Appendix F: Table F-3). A high negative CCF was observed between leptospirosis and rainfall, humidity and NDVI at lag of 6 months, 4 months, and 2 months, respectively. MNDWI at lag 0 have positively strong correlation with leptospirosis. LST at lag 0 to 4-months was correlated with leptospirosis cases with the highest coefficient observed at lag 1.

In Yilong County, the power of associations between leptospirosis and rainfall were also heterogeneous over time lags, with the highest CCF being observed in lag 2. Correlation between leptospirosis and humidity was relatively weak from lag 0 to lag 4. Leptospirosis was found to have strong positive correlation with a 1-month lag of NDVI and a 4-month lag of MNDWI. Positive CCF was also identified between leptospirosis and LST at lag 1 to lag 4 months, with the maximum correlation at lag 2.

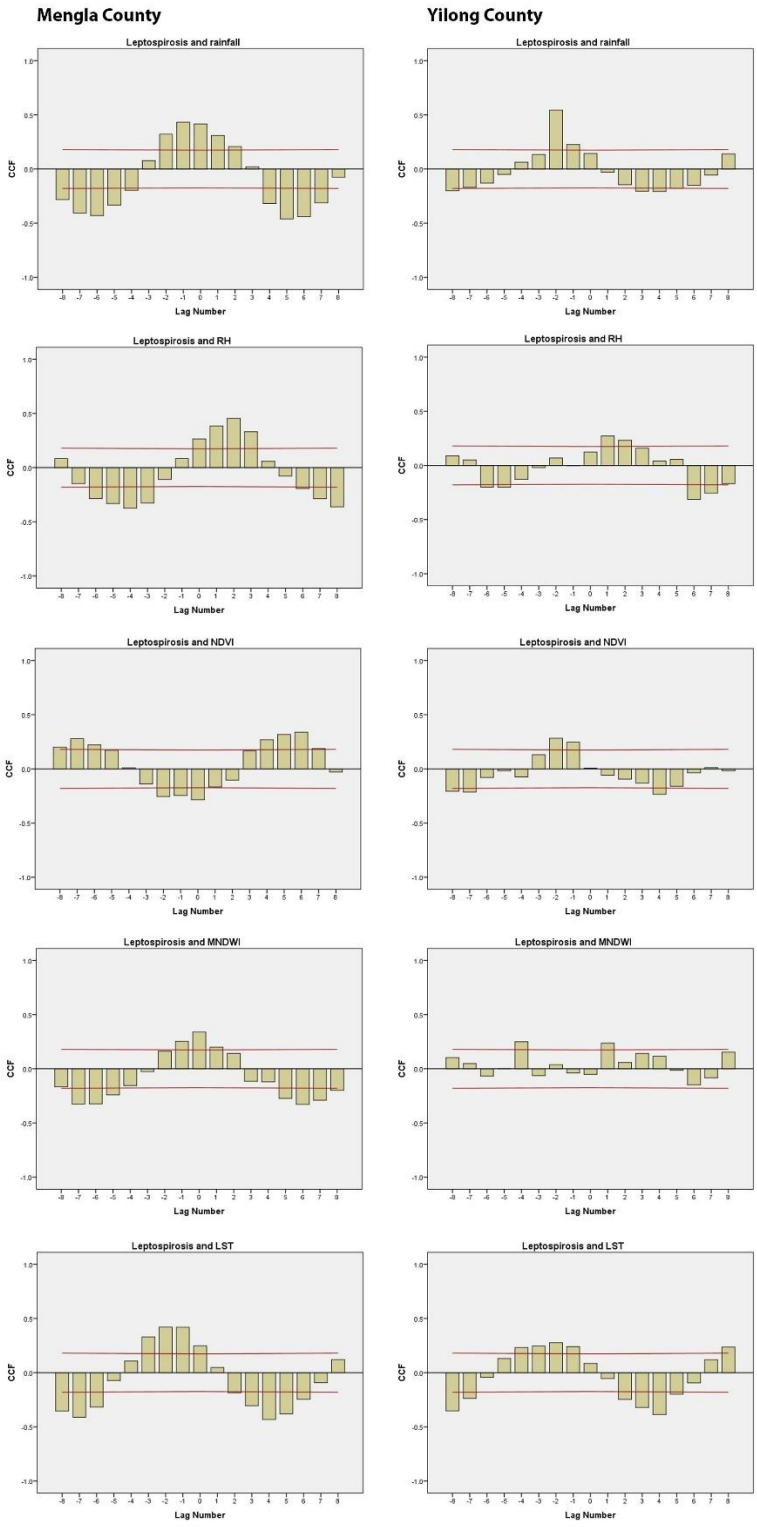

Figure 8-3 Cross-correlation analysis on human leptospirosis with rainfall, humidity, normalized difference vegetation index (NDVI), modified normalized difference water index (MNDWI) and land surface temperature (LST) in both Mengla County (left) and Yilong County (right).

8.4.4 Associations between leptospirosis incidence and weather and remote-sensed environmental indicators

A total of 23 model candidates were constructed for both Mengla County (11 models) and Yilong County (12 models) (Table 8-2). In Mengla County, we identified 5 univariable models. Our univariable analysis shows that leptospirosis was significantly associated with a 6-month lag for humidity, 2-month lag for MNDWI, 2-month lag for NDVI and 6-month lag for rainfall. However, among these five univariable models, model 5 (rainfall at lag of 6 months) showed the lowest BIC value (549.24). Seven multivariable models were identified in Mengla County. The final model included a 6-month lag for rainfall and a 0-month lag for LST which yielded a substantial reduction in BIC values (BIC = 538.92).

In Yilong County, the univariable analysis showed that rainfall at a lag of 1 month was the best predictor of leptospirosis (BIC = 288.28) compared with other climate and environmental variables. In the multivariable model, the inclusion of a 1-month lag for rainfall, a 5-month lag for NDWI and a 3-month lag for LST greatly reduced the BIC values by 20.67 points (BIC = 267.61). We did not identify a statistically significant interaction effect in both counties. Moreover, there was no indication of multi-collinearity in both final models (Appendix F: Table F-4; Table F-5).

Table 8-3 summarised the parameter estimates of the final model for both counties. In Mengla County, the final model suggests that for one unit (mm) increase in the rainfall at a lag of six months, the expected incidence rate ratio (IRR) for leptospirosis in a given month would be 1% less, while holding the LST constant. Similarly, an increase in LST (1°C) would reduce the rate in the current month by 14%.

Whereas, in Yilong County, the model estimates indicated that one unit increase in rainfall during the previous month would increase the IRR by 1% in the current month. A 0.1 increase in MNDWI at five months earlier would be likely to increase the incidence by 7.7 times. A one degree increases in LST at lag of 3 months, would increase the expected IRR for leptospirosis in the current month by 19%, when rainfall and MNDWI is assumed to be constant in the model.

Table 8-2 Summary of model selection in predicting leptospirosis incidence in both Mengla County and Yilong County

Study site	Model	Predictor(s) $_{lag}$	BIC	Deviance
Mengla County	1	SAF	561.73	1.220
	2	SAF+RH_6	562.65	1.198
	3	SAF+$MNDWI_2$	562.18	1.194
	4	SAF+$NDVI_2$	560.98	1.185
	5	SAF+$Rainfall_6$	549.24	1.089
	6	SAF+$Rainfall_6$+RH_3	547.95	1.048
	7	SAF+$Rainfall_6$+$NDVI_5$	545.62	1.029
	8	SAF+$Rainfall_6$+RH_6+$NDVI_5$	545.68	0.998
	9	SAF+$Rainfall_6$+$MNDWI_5$+RH_6	544.40	0.987
	10	SAF+$Rainfall_6$+$MNDWI_5$ + $NDVI_6$	542.75	0.974
	11	SAF+$Rainfall_6$+LST_0	538.92	0.974
Yilong County	1	SAF	330.41	1.187
	2	SAF+$MNDWI_3$	328.66	1.153
	3	SAF+RH_0	323.48	1.111
	4	SAF+$MNDWI_5$	318.50	1.071
	5	SAF+$NDVI_2$	316.51	1.054
	6	SAF+$Rainfall_1$	288.28	0.825
	7	SAF+$Rainfall_1$+$NDVI_2$	288.61	0.797
	8	SAF+$Rainfall_1$+RH_0	289.18	0.793
	9	SAF+$Rainfall_1$+$MNDWI_3$	287.68	0.787
	10	SAF+$Rainfall_1$+$MNDWI_3$+$NDVI_2$	287.41	0.751
	11	SAF+$Rainfall_1$+RH_0+LST_2	275.73	0.649
	12	SAF+$Rainfall_1$+$MNDWI_5$+LST_3	267.61	0.585

Abbreviations: SAF, RH, NDVI, MNDWI and LST indicate seasonal factor, relative humidity, normalized difference vegetation index, modified normalized difference water index and land surface temperature, respectively.

Table 8-3 Parameter estimates of the fitted generalized linear models of the association of climatic and remotely-sensed variables with leptospirosis incidence in Mengla County and Yilong County, China

Study site	Predictor	Lag (months)	IRR	95% CI	
				Lower	Upper
Mengla County	SAF	0	3.388	2.400	4.783
	Rainfall (mm)	6	0.989	0.985	0.993
	LST (°C)	0	0.857	0.792	0.929
Yilong County	SAF	0	1.485	1.371	1.609
	Rainfall (mm)	1	1.013	1.003	1.023
	MNDWI (per 0.1)	5	7.690	1.241	47.66
	LST (°C)	3	1.193	1.095	1.301

Abbreviations: SAF, seasonal factor; MNDWI, modified normalized difference water index (per 0.1 MNDWI); LST, land surface temperature; 95%CI, 95% confidence interval.

8.5 Discussion

In the present ecological study, we looked at the temporal variation of human leptospirosis and its association with meteorological and satellite-derived physical environmental parameters in two of the remaining hotspots of leptospirosis in China. Both areas are located in different climatic zones in southwest China and our analysis revealed strong seasonality and unique annual cycles for leptospirosis incidence in each county. In addition, our study extends current knowledge in that it demonstrates that the effect of rainfall appears to play a pivotal role on leptospirosis transmission in both locations; however, we observed that its effect differs between locations. In addition to rainfall, our models demonstrated the importance of RS-based parameters including flooding, vegetation and land surface temperature (LST) on the seasonality of leptospirosis in the two hotspots. The findings of this study improve our knowledge about the role of climate and environmental factors in the temporal variability of human leptospirosis at local level. This work lays the foundation for establishing an integrated spatial-temporal prediction model for leptospirosis in China.

In this present study, we identified a bimodal annual cycle of leptospirosis incidence in Mengla County, peaking in May and September. Such a pattern suggests that the drivers of leptospirosis transmission in this area might be multifactorial. This finding may be partially explained by the unique climatic and socioecological profile (e.g. agricultural behaviours of the communities) of this area. To illustrate, Mengla County lies in the tropical zone with a wet season that occurs during May to October and the majority of rural communities in this area are involved in agricultural activities all-year round including rubber tree tapping (from March to November), tea collection (February to October), vegetable and rice harvesting (May to June). In addition, households also raise a wide range of livestock, such as cattle, buffaloes, pigs, and goats for a variety of purposes (e.g. transport, plowing, consumption, economy, and traditional events) (Shen et al., 2017). Moreover, since there was a rapid expansion of monoculture rubber plantations leading to massive land transformation, the ecological conditions of the area were also affected (e.g. excessive surface runoff during wet season and water scarcity during the dry season as well as habitat fragmentation) (Xu et al., 2014). Such anthropogenic-driven land cover changes may bring impacts such as increasing the likelihood of flash flooding during wet season, water contamination, and the transmission of *Leptospira* among animals (rodents, wildlife and livestock) due to loss of their natural habitats which might directly or indirectly contribute to the cycle of leptospirosis transmission. These factors could amplify

leptospirosis risk and transmission in Mengla County and therefore further empirical studies are needed to investigate in more idetail the role of these socioecological processes.

In contrast, Yilong County exhibits a strong single peak seasonal pattern with the highest incidence typically in September. This finding may partly reflect the modifiable effect of climate on leptospirosis occurrence in the area. This finding is also consistent with other local studies conducted elsewhere in Sichuan (Wang et al., 2014). Similar seasonality behaviour has also been observed by researchers in several countries such as in Thailand (Chadsuthi et al., 2012), Brazil (Coelho and Massad, 2012), Korea (Joshi et al., 2017), Reunion Island (Desvars et al., 2011) and Trinidad and Tobago (Mohan et al., 2009), where the majority of leptospirosis cases were found following the season when the rainfall and flooding events were high. The hilly and fertile subtropical region of Yilong County is situated in the mainstream of the Jialing River (part of Sichuan Basin), with a wet season ranging from April to September and peaking in July and August which often leads to flooding events (Song, 2013; Zhang et al., 2016). At the same time, Yilong's people are involved in rain-fed paddy cultivation and pig rearing, which is likely to give them a higher probability of exposure to *Leptospira*. Local reports have shown that flooded paddy fields, proximity to flooded areas, and pigsties are important risk factors associated with leptospirosis transmission in this rural area (Tang and Zhou, 2018). Further local epidemiological studies, however, are still required to better understand the causal link between climate and socioecological factors on leptospirosis transmission within these two hot-spot counties.

Indeed, our study confirmed the association between temporal patterns of leptospirosis incidence in both counties and climate. Our negative binomial models indicated variation in response and a lagged effect of rainfall on leptospirosis incidence in both locations. Surprisingly, our best-fitting model for Mengla County indicated a negative relationship between rainfall and leptospirosis as well as a long lag effect (6-months lag) of rainfall on leptospirosis emergence. Previous studies have documented that *Leptospira* could survive in the water for months, even years (Levett, 2001). The findings of a negative relationship between rainfall and leptospirosis suggests that there are other factors (most likely socioecological in nature) that are likely to drive leptospirosis emergence in this county. However, for Yilong County our study indicated positive relationships between rainfall and leptospirosis in which an increase in rainfall intensity is followed by an increase in leptospirosis incidence in the subsequent month. The finding of a temporal delay in the

association between leptospirosis incidence in Yilong County and rainfall is in line with other studies (Herrmann-Storck et al., 2005; Mohan et al., 2009). In addition, the 1-month lag identified in the present study is consistent with the length of incubation period for leptospirosis (from exposure to the onset of clinical signs), which ranges from 1 week to a month (Haake and Levett, 2015; Levett, 2001).

In addition to climatic factors, our study demonstrated that RS-based indicators, such as MNDWI, NDVI and LST, were also associated with leptospirosis incidence, highlighting the important role of flooding, vegetation greenness, and temperature on disease transmission and that these factors could be used to forecast the risk of leptospirosis in these high-risk areas. Our study showed significant temporal associations between these three indicators and leptospirosis in both counties; although, the magnitude and direction of the estimated effects differed among the two counties. Within the context of leptospirosis epidemiology, the satellite-derived environmental data used in this study have helped explain the possible socioecological mechanisms of leptospirosis transmission in our study sites. MNDWI describes the existence of excess inundation/flooding (Ledien et al., 2017) while NDVI reflects vegetation productivity in both areas. Our analysis revealed different lagged effects of MNDWI on leptospirosis in both counties. The findings indicated that current increases in leptospirosis notifications were associated with a one unit increase in MNDWI 2 to 5 months earlier. In Yilong County, for instance, our final multivariable model showed that a 0.1 increase in MNDWI lead to an increase in incidence by 7 times in the next five months while the rainfall intensity remained constant. Our study is consistent with local reports showing that flooding is an important factor in Yilong County (Tang and Zhou, 2018). The use of MNDWI in our present study also supports findings from elsewhere (Ledien et al., 2017) which demonstrated that the MNDWI is a good flooding indicator for predicting leptospirosis outbreaks in Cambodia. Since most counties in the Sichuan Basin including Yilong County are prone to frequent flooding events (Han et al., 2016), the utilisation of a RS-based flooding indicator in an early warning system would be helpful for anticipating the risk of leptospirosis outbreaks.

In the present study, our findings in Yilong County indicated a strong positive correlation between leptospirosis notification and NDVI (a vegetation indicator) at 2 months before. In contrast, in Mengla County a 0.1 decrease in NDVI in the present month was found to be associated with an increasing number of leptospirosis notifications in the following 2 to 6 months: a contradictory response which can possibly be explained by variation in land-cover (vegetation type) and seasonal agricultural practices undertaken by villagers

between counties. For instance, Mengla County's landscape is comprised of diverse patches containing large deciduous rubber plantations that experience seasonal defoliation, primary tropical forest fragments, and rice fields. Villagers are also engaged in a slash-and-burn (swidden agriculture) practice (Shen et al., 2017) that may affect vegetation cover and small-mammal habitats and, thus, enforce runoff and migration of rodents towards rice fields and human settlements. In the case of Yilong County, we hypothesised that high rainfall increases biomass (increases in the greenness index) and thus increases rodent abundance (as first-level consumer) in the ecosystem, which leads to an increased risk of leptospiral environmental contamination (Theuerkauf et al., 2013). The NDVI provides an estimate of the greenness of a landscape as well as an indicator of vegetation productivity (biomass) (Lumbierres et al., 2017) also reflects the availability of food in the ecosystem. The vast amount of biomass could be associated with an increase in livestock grazing, agricultural activities (e.g., cropping cycle) (Zhang et al., 2015) as well as rodents' abundance (Yu et al., 2017). However, the link between NDVI, rodent abundance and leptospirosis in these counties is still unclear. Further epidemiological observations are, hence, required to investigate the leptospirosis transmission mechanism in these two areas.

A different effect was also observed in the relationship between LST and leptospirosis among counties. In Yilong County, leptospirosis notifications had a positive association with temperature, where increasing temperature would be likely to increase leptospirosis notification in the next 3 months by 20%. Previous evidence indicates that hot and wet conditions heightens the survival rate of *Leptospira* in the environment (Weinberger et al., 2014). Leptospira can survive in temperatures ranging from 4°C to 40°C (Parker and Walker, 2011). This positive relationship is also consistent with previous studies in Thailand (Chadsuthi et al., 2012) and Reunion Island (Desvars et al., 2011), with a lag of 8 months and 2 months, respectively. In Mengla County, higher ambient temperature at the current month was associated with a reduction in leptospirosis notifications. Our findings are consistent with a recent study in Brazil (Baquero and Machado, 2018). These results can be partly explained by the fact that higher temperature may severely reduce the soil moisture, thus limiting the survival rate of *Leptospira* in the environment (Levett, 2001).

Our results should be interpreted in light of some limitations. Since our leptospirosis data were mainly based on a passive notification system, reporting biases (e.g., under-reported cases) could not be discarded. However, as we used a long time-series of laboratory confirmed leptospirosis cases (i.e. from 2006 to 2016), we believe that such an issue

would not substantially influence our results. Second, the accuracy of values of environmental variables (e.g. NDVI, MNDWI, and LST) extracted from the satellite images might be influenced by atmospheric conditions such as cloud cover. In this study, however, we attempted to minimise such effects by selecting best cloud-free images over the period of study. Third, given the ecological nature of our study, our findings might be influenced by other potential confounders which may vary between locations. For example, the variation may also be driven by the presence or density of animal reservoirs (e.g. livestock, rodents), previous or existing control and prevention measures (e.g. vaccination, deratisation) and local socioeconomic features, including ethnicity and accompanying agricultural behaviours and poverty, as well as access to safe water and sanitation. Unfortunately, in our study we did not take into account such factors since such data were not available in our notification dataset. Hence, local primary epidemiological studies should be carried out to investigate the role of animal and socioeconomic factors on leptospirosis transmission in these high-risk counties, so that it can provide a sound evidence base for the design of intervention studies targeting modifiable factors through health promotion. Fourth, in the study, I used 'month' as the temporal unit of analysis instead of 'week'. This decision is grounded on a couple of reasons: i) In this study, I used "monthly" case counts per area based on the results of a preliminary temporal data analysis which demonstrated that there was an excess zero cases (this has been indicated by small mean monthly numbers and high SD (*see* Table 8-1). Consequently, the weekly data sparseness would be problematic to fit temporal models; and ii) remote-sensed data (e.g., NDVI, MNDWI and LST) are not commonly available in "weekly" window.

Despite these limitations, this study has provided important evidence on the epidemiology of leptospirosis at local level in areas known as the residual hotspots for leptospirosis in China.

8.6 Conclusion

In summary, our study adds to evidence on the short-term effects of climate and environmental variability in leptospirosis incidence in two primary hotspots in China, Mengla and Yilong County. This study demonstrated the value of satellite-derived environmental data in combination with weather records in improving our understanding about leptospirosis risk factors. An important finding is that the effects of climate and environment on leptospirosis varied between locations, which call for local specific control

and intervention strategies to reduce the burden of leptospiral infection. Our models provided an objective foundation for the development of local leptospirosis early-warning systems in China.

Chapter 9 Discussion and conclusions

9.1 Introduction

Annually, more than one million human leptospirosis cases and 58,900 deaths are reported worldwide, and the most recent burden of disease estimates indicate that more than 2.9 million DALYs are lost due to *Leptospira* infections (Costa et al., 2015; Torgerson et al., 2015), with the highest estimated burden in tropical and subtropical countries. Despite its population health importance, leptospirosis remains a neglected zoonotic disease, especially in low- to middle-income countries (LMICs) where surveillance and diagnostic capacity is lacking (Bharti et al., 2003). As a result, many affected countries have no adequate data on where incidence and burden are predicted to be highest and what are factors determining the geographical and temporal variation on the burden either at national or sub-national level.

The *Leptospira* infection in humans involves complex transmission pathways. Factors driving the transmission are likely to vary between locations, depending on demographical and socioeconomic factors, local reservoir host diversity, climatic and physical environment conditions. Traditionally, leptospirosis is a common bacterial infection found in rural settings and more likely associated with agricultural processes such as harvesting and livestock farming (Levett, 2001). Today, leptospiral infection is also of public health importance in overcrowded tropical and subtropical cities due to rapid urbanisation and extreme weather events and is becoming more intense. Leptospirosis outbreaks have been reported in major cities worldwide, affecting flood-prone areas and urban slum communities where water and sanitation infrastructure, drainage systems, waste management, and risk awareness are lacking (Ko et al., 1999; Barcellos et al., 2001; Togami et al., 2012; James et al., 2018; Marinova-Petkova et al., 2019).

In China, leptospirosis is of public health importance as disease outbreaks have been reported in more than 80% of Chinese provinces (34 provinces) with a total of more than 2.5 million cases and 20,000 deaths reported since 1955 (Zhang et al., 2012; Shi et al., 2000). Since 1977, the incidence of leptospirosis has been on the decline, reaching a relatively low incidence of less than 1 per 100,000 (Zhang et al., 2012; Hu et al., 2014). Despite this reduction, local outbreaks still occur in parts of the country (Li et al., 2013; Fan et al., 2014; Wang et al., 2014; Wu et al., 2015; Xu et al., 2016a; Tang et al., 2017), indicating that residual transmission foci of leptospirosis still exist. This low-level of

transmission has been viewed by China's health authorities as an opportunity for eliminating leptospirosis in the country. To achieve this operational goal, clear evidence on which demographic groups are at highest risk of leptospirosis, the location of residual high-risk areas for leptospirosis, as well as information on local drivers of infection (e.g., demographical, climatic, environmental and socioeconomic) are required.

Evaluating the spatiotemporal heterogeneity of leptospirosis risk and associated drivers can help improve the implementation of disease control interventions locally. In this case, an investigation into the spatiotemporal dynamics of leptospirosis incidence across China is an important first step to identifying areas at highest risk of transmission (hotspots) and whether or not hotspots exist and whether these are geographically stable over time. Such investigation also allows the exploration of plausible factors (e.g. climate, sociodemographic, environment) that likely explain the spatiotemporal variation in leptospirosis incidence. Furthermore, by collating information on the historical trends in incidence over space and its potential drivers over time, spatial decision support tools can be designed to assist health authorities and associated 'One Health' stakeholders (such as the animal and the environmental sector) in planning and implementing spatially targeted collaborative surveillance and control strategies for effective reduction of the burden of leptospirosis.

The overall aim of the body of research outlined in this thesis was to apply spatial epidemiological techniques to gain operational insights on the epidemiology and disease ecology of leptospirosis in China to assist local health authorities in the design of leptospirosis control programs to pursue the disease elimination goal. The overall aim of the thesis was achieved by conducting a program of research outlined by the following objectives: 1) first, to review spatial epidemiological techniques applied in previous leptospirosis studies in both human and animal populations and to critically evaluate the methods used (Chapter 4); second, to quantify the historical trend of notified leptospirosis incidence and burden in terms of DALYs in China and to map the geographical and temporal variation of DALYs of leptospirosis at sub-national level across the country (Chapter 5); third, to use spatial analytical tools to investigate the spatial and temporal pattern of leptospirosis incidence at county-level and to profile high-risk counties in terms of their socio-demographical and environmental conditions (Chapter 6); fourth, to assess the effects of local weather and physical environmental variability on leptospirosis incidence (Chapter 7); and finally, to quantify the effects of environmental and socioeconomic factors on the spatial heterogeneity leptospirosis incidence in order to

develop smoothed predictive incidence maps to identify residual high-risk counties in high-risk regions in China where disease elimination could be achieved (Chapter 8).

This thesis provides new insights on the use of geographic information systems (GIS)/ remote sensing (RS) technology and geostatistical approaches for understanding the epidemiology of leptospirosis, which contribute to the extension of the body of knowledge in the field. A number of advancements are presented in the research chapters of this thesis including: a) a general framework for the application of spatial analytical tools for future leptospirosis studies; b) identification of small-scale geographical variation in the DALYs of leptospirosis across China in the past two decades; c) the identification of the residual high-risk counties and their socio-demographical and ecological profiles; d) evidence on the role of climatic and remotely-sensed physical environment indicators in leptospirosis incidence, which form the foundation for an early warning system (EWS) for leptospirosis; and e) evidence on the geographical variation in the role of environment and socioeconomic factors on the incidence of leptospirosis in China, which highlights the need for local-specific public-health interventions. This research has important practical implications for future research on the use of spatial analytical tools as decision-support tools for leptospirosis control and the role of climate, environmental and socioeconomic factors on the geographical and temporal heterogeneity of the risk of leptospirosis.

9.2 Key research findings

9.2.1 Critical assessment and the development of general framework for spatial epidemiological tools for leptospirosis control

In the past decades, the use of GIS/RS and geostatistical modelling has become increasingly utilised in epidemiological studies along with the advancement in the geospatial technology and remote sensed data availability. This opportunity has been used in a way to better understand the epidemiology of infectious diseases to provide evidence to support leptospirosis control strategies. Yet, before I began the research described in Chapter 4, there were no studies in the literature which presented a comprehensive review and evaluation of the adequacy of spatial analytical methods used in past leptospirosis studies. This is important as this information could help guide future research as well as help to improve the applicability of the evidence or outputs so that it can be optimally applied for supporting leptospirosis control. In Chapter 4, I provided the first comprehensive review on how spatial analytical tools had been used in previous studies to

further understand the epidemiology and risk factors associated with leptospirosis, both in humans and animals. Based on pre-defined eligibility criteria detailed in Chapter 4, I reviewed a total of 115 papers retrieved from six databases: 65 studies on humans, 39 studies on animals and 11 studies that used both human and animal data.

In general, my systematic review in Chapter 4 demonstrated that visualisation (mapping) techniques were the most common approaches used by authors of published studies. However, none had mapped the geographical variation in the burden (in terms of DALY) at sub-national level before the publication of Chapter 5. Other spatial techniques, such as exploratory analyses to investigate spatial patterns and detect leptospirosis clusters and modelling studies of factors associated with geographical variation, were under-utilised. Furthermore, I identified only a few studies where the authors had quantified the role of environmental and socioeconomic factors on the leptospirosis distribution and even fewer had developed predictive maps for leptospirosis incidence or prevalence (Lau et al., 2012a; Zhao et al., 2016; Rood et al., 2017; Mayfield et al., 2018b; Ahangarcani et al., 2019). In addition, the results of the systematic review in Chapter 4 show that there have been few studies attempting to develop outbreak detection models. From a programmatic perspective, lack of adequate knowledge on where hotspots or areas at higher risk are located, when is the incidence at its highest, what are the drivers, and how much of the population is at highest risk within an area, could hinder operational activities of leptospirosis control. Such evidence is central for scaling-up intervention programs and the evaluation of interventional coverage in the identified hotspots.

In addition, the results of the systematic review in Chapter 4 show that most studies that used spatial analytical tools for leptospirosis are reported from countries in the America continent such as Brazil and the United States. My systematic review indicates that despite its public health significance, the spatial analytical approach to support decision making in planning and implementation of leptospirosis control and surveillance was under-utilised, especially in developing countries such as China. There was only one study (Zhao et al., 2016) where the authors used spatial analytical tools to predict the occurrence of leptospirosis cases based on an ecological niche model (ENM). Before the publication of Chapter 6 and Chapter 8, none had explored the geographical leptospirosis hotspots and its drivers. Most importantly, none had developed spatial structured predictive risk maps for leptospirosis in China.

Ultimately, of the 115 studies evaluated, I found significant variation in terms of methodology, indicating there is substantial room for improvement. Based on my systematic review detailed in Chapter 4, I identified some limitations in past studies which can be summarised into five main issues. These include: i) variation in reporting case ascertainment (e.g. case definitions and diagnostic tests are not clearly stated in the report); ii) inconsistency in the application of the analysis and type of data used (e.g. using Moran's *I* analysis in point data); iii) unsystematic or inadequate exploration of disease clustering (e.g. many studies had poorly addressed spatial dependency in the data); iv) complexity of explanatory variables included in the model (e.g. the role of socioeconomic and animals factors on the variation of leptospirosis distribution had been less explored) and; v) paucity of robust spatially-explicit prediction maps and temporal prediction models (e.g. most studies used non-spatial modelling and did not fully address spatial autocorrelation and uncertainties). Hence, according to these identified limitations, in Chapter 4, I developed a general framework for the application of spatial analytical approaches to provide clear guidance for future work in mapping epidemiological data and exploring and assessing drivers of leptospirosis. The framework provided in Chapter 4 discussed several factors that need to be considered in future spatial epidemiological research for leptospirosis. The key principles highlighted in my framework include the following needs: i) to clearly explain the source of the epidemiological data, case definition and diagnostic methods used to ascertain leptospirosis cases to allow comparison with other available studies; ii) to carefully define the type of spatial data (e.g., point or areal data), aggregation technique, spatial and/or temporal unit of analysis; iii) to integrated data on a range of attributes (e.g., hosts, environment, climate and sociodemographic) to better understand the role of such factors in the heterogeneity of leptospirosis in human communities; iv) to carefully select the methodology of analysis; and v) to adequately and systematically address spatial autocorrelation and uncertainties so that the mapping output can enable the decision making processes. The proposed framework is expected to help improve the validity and comparability of leptospirosis spatial epidemiological through the development of a reliable and robust pipeline of analyses that will support leptospirosis control programs at different spatial scales.

9.2.2 Geographical pattern of the burden of leptospirosis and its epidemiological transition

In light of the findings of the systematic review detailed in Chapter 4, and while numerous maps had been produced, in no studies was there an attempt to map the burden of leptospirosis (in terms of DALY) at sub-national level. The only relevant study before the publication of Chapter 5 was a study in which the country-level DALY estimates and distribution were mapped (Torgerson et al., 2015), based on global historical notification data, reports, and simulations. A major limitation of this study is that such coarse mapping of DALYs has limited functionality, given that leptospirosis is likely to vary at very fine spatial scales. This is because leptospirosis transmission operates locally at much finer spatial resolutions and transmission is highly dependent on the diversity of reservoirs and serovars, which are strongly linked with local socioecological conditions (Vinetz, 2001; Gracie et al., 2014).

Indeed, previous studies had indicated that in China there were approximately 301,688 DALYs lost annually due to leptospirosis (Torgerson et al., 2015). Other studies had shown that during 1960 to 2010, leptospirosis incidence has been reported to reduce from 10.73 cases per 100,000 people in the 1960s to 0.11 cases per 100,000 people in 2010 (Shi et al., 2000; Zhang et al., 2012; Hu et al., 2014). In the light of this dramatic reduction in incidence, and the variation in environmental and socio-demographic conditions plus changes in socioeconomic and environmental conditions, which have been occurring for the last two decades, there was a need to re-estimate the burden of leptospirosis and to identify areas where the burden of leptospirosis remained high. Thus, my study was directly aimed at filling this gap in knowledge.

Using the most recent nationwide comprehensive individual-level notification data reported from the past 11 years, the research detailed in Chapter 5 provides the first account for China of the epidemiological transition in leptospirosis burden estimates and sub-national level leptospirosis burden estimates. Using a 10-year time-series dataset of leptospirosis, I have been able to demonstrate that at least 10,000 DALYs had been lost due to leptospirosis during 2005–2015. The findings of research detailed in Chapter 5 demonstrate significant geographical heterogeneity in burden (as measured by DALY) at sub-national level in China that had not been reported by authors of any previous studies. The findings suggest that leptospirosis infection was driven by geographic-specific socioecological determinants. The analysis identified areas with the highest DALY estimates, namely, the southwest and south provinces. The estimated 10-year trend in the

burden, however, gradually decreased over the period with the lowest burden estimate observed during 2011–2015, reflecting changes in demographic and socioecological conditions in China as well as the effect of control measures that have been undertaken in China (e.g. agricultural intensification and mechanisation, vaccination, rodent control, improvement in water and sanitation) (Dai, 2010; Hu et al., 2014; Yang et al., 2011; Hu et al., 2014; Wang et al., 2014; Zhou et al., 2015; Xu and Ye, 2018).

The research detailed in Chapter 5 demonstrated that leptospirosis disproportionately affected farmers and children. We posited that the high burden estimates in children in China could be indirectly driven by the sociodemographic changes following massive urbanisation. Arguably, urbanisation in China has driven labourers from rural areas towards major cities to seek better economic conditions, leaving behind their children with their grandparents (Chang et al., 2011; Mu and van de Walle, 2011). According to the National Bureau Statistics of China (NBSC) report, during the 20 years from 1990 to 2010, the migrant population, which was predominantly peasant workers, grew rapidly with an average annual growth rate of approximately 12%. By 2010, China had a migrant population of 223.43 million people (He et al., 2019). One of the impacts of parents' migration to cities is the shifting role in agricultural practices in rural areas where the elderly and children are left behind and were noted to be more likely to engage in farm work (Jingzhong, 2011; Jingzhong and Lu, 2011) which, in the context of leptospirosis transmission, could contribute to an increased risk of leptospiral exposure. Additionally, these left-behind children have less parental supervision resulting in higher prevalence of health-risk behaviour and inadequate hygiene and nutrition—factors which are known to increase risk of acquiring infections (Li et al., 2015).

9.2.3 Environmental and socioeconomic profiles of high-risk counties for leptospirosis

To guide effective targeted disease control and public health interventions, local health authorities and policy makers require detailed information regarding areas where disease is prevalent, how it spreads geographically, and the potential risk factors that drive its patterns (Pfeiffer et al., 2008). Prior research detailed in Chapter 5 identified significant spatial heterogeneity in leptospirosis DALYs that could be strongly correlated with demographical, environmental, and socioeconomic conditions. Yet, when I conducted this research, evidence on the profile of risk factors that characterise high-risk areas for leptospirosis transmission in China was extremely scarce, making it difficult to implement

an efficient resource allocation and control program. As explained in Chapter 6, I addressed this gap in knowledge, by designing and conducting research with the aim of identifying high-risk areas for leptospirosis at county level and profiling key demographical, ecological and socioeconomic characteristics of these identified high-risk counties, using spatial analytical tools.

I found that high-risk counties for leptospirosis incidence during 2005–2016 in China were mostly situated in the southwestern, central and southern part of the country. Persistent high-risk counties (22 counties in total) were identified across the study period and were clustered over space in the tropical and sub-tropical provinces within China's two main river basins (Yangtze River and Pearl River): Sichuan, Yunnan, Chongqing, Hubei, Guizhou, Guangdong and Guangxi. There were two counties that consistently identified as high-risk clusters for leptospirosis: Mengla County (Yunnan province) and Yilong County (Sichuan province). My research showed that persistent hotspots of leptospirosis typically follow ecological and socioeconomic conditions where leptospirosis transmission is common. In this regard, the research in Chapter 6 showed that from an ecological perspective, high-risk areas for leptospirosis were situated in areas with higher monthly mean precipitation (106.82, range: 97.45–116.19 mm/month) and moderate elevation (576.01, range: 451.17–700.25 m.a.s.l). In addition, in terms of its sociodemographic conditions, these high-risk areas were identified as poor rural areas where more farmers engaged in small-scale subsistence farming as evidenced by having low GDP, low production, and high livestock density. Such conditions are common where leptospirosis is endemic (Lacerda et al., 2008; Pappas et al., 2008; Mayfield et al., 2018b). These findings strongly indicate that leptospirosis transmission in these residual high-risk areas may be primarily driven by the interplay between climate, flooding, agricultural behaviour and poverty. In addition, the finding of this research was central in generating other hypotheses: first, there is a temporal association between such climatic and environmental factors and leptospirosis emergence and, if this is so, second, climate and environmental factors can be used as early warning predictors of the risk of leptospirosis. Lastly, the socioecological drivers of leptospirosis incidence are geographic specific within southwestern (Upper Yangtze River Basin) and southern China (Pearl River Basin). Evidence have shown that these factors may be used to predict risk in both regions. These hypotheses led to another hypothesis presented in the last two chapters (Chapter 7 and Chapter 8), which is was formally tested.

9.2.4 The role of climate, environment and socioeconomic in the geographical variation of incidence of leptospirosis

The results reported in Chapter 5 had shown that the burden of leptospirosis remains high in China although the incidence was very low. Persistent small pockets of high-risk incidence counties exist in tropical and sub-tropical provinces in southwestern and southern China where China's two main rivers flow—the Yangtze River and the Pearl River (Chapter 6). Prior research detailed in Chapter 5 suggested that leptospirosis incidence is apparently indicate different pattern of seasonality, suggesting that risk factors are likely to be heterogeneous between regions. From these findings, it is hypothesized that the role of climate and environmental and socioeconomic factors in leptospirosis transmission in southwestern (Upper Yangtze River Basin) and southern (Pearl River Basin) regions of China are region specific. Evidence indicates that hydroclimatic processes and socioecological conditions in Southwest China and South China are unique, thus resulting in different patterns of flooding and drought (Guo et al., 2013; Zhang et al., 2010) which in turn may influence the annual trends of reported leptospirosis notifications. The UYRB lies in a subtropical monsoon zone and the precipitation in this region is primarily influenced by the Indian monsoon cycle, with an annual precipitation of less than 500 mm. The monsoon system brings abundant precipitation, and accounts for approximately 70–80% of the basin's total annual precipitation during the summer (May to October) and may cause long lasting rainfall for several weeks, leading to frequent floods. In contrast, the PRB is situated in the tropical and sub-tropical zones, with precipitation during April to September accounting for 80% of the total yearly precipitation rate (Zhang et al., 2010). The precipitation variability in the region is significantly influenced by the Indian Ocean Dipole (IOD) and El-Niño Southern Oscillation (ENSO), especially for the central and eastern part of the PRB, triggering extreme events such as floods and droughts (Niu, 2013). In addition, the local socioecological conditions in both regions (e.g. topographical, landcover, population density, agricultural practices) are also heterogeneous, which may influence the geographical distribution of the risk of leptospirosis between regions that greatly differ.

The role of climate and environmental and socioeconomic factors in the geographical variation associated with the risk of leptospirosis in both regions is far from clear; though the incidence of leptospirosis in these parts of China is known to be the highest as evidenced in Chapter 5 and Chapter 6. Understanding the definitive socioecological drivers of leptospirosis in both regions could help to estimate risk of leptospirosis. In order

to plan and implement effective specific leptospirosis control and interventions, local health authorities need visual tools such as prediction maps. My research presented in Chapter 7 demonstrates a novel approach to identifying areas most at risk and to estimating populations that are most affected. I used spatial conditional autoregression (CAR) Bayesian models to developed smoothed leptospirosis incidence maps for two major residual high-risk regions in China, the UYRB and PRB, by accounting for socioecological factors (e.g., climate, NDVI, MNDWI, livestock density and poverty) and uncertainties.

My research in Chapter 7 revealed that the effect of environmental and socioeconomic factors incorporated in the models differed between UYRB and PRB, confirming my research hypothesis that leptospirosis transmission is highly local specific between regions. In the UYRB, incidence of leptospirosis was predicted to be high in counties along the border of Chongqing-Hubei-Guizhou and in counties in the central Yangtze Valley. My study estimated that more than 100 million people in 179 counties were affected by leptospirosis. This region is characterised by natural hydro-ecological conditions and socioeconomic factors that are favourable for leptospirosis transmission, such as high humidity and abundant precipitation that often leads to the frequent flooding. In addition, this region is highly populated and is one of the central areas for crop production in China (Yu et al., 2009; Xu et al., 2019). Based on my geospatial model, environmental factors, such as rainfall, MNDWI, and elevation can explain the spatial variation in incidence of leptospirosis in the UYRB. The finding suggests that climate and flooding have the potential in modifying the spatial variation in risk of leptospirosis.

In the PRB, high-incidence areas were found in the central and lower reaches of the Basin. I estimated that approximately 50 million people in 105 counties are at higher risk for contracting leptospirosis infection. This may be partly explained by PRB's climate and socioecological features. This region lies in a subtropical humid monsoonal climate zone and has a high population density since the region has experienced significant urbanisation during the past several decades. Additionally, extreme rainfall events and flash flooding are common in the PRB catchment areas, especially in the lower reaches of PRB (Zhang et al., 2019; Liao et al., 2011). The results for the PRB region were in contrast with those from the UYRB region. According to 95% Credible interval (CrI), environmental variables—including rainfall, NDVI, livestock density and land cover—explained the spatial variation of the incidence of leptospirosis in the PRB. This finding suggests that in PRB, leptospirosis transmission was primarily associated with agricultural practices and occupational/behavioural factors. Increased greenness or biomass (as indicated by NDVI)

means an abundant supply of food in the ecosystem, which could be linked with an increased rodent population and intense livestock grazing (Lumbierres et al., 2017; Zhang et al., 2015; Yu et al., 2017). As a result, *Leptospira* concentration in the environment could be much higher. This may likely put livestock animals and humans at highest risk, especially farmers during the harvesting period. Further, people living in areas with a dense livestock population have the greatest risk of acquiring infection from animals or a contaminated environment. The presence of rodents in combination with poor farm/herd biosecurity measures (e.g. poor fencing/housing and rodent control, unvaccinated livestock, leftover feed, movement of infected cattle), especially among subsistence farming, has been found to increase the risk of zoonotic transmission (Mughini-Gras et al., 2014; Ellis, 2015; Pimenta et al., 2019). Higher incidence was also found in areas with abundant waterbodies such as lakes or in proximity to rivers; this could be partly associated with behavioural risk factors associated with recreational activities—such as swimming, fishing, and bathing—as well as occupational (Mwachui et al., 2015; Hinjoy et al., 2019). Leptospiral infection is likely resulted from exposure to flood water which is contaminated by the urine of infected rodents or livestock animals.

9.2.5 Using weather and remote sensed environmental data to anticipate leptospirosis outbreak

Prior research detailed in Chapter 5 suggested that leptospirosis incidence is appears to be seasonal but its annual pattern tended to be different between localities. In addition, it has also been suggested that weather is one of the important determinants of leptospirosis, which means that areas differ from each other in terms of their risk because of precipitation (i.e. areas with higher monthly precipitation are more likely to have a higher leptospirosis incidence) (Chapter 6). Moreover, research presented in Chapter 7 revealed that the role of socioecological factors on leptospirosis incidence was significantly varied geographically. Together, these findings emphasise that to deliver effective public health interventions in a timely manner, localised risk forecasting tools are required to better improve prevention and preparedness for leptospirosis outbreaks, as leptospirosis transmission is likely to operate at a local level.

Research presented in Chapter 8 was focused on the two counties, Yilong County (Sichuan province) and Mengla County (Yunnan province). I selected these two counties due to several number of reasons. First, both counties were identified as high-risk counties

as evidenced in Chapter 6. Second, both counties have different socio-ecological conditions in terms of climate, landscape, and sociocultural factors (Chen et al., 2016; Xu et al., 2017).

Before the publication of Chapter 8, outbreak prediction models for leptospirosis in China, especially in Yilong County and Mengla County, had not been developed in any studies. Although climate is a known determinant of leptospirosis incidence (Desvars et al., 2011; Chadsuthi et al., 2012; Wang et al., 2014; Sumi et al., 2017; Filho et al., 2018), it was unclear—before conducting the research outlined in Chapter 8—whether climate was a major driver of the leptospirosis epidemic and whether it could be used to predict the risk of leptospirosis outbreaks in these high-risk areas.

The available risk prediction models for leptospirosis are solely based on the relationship between weather attributes and leptospirosis incidence (Chadsuthi et al., 2012; Weinberger et al., 2014; Matsushita et al., 2018), and very few had incorporated attributes of the physical environment. As indicated in the systematic review in Chapter 4, limited studies had modelled the association between such changes in the physical environment (flooding and vegetation) and the emergence of leptospirosis.

Previous research suggests that leptospirosis is a waterborne disease that is strongly linked with flooding after heavy rainfall (Lau, Smythe, 2010, Socolovschi et al., 2011; Amilasan et al., 2012; Smith et al., 2013; Mohd Radi et al., 2018; Matsushita et al., 2018). Rainfall also encourages excessive biomass or vegetation production which can then assist with the proliferation in rodent population numbers—an important reservoir species for leptospirosis (Diaz, 2014). In the absence of locally measured temporal environmental data, high-resolution earth observation (EO) images obtained from satellites can now be used to provide accurate cross-sections of various types of ground objects and landscape features over time to characterise environmental risk and host habitats; many of these images have been commonly used to monitor and predict the spatial and temporal variation of infectious diseases (Tatem 2004, 2012; Palaniyandi, 2012; Ebhuoma and Gebreslasie, 2016). In light of such a strong interplay between climate, environment and leptospirosis emergence, it became important to be able to measure the temporal association between climate, physical environment, and the incidence of leptospirosis. Such evidence can be used to lay a foundation for developing an outbreak prediction system to better prepare and estimate the impact of a leptospirosis outbreak.

To address this gap in knowledge as well as to examine the hypotheses raised from the findings of research, detailed in Chapter 6, I conducted research (Chapter 8) aimed at investigating i) the short-term effects of weather variability and environmental factors (NDVI, MNDWI, LST) and ii) whether weather and environmental data could be used to predict leptospirosis outbreak. In this study, I used NDVI as a surrogate for biomass which could indicate rodent dynamics, livestock grazing patterns and vegetation density; whereas, I used MNDWI as a flood indicator.

The results of Chapter 8 revealed strong seasonality and unique annual cycles of leptospirosis incidence, in that we identified a bimodal annual cycle of leptospirosis incidence in Mengla County, reaching a peak in May and September. In contrast, in Yilong County, the incidence of leptospirosis exhibited a strong seasonal pattern of a single peak, with the highest incidence typically in September. This finding clearly reflects that the determinants for leptospirosis incidence are strongly local-specific. The discrepancy in seasonality between Mengla County and Yilong County, identified by the research in Chapter 8, suggests that drivers of leptospirosis incidence are multifactorial and tend to be related to its socio-ecological context. The findings in Mengla County, for instance, suggest that the key driver of leptospirosis transmission could be behavioural rather than climate driven. This is evidenced by the negative relationship between rainfall and leptospirosis incidence. Such bimodal seasonality may be partially explained by the unique climatic and behavioral profile of Mengla County communities combined with their associated agricultural behaviors. Mengla County lies in the tropical zone with a wet season occurring from May to October. Most rural communities in this area are involved in agricultural activities all-year round, including rubber tree tapping (from March to November), tea collection (February to October), and vegetable and rice harvesting (May to June). In addition, households also raise a wide range of livestock, such as cattle, buffaloes, pigs, and goats, for a variety of purposes (e.g., transport, plowing, consumption, economy and traditional events) (Shen et al., 2017). Such conditions and behaviors induce continuous *Leptospira* exposure and transmission and may explain why leptospirosis outbreaks occur more often. In contrast, leptospirosis outbreaks in Yilong County appear to be strongly driven by climate and flooding. This is confirmed by the strong positive association between rainfall, MNDWI, and leptospirosis incidence. This hilly and fertile subtropical region is situated in the mainstream of the Jialing River (part of Sichuan Basin) which is known as a flood-prone area (Song, 2013; Zhang et al., 2016).

In addition, my research in Chapter 8 confirmed a strong association between climate variability, physical environment, and leptospirosis incidence in both counties. The final temporal models indicated that rainfall, temperature (LST) and MNDWI variability can be used to predict risk of leptospirosis incidence. The findings suggest that an increase in rainfall at lag of one month, MNDWI at lag of 5 months, and temperature at lag of 3 months will likely increase the incidence of leptospirosis in Yilong County. An increase in the MNDWI was likely to increase the incidence rate by 7.7-fold. While in Mengla County, an increase in incidence of leptospirosis is associated with an increased rainfall at lag of 6 months and temperature throughout the current month.

Overall, the research detailed in Chapter 8 demonstrated that incorporating both weather (rainfall and humidity) and remotely-sensed environmental data (LST, NDVI and MNDWI) into the models extends current knowledge by improving our understanding of the effects of climate and environment on leptospirosis incidence and of the possible mechanisms of leptospirosis transmission in these two high-risk counties. Most importantly, the research in Chapter 8 demonstrates the first integrated climate/environmental-based model for predicting incidence of leptospirosis, forming the foundation for an early-warning system for leptospirosis in the two high-risk areas of China.

9.3 Public health implications

The results of the research presented in this thesis have several important public health implications which can be summarised as follows:

9.3.1 Identification of areas most at risk for leptospirosis

Together the analyses outlined in Chapter 5, Chapter 6 and Chapter 7 demonstrate that the incidence and burden of leptospirosis in China is significantly clustered in a limited set of geographical areas, supporting the need for geographic specific intervention programs to the identified areas at highest risk. Additionally, analysis presented in Chapter 8 provides important information for health authorities regarding when interventions programs need to be implemented.

The research in Chapter 5 contributes novel updated evidence on the geographical distribution of DALYs at sub-national level in China. My analysis revealed significant reduction in the morbidity and mortality of leptospirosis during 2005-2015 and indicated provinces in the southwest and south of the country where the highest burden for leptospirosis is located, predominantly the provinces of Sichuan, Yunnan, Guizhou,

Guangxi and Guangdong. From a public health perspective, these findings suggest that it is imperative to plan and sustain healthcare investment efforts to improve diagnosis and health systems in these high-burden areas. In addition, in these high-burden locations, there is a need to reassess and improve the capacity to recognise leptospirosis cases and the availability of diagnostic infrastructure. This is particularly important given the broad spectrum of leptospirosis clinical manifestations which is a contributing factor for misdiagnosis and under-reporting in the absence of formal surveillance—leading to underestimation of disease incidence (Levett, 2001).

The results of the research detailed in Chapter 6 extend knowledge about the geographical distribution of the residual hotspots for leptospirosis at county-level in China as well as its socioecological risk profile. The analyses detailed in Chapter 6 identified persistent high-risk counties in Yunnan and Sichuan provinces. Furthermore, the findings suggest that the high-risk counties were characterised as poor rural areas where small-scale farming is prevalent. From a public health perspective, to ensure the effectiveness of control programs to achieve the elimination goal, strengthened interventions that include the animal sector should be targeting those high-risk rural areas identified in this study. To ensure a package of interventions is delivered to the hard-to-reach rural communities, comprehensive, multi-sectoral and integrated disease-control strategies are critical. It is noteworthy that it is not sufficient to merely focus control efforts on preventing leptospirosis infection in humans, but it is also imperative to manage risk factors in animals and the environment. The control programs for leptospirosis could be improved, for example, by integrating them with the ongoing neglected tropical diseases (NTDs) control programs, such as schistosomiasis or soil-transmitted helminths (STHs). One of the core strategies of NTDs control is the integration of WASH into the mass-drug administration (MDA) strategies (Campbell et al., 2017). Integration may provide a means to optimise program delivery, maximise efficiencies, and improve the impact of interventions.

The Bayesian CAR model and regional smoothed leptospirosis incidence maps for the UYRB and PRB presented in Chapter 7 provide important information on the effect sizes of socioecological determinants, predicted areas most at risk, and the estimated population at risk in both regions. From a public health perspective, as indicated by the maps of smoothed leptospirosis incidence, there remain several areas with a high incidence of leptospirosis within the UYRB and the PRB. This suggests the importance of expanding the geographical coverage of intervention programs. The findings suggest that it may also be necessary to place strong emphasis on improving surveillance and

intersectoral partnerships (i.e., public health and animal health agencies, education, environment and social affairs) to implement interventions (e.g., health education, provision of WASH, waste management, rodent control, flood management, farm biosecurity, and poverty reduction) to reduce the burden of leptospirosis in both regions.

However, as indicated by the research detailed in Chapter 5, leptospirosis outbreaks in China are highly seasonal. Therefore, in order to effectively deliver intervention programs, health authorities should also have adequate information on the best timeframe for conducting interventions. The analyses in Chapter 5 together with the findings presented in Chapter 8 provide important evidence to inform health authorities on how to timely prevent, detect, and mitigate emerging leptospirosis outbreaks. From a public health perspective, the findings presented in Chapter 8 indicate that, in addition to weather data, environmental indicators (NDVI, MNDWI) could be used as a promising signal for initiating early preparedness and interventions which can be integrated into the current web-based Notifiable Infectious Diseases Reporting Information System (NIDRIS) and early warning system in China (the China Infectious Disease Automated-alert and Response Systems, CIDARS). Based on the final model, the population at-risk in flood prone Yilong County, for instance, might benefit from interventions delivered one to five months before the highest risk period. Intensified intervention programs—such as rodent control, waste inspection, modifying or cleaning canals and sewage systems, advocating for protective wear for farmers (e.g. boots), immunisation (when available), and promoting awareness among populations at-risk (e.g. leaflets, educational packages)—might be implemented during the period leading up to the high-risk timing of leptospirosis cases. At the same time, this lag period might also be used by health systems to escalate their preparedness by improving disease awareness among doctors/clinicians, especially in the primary health services, and by ensuring that resources (e.g. antibiotics, diagnostic kits) are sufficient.

9.3.2 Identification of populations most at risk

In general, the analyses outlined in Chapter 5 and Chapter 6 demonstrated that analysis of historical leptospirosis notification data can provide important insights into populations most at risk of leptospirosis infection. In particular, the study in Chapter 5 provides a recent estimate of age and gender specific DALYs for leptospirosis in China, which is important for assisting health agencies in defining target populations for interventions. Together, the analyses presented in Chapter 5 and Chapter 6 emphasise that interventions need to be

targeted primarily at children, males, and farmers, in areas where there is a convergence of a high proportion of the population engaged in subsistence farming and poverty in tropical and sub-tropical regions in southwestern and southern China. These vulnerable populations may benefit from interventions aimed at improving disease awareness and personal hygiene practices. This could be done by providing adequate health education to improve disease awareness and by providing basic services—such as safe water, sanitation and hygiene (WASH) and animal vaccination—in addition to poverty alleviation programs. For example, interventions to reduce morbidity in children could be carried out through aschool-based platform by incorporating health education packages in school curricula. Such an approach has been demonstrated in prevention programs for other diseases and it has proven to significantly improve children's knowledge about a disease and to help in reducing infections, such as worm infections (Bieri et al., 2013; Al-Delaimy et al., 2014). A cluster-randomised intervention trial conducted by Bieri et al. (2013) at Chinese schools in Hunan province, for instance, showed that the health education packages (e.g. workshops, video, pamphlet, classroom discussions) successfully increased students' knowledge about STHs, resulting in an improvement in hand-washing behaviour and a reduction in the incidence of infection by 50%. In the leptospirosis context, there are examples from La Reunion Islands and French Polynesia of leptospirosis awareness materials (e.g., leaflets, posters) being distributed in schools in addition to providing general hygiene education (Goarant, 2016).

To reduce morbidity among farmer communities, interventions—in addition to providing chemoprophylaxis (doxycycline) to prevent infections among farmers which is already being done (Xu and Ye, 2017)—can be focused on reducing the risk of zoonotic transmission through animal vaccinations and improving farmer biosecurity practices (e.g. promoting the use of personal protective equipment). Farmer communities may receive great benefit from One-Health intervention measures—which synergistically target potential sources of transmission in animals and the environment. One measure that could be considered is the scaling-up of livestock vaccination. Livestock vaccination has both economical and public health implication as it is not only beneficial for improving livestock productivity and farmer's economy, but also in preventing potential zoonotic infection in the human population. Vaccination has the potential to reduce urinary shedding and renal carriage in livestock; although the rate of efficacy varies among studies range from 0–100% (Allen et al., 1982; Hodges et al., 1985; Vallée et al., 2016). Moreover, a study in New Zealand has shown that a campaign for vaccination of livestock has helped to reduce

more than 80% of leptospirosis incidence among dairy farmers (Marshall, 1987). An integrated strategy to control leptospirosis in livestock by combining extensive biosecurity measures, vaccination, and chemoprophylaxis has successfully reduced the outbreak at farm level (Mughini-Gras et al., 2014; Pimenta et al., 2019).

Leptospirosis risk could also be reduced by promoting the use of personal protective equipment (PPE), such as boots, gloves, goggles, and clothes, among farmers. While there is discrepancy in the effectiveness of PPE on preventing leptospirosis (Dreyfus et al., 2015; Pittavino et al., 2017), studies have demonstrated the benefits of using PPE to prevent leptospirosis infection (Phraisuwan et al., 2002; Tomcyzk et al., 2014). A meta-analysis conducted by Tomcyzk et al (2014) showed that using footwear is a strong protective measure for leptospirosis infection (OR = 0.59; 95% CI: 0.37–0.94). In this context, the role of public health veterinarians is therefore critical.

9.3.3 Enhancement of surveillance system through the development of local specific spatial-decision support tools and early-warning system

While mapping leptospirosis and the use of spatial analytic tools in this field has been increasingly documented (as evidenced in Chapter 4), its full potential in supporting decision-making processes and in improving health systems to directly support leptospirosis control has not been well recognised. Operationalising intervention programs in the field can be challenging and costly without adequate information on specific locations as to where and when interventions are most needed. Thus, the development of operational tools—such as maps and prediction models to support strategic decision-making and guide the interventions, which is one of the priorities identified by the WHO-LERG (WHO, 2010; 2011)—is essential.

The program of research outlined in this thesis has demonstrated the utilisation of GIS/RS and spatial analytics, which has helped lay the foundation for further development of a spatial decision support system (SDSS) for guiding leptospirosis control and elimination strategies in China. My research findings clearly demonstrate that leptospirosis risk is significantly heterogenous geographically. Therefore, it is important to incorporate a geographical component to the existing health information system in order to achieve effective management of leptospirosis control locally within residual high-risk areas. To support effective implementation of leptospirosis control and the transition from control to elimination, robust health information and surveillance systems are essential as these will

guarantee the effective delivery of scaled-up interventions (Abdussalam et al., 1972; WHO, 2010, 2011). The effective use of a SDSS in a public health context has been demonstrated in elimination programs for vector-borne diseases such as malaria in several countries (Wangdi et al., 2016; Kelly et al., 2011). A SDSS is a user-friendly computerised system incorporating geographical or spatial data, disease notification data, and other data (e.g. resources, demographics). It provides automated analyses to generate enriched and interactive visual graphics or maps and tables to guide decision-making for planning and implementation of interventions.

Based on the results of my program of research presented in this thesis, I propose a framework for a STDSS—a localised support system—which can be applied to support leptospirosis control in China also in other endemic countries (Figure 9-1). The STDSS consists of three main/broad components: inputs, processes, and expected outputs. Based on the findings of the research outlined in Chapter 6, Chapter 7 and Chapter 8, in addition to routine passive human leptospirosis notification data, data inputs could be enriched by adding (i) data about animal leptospirosis cases from local animal health agencies; (ii) various high-resolution spatial data, including environmental (e.g. NDVI, MNDWI, LST, LULC, livestock density), weather (rainfall, humidity, temperature) and socioeconomic data (population, GDP) obtained from a GIS/RS database similar to what I have used; and (iii) survey or census data when available (e.g. individual/household level risk factors). For effective implementation, monitoring, and evaluation of targeted controls and preventions in high-risk countries, geographical reconnaissance (GR) may be needed prior to the development of a STDSS. For instance, all households, farms and clinics in Yilong County or Mengla County could be geo-referenced by using a device such as a GPS to provide high-resolution spatial data. In addition, data for individual/household-level risk factors and socio-environmental data (e.g. occupation, household size, presence of animals, access to safe WASH, etc.) could be also collected during the survey. Based on the GR, the proportion of a population at-risk and resources (e.g. number of clinicians, vaccines, antibiotic required) can be also estimated.

Once all these data are available, a set of algorithms / commands can be used in the spatial-temporal analyses as outlined in this thesis—visualization/mapping (Chapter 5 – Chapter 7), exploration (e.g., cluster detection module) (Chapter 6), spatial modelling (Chapter 7) and outbreak detection models (Chapter 8). These can be embedded into the system to automatically run the analysis and generate outputs—such as tables, graphs, and maps—in an interactive way. The main outputs of the STDSS would range from

simple positive case distribution or incidence/burden maps (Chapter 5), risk (hotspots) maps (Chapter 6) to predictive risk maps and maps of uncertainty (Chapter 7). These maps and/or tables would provide an evidence-base for decision-making processes. All parties (e.g. health workers, veterinarians, etc.) should be involved in the decision-making processes to ensure control and prevention at optimum level. A more localised STDSS that accounting for local heterogeneities in leptospirosis epidemiology and risk factors would help enhance the operationalisation of targeted intervention in every stage, including planning (e.g., allocating diagnostic resources, antibiotics, rodent control), surveillance, and monitoring (e.g., active surveillance, interventions coverage), during the identified epidemic period. The variables incorporated in the STDSS can be adjusted depending on the local epidemiological conditions. For instance, in urban areas, data including flooding risk indicators and socioeconomic factors (e.g., population density) and rodent abundance (if available) in addition to climate variables can be incorporated in the system.

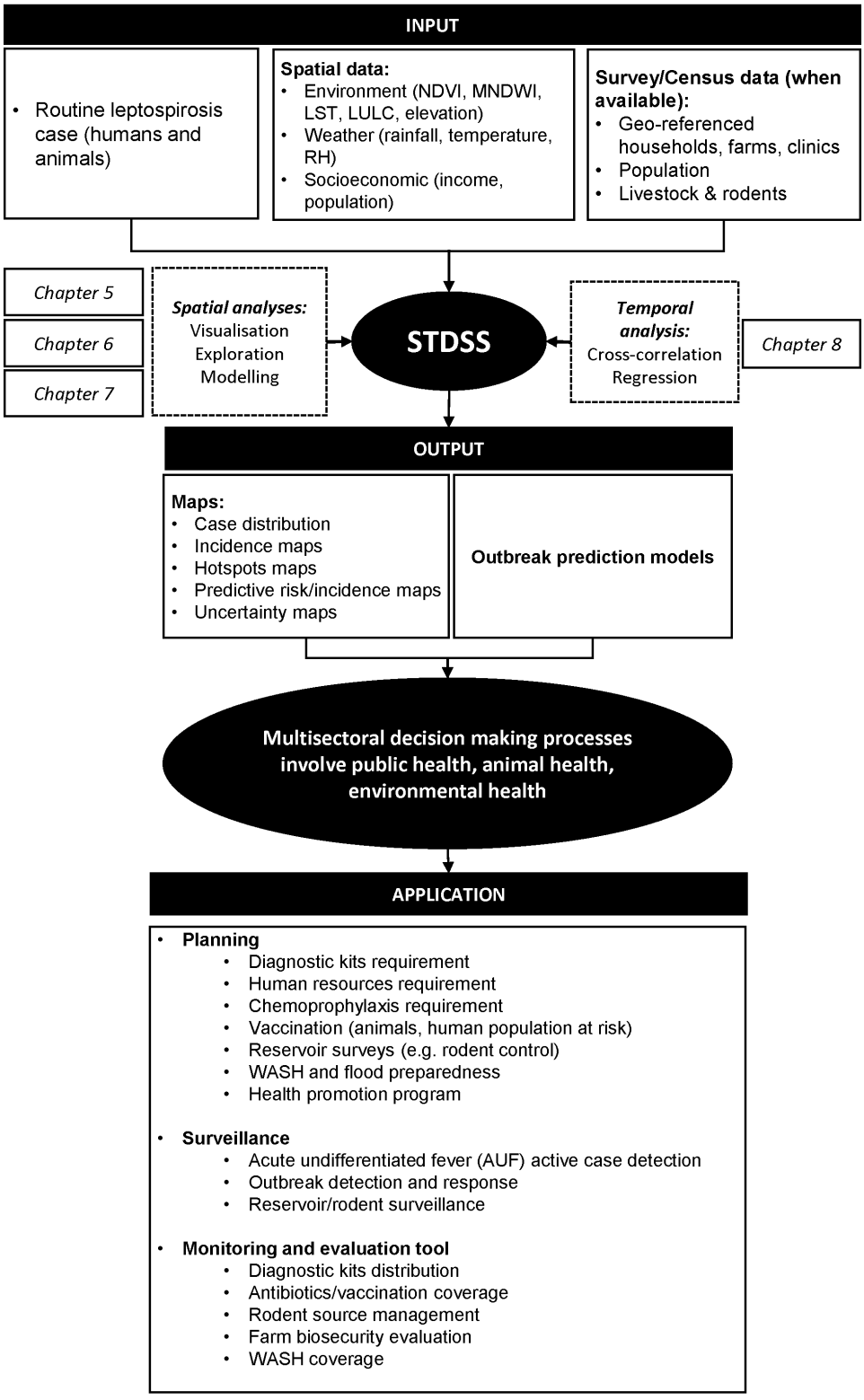

Figure 9-1 Framework of spatial-temporal decision support system (STDSS) for leptospirosis control and prevention

9.4 General limitations

9.4.1 Publication bias

The literature captured by the systematic search in Chapter 4 originated from a limited number of countries with most studies reported from the American continent. This is inconsistent with the distribution of the global burden of leptospirosis as suggested by Torgerson et al (2015). This limited number of studies focusing on spatial-temporal analyses may be explained by the challenges facing most endemic countries, especially those in developing countries. The challenges include the availability of high-quality epidemiological data (e.g. poor reporting systems, variation in case ascertainment and surveillance systems) and inadequate technical capacity (Faine et al., 1999; Musso and La Scola, 2013; Schreier et al., 2013, Costa et al., 2012, Goarant, 2016).

In the systematic review detailed in Chapter 4, I only considered published refereed, original research articles indexed in selected databases. Despite this, the evidence presented in my systematic review is the most comprehensive and recent in the field. The review has added to current knowledge on how spatial epidemiological approaches have been applied in past studies to inform leptospirosis control in humans and animals; and it has provided a general guideline for future medical geography studies into leptospirosis in different settings.

9.4.2 Case ascertainment

The leptospirosis notification dataset that I used was based on passive surveillance which means that the findings presented in this thesis only represent leptospirosis cases that ended-up being reported to health facilities around China. Thus, the incidence and DALY estimates presented in Chapter 5 might not represent the actual level of exposure to *Leptospira* occurring in China. Variation in surveillance capacity and limited diagnostic capacity, especially in remote rural areas, may introduce reporting biases into my results. Moreover, the major problem in leptospirosis confirmation is that it commonly exhibits a wide spectrum of clinical symptoms, making it difficult to be recognise under conventional diagnostic tests, leading to misdiagnosis (Bharti et al., 2003). People who lack awareness about the disease and live in areas where point-of-care is inadequate are less likely to seek medical care, which potentially leads to under-reporting (Wu et al., 2017).

The research detailed in Chapter 5 (*see* Table 5-1) indicates that the proportion of laboratory-confirmed cases was significantly lower (31%) compared with the clinically

diagnosed (69%) leptospirosis cases. Moreover, an additional analysis found that the proportion of laboratory-confirmed cases was also varied among provinces (see Appendix C Table C.1) which may suggest heterogeneity in diagnostic capacity across provinces within China. As discussed in Chapter 5, it is important to note that the surveillance system in China is primarily hospital-based, but the capacity to diagnose leptospirosis through MAT, ELISA, or PCR varies across hospitals. However, there was no change in the diagnostic tests used for leptospirosis over the period studied.

9.4.3 Uncertainty in DALY estimation

Although the research detailed in Chapter 5 was able to quantify DALY estimates of leptospirosis in China, these DALY estimates were based on all notified suspected/probable and confirmed leptospirosis cases. This was done to allow comparison with the official government reports and local studies.

Other important limitations to consider are estimates of disability weights used in DALY calculation. Since there was no detailed data available on patient's clinical presentations in the dataset, I was not able to accurately determine the severity of illness. To address this, I used the general assumptions developed by Torgerson et al. (2015) in estimating the disability weight (DW) which is detailed in Section 5.3.4. Despite these limitations, my study in Chapter 5 has contributed to the recent sub-national heterogeneity in leptospirosis DALY estimates in China.

9.4.4 Ecological approach and regression dilution

Among potential limitations, I acknowledge that the research studies detailed in Chapter 5 through to Chapter 8 are purely ecological. One of the major limitations of such an ecological approach to data analysis is the difficulty in establishing causal inferences (Morgenstern et al., 1995). However, my ecological approach to leptospirosis modelling allowed the exploration of the broad-scale epidemiology and potential risk factors of leptospirosis. This also has helped in generating hypothetical mechanisms of leptospirosis transmission and risk factors at different spatial scales, from national to local level across China. The overall purpose of the program of research detailed in this thesis was to use spatial analytical tools to identify and quantify the effects of ecological and socioeconomic factors on the geographical and temporal distribution of leptospirosis. Despite its limitation, the findings outlined in this thesis have shed light into the epidemiology of leptospirosis

and the value of spatial analytical tools in providing evidence to better inform leptospirosis control.

Another important limitation is regression dilution bias. Although I used high-resolution remote-sensed data, the resolution of the data was not completely perfect. I estimated and used the areal mean value of each remote-sensed covariate as a proxy for the actual exposures. However, this technique could lead to regression dilution bias due to imprecise exposure estimation, which may in turn underestimate the observed effects (Frost and Thompson, 2000; Hutcheon et al., 2010). Additionally, findings presented in the thesis may be also influenced by the accuracy of remote-sensed data. Poor atmospheric conditions such as cloud cover is likely to alter the satellite images, which in turn may under or overestimate the values of environmental data. To address this issue, however, I carefully selected best available cloud-free images over the period of study.

9.4.5 Confounding factors

A significant reduction in the leptospirosis notification data (incidence and mortality) and the geographical distribution of its incidence as shown in this thesis may not only be affected by changes in social and environmental conditions (e.g. urbanisation, agricultural modernisation, land use change) (Deng et al., 2015; Long et al., 2018) but also may be confounded by the changes in the quality of the surveillance system and case ascertainment (Yang et al., 2011), and by the effects of the implementation of disease control, such as health education programs, water sanitation and hygiene (WASH) improvement, and vaccination programs (Hu et al., 2014; Xu and Ye, 2018), which may affect the diversity of reservoirs and circulating serovars in the country. However, such data were not available at county level for the entire sequence of studies within this thesis.

9.5 Future directions

In the light of limitations discussed above, there are number of research opportunities that can be done in the future. These include:

1. The findings provided in Chapter 5 have given important insight into the plausible effects of environmental and social change on the epidemiological transition of leptospirosis morbidity. Using data presented in this thesis, further investigation could be carried out to better understand the associations between socioecological

changes and leptospirosis. For instance, when the data are available, further studies could be directed to investigate the effects of land-use changes and WASH improvement on the spatial distribution of the burden of leptospirosis.

2. Researchers could examine the association between climate change and the spatial-temporal distribution of leptospirosis and develop spatial and temporal predictive maps by taking into account emission scenarios /representative concentration pathways (RCPs) as the incidence of leptospirosis is expected to increase due to climate change and urbanisation (Lau et al. 2010). Additionally, leptospirosis data with finer temporal resolution (daily or weekly), reservoir animal data (e.g., rodent density) or *Leptospira* concentration in the environment should be included into the models.
3. Further research could be focused on the development of a spatial decision support system (SDSS) to aid leptospirosis elimination. SDSS is an integrated computer-based system that utilises available routine health databases (e.g. diseases, resources), GIS and spatial statistics which allow health authorities to organise, visualise and analyse data for decision making (Eisen and Eisen, 2011). Several studies have been employed to develop SDSS to help control zoonotic diseases (Beard et al., 2018) but so far none of these studies have been aimed at designing SDSS for leptospirosis. SDSS for leptospirosis could incorporate data, including epidemiological (e.g. human and animal infection, serovars, vaccination), environmental (e.g. rodent/livestock density, farm location, flood risk index) and socioeconomic (e.g. population, health services) data.
4. Local-scale population-based epidemiological studies in the identified high-risk counties could lead to better understanding of the associated risk factors—individual, environmental, and socioeconomic—and the dynamics of leptospirosis infections in both humans and animals. Additionally, studies aiming at assessing knowledge, attitude and practices (KAPs) among the high-risk populations identified in this thesis (e.g., small-scale subsistence farmers) are also warranted.
5. Lastly, implementation or interventional research is needed with focus on: (i) assessing the effectiveness of integrated disease-control strategies on reducing the morbidity of leptospirosis, (ii) the impact of school-based interventions on the morbidity of leptospirosis in children and (iii) the effectiveness of One-Health collaborative actions on leptospirosis control.

9.6 Conclusions

This thesis contributes the first comprehensive review on the use of spatial analytical methods for both human and leptospirosis studies. The review I presented highlights the urgency of taking into account case ascertainment, spatial dependency, and uncertainties and of carefully defining the type of data, covariates, geographical unit of analysis, and type of analysis, so that it can be reliably and effectively operationalised to support leptospirosis control in the communities. To guide future studies and to enhance the usefulness and validity of the cartographic outputs, this thesis provides the first general framework for the application of spatial analytical tools for combating leptospirosis, with the potential application for combating other diseases of interest. This thesis extends current knowledge on the use of spatial epidemiological analysis in the field of leptospirosis.

This thesis adds new knowledge in that it provides the first evidence of the burden of leptospirosis in terms of DALYs at the sub-national level within China. The research in Chapter 5 demonstrates that males and children under 19-years old are the most affected by leptospirosis. From a public health perspective, the findings suggest the need for strengthening public health interventions towards improving awareness among these populations about the risks of leptospirosis. Furthermore, the study also revealed that the geographical distribution of DALYs is strongly heterogeneous within China, signaling the variation in demographical, environmental, and socioeconomic determinants. Research in Chapter 6 implies that whilst there has been a substantial reduction in the morbidity and burden of leptospirosis in China over the past years, the residual high-risk counties remain, suggesting that transmission is continuously occurring locally. These high-risk counties are characterised by a larger share of farmers, rural landscapes, lower cattle density but high pig density, and lower GDP, and are situated in moderate elevation and receive higher monthly rainfall. In terms of implications for public health, improved interventions should be directed towards these identified high-risk counties, especially in the tropical and subtropical regions in the south of China.

In this thesis, I emphasize taking into consideration the local sociodemographic and environmental conditions when designing and implementing interventions. Research in Chapter 7 and 8 has shown that the role of climate, environmental, and socioeconomic factors are geographically heterogeneous within the country. The study in Chapter 7 reveals significant variation in the effects of environmental factors on the spatial heterogeneity of leptospirosis incidence in the UYRB and the PRB. The study in Chapter 8 confirmed that weather and environmental indicators, such as biomass and floods,

significantly explained the temporal variability of incidence of leptospirosis at local level; thus, such parameters can be used as predictors for the emergence of leptospirosis outbreaks. Together, these findings call for the need of local-specific control and intervention programs.

Finally, this thesis generates evidence on how spatial analytical approaches can be used for a better understanding of the epidemiology and potential factors driving leptospirosis distribution, and for identifying areas most at-risk and estimating populations-at-risk. This thesis lays the foundation for further development of an integrated spatial-temporal decision support system (STDSS) for leptospirosis control to support health authorities in planning and implementing effective and timely spatially targeted public health interventions in identified residual high-risk regions.

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Appendices

Appendix A. Ethics approval

THE UNIVERSITY OF QUEENSLAND

Institutional Human Research Ethics Approval

Project Title:	Spatial Epidemiological Tools for Quantifying the Burden of Disease of Leptospirosis Infections in China
Chief Investigator:	Mr Pandji Wibawa Dhewantara
Supervisor:	Dr Ricardo J.Soares Magalhaes, A/Prof Abdullah Mamun, A/Prof Wenbiao Hu, Wen Yi Zhang, Danhuai Guo
Co-Investigator(s):	Dr Ricardo J.Soares Magalhaes, A/Prof Abdullah Mamun, A/Prof Wenbiao Hu, Wen Yi Zhang, Danhuai Guo
School(s):	Veterinary Science
Approval Number:	2016001608
Granting Agency/Degree:	PhD
Duration:	30th November 2019

Comments/Conditions:

Expedited Review - Low Risk

Please note: Approval is subject to gatekeeper approval being obtained and supplied to this office prior to commencing research

Note: if this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee:
Medical Research Ethics Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Dr Jennifer Paratz
Chairperson
Medical Research Ethics Committee

Signature  Date 26/10/16

Appendix B. Chapter 4 Supplementary information

Table B-1. Keyword combinations used in the selection process for the systematic review

Database	Search string
Scopus (1960–2018)	(TITLE-ABS-KEY ("remote sens*") AND TITLE-ABS-KEY (leptospir*)) OR (TITLE-ABS-KEY (predict*) AND TITLE-ABS-KEY (outbreak) AND TITLE-ABS-KEY (leptospir*)) OR (TITLE-ABS-KEY (mapping) AND TITLE-ABS-KEY (leptospir*)) OR (TITLE-ABS-KEY ("geographic information system") AND TITLE-ABS-KEY (leptospir*)) OR (TITLE-ABS-KEY (spati*) AND TITLE-ABS-KEY (leptospir*)) OR (TITLE-ABS-KEY ("remote sens*") OR (TITLE-ABS-KEY (cluster*)) AND TITLE-ABS-KEY (leptospir*)) OR (TITLE-ABS-KEY ("GIS") AND TITLE-ABS-KEY (leptospir*))
EMBASE (1930–2018)	(mapping OR 'geographic information system'/exp OR spati* OR 'remote sens*' OR cluster* OR 'gis' OR 'outbreak prediction') AND leptospir*:ab
Pubmed (1930–2018)	((((((((((leptospirosis[MeSH Terms]) OR leptospira[MeSH Terms])) AND (spati*[Title/Abstract] OR "geographic information system"[Title/Abstract] OR "spatial analysis"[Title/Abstract] OR "remote sens*"*[Title/Abstract] OR map*[Title/Abstract] OR cluster*[Text Word] OR map*[Text Word] OR "geographic information system[MeSH Terms] OR 'outbreak prediction'[Title/Abstract] OR 'spatial analysis'[MeSH Terms]))))) Sort by: Relevance
Web of science Core Collection (1900–2018)	TS=("outbreak prediction" AND leptospir*) OR TS=(map* AND leptospir*) OR TS=("geographic information system" AND leptospir*) OR TS=(spati* AND leptospir*) OR TS=("remote sens*" AND leptospir*) OR TS=(cluster* AND leptospir*) OR TS=("GIS" AND leptospir*)
ScieLO (1930–2018)	TS=("outbreak prediction" AND leptospir*) OR TS=(map* AND leptospir*) OR TS=("geographic information system" AND leptospir*) OR TS=(spati* AND leptospir*) OR TS=("remote sens*" AND leptospir*) OR TS=(cluster* AND leptospir*) OR TS=("GIS" AND leptospir*)
Zoological Record (1930–2018)	TS=("outbreak prediction" AND leptospir*) OR TS=(map* AND leptospir*) OR TS=("geographic information system" AND leptospir*) OR TS=(spati* AND leptospir*) OR TS=("remote sens*" AND leptospir*) OR TS=(cluster* AND leptospir*) OR TS=("GIS" AND leptospir*)

Table B-2. Summary of the characteristics of studies included in the systematic review (N = 115)

Reference	Location	Study scale	Data sources	Leptospirosis diagnosis methods	Case definitions described	Study design	Spatial/Temporal analysis
Human studies (n=66)							
Lau et al. (2016)	Fiji	National	Survey	MAT, ELISA	Y	CS	V+M
Lau et al. (2012c)	American Samoa	National	Survey	MAT	Y	CS	V
Lau et al. (2012b)	American Samoa	National	Survey	MAT	Y	CS	V+M
Lau et al. (2012a)	American Samoa	National	Survey	MAT	Y	CS	V+E+M
Robertson et al. (2012)	Sri Lanka	National	Notification	Suspect cases	Y	CS	V+E+M
Sanchez-Montes et al. (2015)	Mexico	National	Notification	ELISA/MAT	Y	CS	V+M
Schneider et al. (2012)	Nicaragua	National	Notification	ELISA	Y	CS	V+M
Stevens et al. (2011)	Palau	National (Island)	Notification	n.d	N	CS	V
van Alphen et al. (2015)	Denmark	National	Notification	MAT	Y	CS	V
Zhao et al. (2016)	China	National	Notification	n.d	N	CS	V+M
Lau et al. (2015)	Australia	Sub-national	Notification	MAT, PCR, CAAT	Y	CS	V
Sulistyawati et al. (2016)	Indonesia	Sub-national	Notification	n.d	N	CS	V+E
Barcellos & Sabroza (2000)	Brazil	Sub-national	Notification	n.d	N	CS	V+M
Barcellos & Sabroza (2001)	Brazil	Sub-national	Notification	MAT	N	CS	V+M
Barcellos et al. (2003)	Brazil	Sub-national	Notification	n.d	N	CS	V
Tassinari et al. (2004)	Brazil	Sub-national	Notification	n.d	N	CS	V
Reis et al. (2008)	Brazil	Sub-national	Survey	MAT	Y	PC	V+M
Tassinari et al. (2008)	Brazil	Sub-national	Notification	Culture/Isolation/ MAT	Y	CS	V+E+M
Garcia-Ramirez et al. (2015)	Colombia	Sub-national	Notification	n.d.	N	CS	V
Soares et al. (2010)	Brazil	Sub-national	Notification	Culture/Isolation/ ELISA/ MAT	Y	CS	V+E+M
de Melo et al. (2011)	Brazil	Sub-national	Notification	ELISA, MAT	N	CS	V
Sunaryo & Widiastuti (2012)	Indonesia	Sub-national	Survey and notification	Lateral flow	N	CS	V
Widayani et al. (2016)	Indonesia	Sub-national	Notification	n.d.	N	CS	V+M
Dozsa et al. (2016)	Brazil	Sub-national	Notification	n.d.	N	CS	V+M
Goncalves et al. (2016)	Brazil	Sub-national	Notification	n.d.	N	CS	V+M
Gracie et al. (2014)	Brazil	Sub-national	Notification	MAT	N	CS	V+E+M
Hagan et al. (2016)	Brazil	Sub-national	Survey	MAT	Y	PC	V+M
Hassan & Tahar (2016)	Malaysia	Sub-national	Notification	n.d	N	CS	V+E
Suwanpakdee et al. (2015)	Thailand	Sub-national	Notification	Latex agglutination/ MCAT/lateral flow/RDT/MAT/IFA/ ELISA/PCR/culture	Y	CS	V+E+M
Suryani et al. (2016)	Indonesia	Sub-national	Medical records	Serological test (n.d)	N	CC	E+M
Schneider et al. (2015)	Brazil	Sub-national	Survey	IgM ELISA, MAT	Y	CS	V+M
Coelho & Massad (2012)	Sao Paolo, Brazil	Sub-national	Notification	n.d	N	CS, TS	TM
Chadsuthi et al. (2012)	Thailand	National	Notification	n.d	N	CS, TS	TM
Desvars et al. (2011)	Reunion Island	National (Island)	Notification	Culture (blood)/MAT/PCR	Y	CS, TS	TM
Weinberger et al. (2014)	New Caledonia	National (Island)	Notification	Culture/MAT/PCR	Y	CS, TS	TM

Reference	Location	Study scale	Data sources	Leptospirosis diagnosis methods	Case definitions described	Study design	Spatial/Temporal analysis
Bennett & Everard (1991)	Barbados	National	Medical records	n.d	N	CS	E
Chaiblich et al. (2017)	Brazil	Sub-national	Notification	n.d	N	CS	V
Cook et al. (2017)	Kenya	Sub-national	Survey	IgM ELISA,	N	CS	V+E+M
Herbreteau et al. (2006)	Thailand	Sub-national	Notification	n.d	N	CS	V
Joshi et al. (2017)	Korea	National	Notification	n.d	N	CS	TM
Ko et al. (1999)	Brazil	Sub-national	Active surveillance	MAT	Y	PC	V
Ledien et al. (2017)	Cambodia	Sub-national	Active surveillance	IgM ELISA	N	PC	M
Massenet et al. (2015)	Futuna Island	National (Island)	Surveillance	IgM ELISA, MAT, PCR	Y	CS	V+E+TM
Mišić-Majerus (2014)	Croatia	National	Active surveillance	MAT	N	PC	V
Myint et al. (2007)	Cambodia	Sub-national	Medical records	IgM ELISA, MAT	Y	CS	V
Jansen et al. (2005)	Germany	National	Notification	Culture/PCR/ MAT/ELISA	Y	CS	V
Schneider et al. (2017)	Latin America	Regional	Notification	MAT/ELISA	Y	CS	V
Slack et al. (2007)	Australia	National	Notification	Culture (blood), IgM ELISA, MAT, PCR (*gyrB*), CAAT	Y	CS	V
Slack et al. (2006)	Australia	Sub-national	Notification	Cultures, IgM ELISA, MAT, CAAT	Y	CS	V
Vega-Corredor & Opadeyi (2014)	Trinidad and Tobago	Sub-national	Notification	n.d	N	CS	V+M
Shi et al. (1995)	China	National	Notification	n.d	N	CS	V
Rood et al. (2017)	Netherlands	National	Notification	Culture/IgM ELISA/MAT/ELISA	N	CS	V+E+M
Mohammadinia et al. (2017)	Iran	Sub-national	Medical records	ELISA	N	CS	V+E+M
Gonwong et al. (2017)	Thailand	National	Serum repository	IgG IgM ELISA	Y	CS	V
Mohd Radi et al. (2018)	Malaysia	Sub-national	Notification	ELISA, MAT	Y	CS	V+E+M
Rahayu et al. (2018)	Indonesia	Sub-national	Notification	n.d	N	CS	V
Deshmukh et al. (2019)	India	Sub-national	Hospital-based surveillance	IgM ELISA, MAT	Y	PC, TS	V+E+TM
Mayfield et al. (2018a)	Fiji	National	Survey	MAT, ELISA	Y	CS	V+E+M
Matsushita et al. (2018)	Philippines	Sub-national	Hospital-based surveillance	n.d (as most cases were diagnosed clinically)	Y	CS,TS	TM
Gutierrez & Martinez-Vega (2018)	Colombia	National	Notification	MAT, IgM ELISA, Culture, or PCR	Y	CS	V+E
Koffi SK et al. (2018)	Côte d'Ivoire, Africa	Sub-national	Serum repository	ELISA, MAT	Y	CS	V
Baquero & Machado (2018)	Brazil	National	Notification	n.d	n.d	CS	V+M
Mayfield et al. (2018b)	Fiji	National	Survey	MAT, ELISA	Y	CS	V+M
Dhewantara et al. (2018)	China	National	Notification	MAT, ELISA, PCR	Y	CS	V
Le Turnier et al. (2018)	French Guiana	National	Hospital admission report	IgM ELISA, PCR, MAT	Y	CS	V
Animal studies (n=39)							
Gautam et al. (2010)	USA	National	Laboratory database	MAT	Y	CS	V+E
Ward (2002a)	USA, Canada	National	Medical records	n.d	N	CC	E
Filho et al. (2014)	Brazil	Sub-national	Survey	MAT	Y	CS	V
Dobigny et al. (2015)	Niger	Sub-national	Survey	PCR (*rrs*)	n.a	CS	V

Reference	Location	Study scale	Data sources	Leptospirosis diagnosis methods	Case definitions described	Study design	Spatial/Temporal analysis
Ayral et al. (2015)	France	Sub-national	Survey	PCR (*rpoB*), MST	n.a	CS	V
Hesterberg et al. (2009)	South Africa	Sub-national	Survey	MAT	N	CS	V
Ghneim et al. (2007)	USA	Sub-national	Medical records, Survey	MAT	Y	CC	V+M
Grayzel & DeBess (2016)	Canada	Sub-national	Medical records	MAT	Y	CS	V
Hennebelle et al. (2013)	USA	Sub-national	Medical records	MAT, IHC	Y	CC	V+E
Raghavan et al. (2012)	USA	Sub-national	Medical records	Culture + MAT	Y	CC	V+E+M
Raghavan et al. (2011)	USA	Sub-national	Medical records	Culture + MAT	Y	CC	V+M
Raghavan et al. (2013)	USA	Sub-national	Medical records	Culture + MAT	Y	CC	V+M
Ward et al. (2004)	USA	Sub-national	Medical records	Culture + MAT	Y	CC	V+M
White et al. (2017)	USA	Sub-national	Laboratory database	MAT	Y	CS	V+M
Bier et al. (2013)	Brazil	Sub-national	Survey	MAT	Y	CS	V+M
Himsworth et al. (2013)	Canada	Sub-national	Survey	PCR (*lipL32*)	n.a	CS	V+E+M
Nicolino et al. (2014)	Brazil	Sub-national	Survey	MAT	Y	CS	V+E
Bier et al. (2012)	Brazil	Sub-national	Survey	MAT	Y	CS	V
Alton et al. (2009)	Canada	Sub-national	Laboratory database	MAT	Y	CS	E+M
da Silva et al. (2006)	Brazil	Sub-national	Laboratory database	MAT	Y	CS	V+E
Elder et al. (1986)	Australia	Sub-national	Laboratory database	MAT	Y	CS	V+M
Elder & Ward (1978)	Australia	Sub-national	Laboratory database	MAT	Y	CS	V+M
Hashimoto et al. (2015)	Brazil	Sub-national	Survey	MAT	Y	CS	V+M
Ivanova et al. (2012)	Cambodia	Sub-national	Survey	Culture + PCR (*rrs*)	n.a	CS	V+M
Koizumi et al. (2008)	Japan	Sub-national	Survey	Culture, MAT, PCR (*flaB*)	N	CS	V
Lee et al. (2014)	United States	Sub-national	Laboratory database	MAT	Y	CS	TM
Machado et al. (2016)	Brazil	Sub-national	Survey	MAT	Y	CS	V
Magalhães et al. (2006)	Brazil	Sub-national	Survey	MAT	Y	CS	V
Major et al. (2014)	Switzerland	National	Laboratory database	MAT	Y	CS	V
Paixão et al. (2016)	Brazil	Sub-national	Survey	MAT	Y	CS	V
Scolamacchia et al. (2010)	Cameroon	Sub-national	Laboratory database	ELISA	Y	CS	V+E
Shearer et al. (2014)	Canada	Sub-national	Survey	Culture, PCR, IHC	n.a	CS	V
Suwancharoen et al. (2016)	Thailand	National	Survey	Culture, LAMP	Y	CS	V
Thompson et al. (2006)	Brazil	Sub-national	Survey	MAT	Y	CS	M
Ward (2002b)	United States	National	Medical records	n.d	N	CS	TM
Wongbutdee & Jittimanee (2016)	Thailand	Sub-national	Survey	PCR (*lipL32, rrs*)	n.a	CS	V
Hartman (1984)	Netherlands	National	Notification	MAT, ELISA	Y	CS	V
Miyama et al. (2018)	Japan	Sub-national	Survey	IgG ELISA	Y	CS	V+E+M
Silva et al. (2018)	Teresina, Brazil	Sub-national	Survey	MSA	Y	CS	V
Human and animal studies (n=11)							
Chadsuthi et al. (2017)	Thailand	National	Passive surveillance report	MAT	Y	CS	V+M
Assenga et al. (2015)	Tanzania	Sub-national	Survey	Culture+MAT	Y	CS	V
Villanueva et al. (2014)	Philippines	Sub-national	Survey	Culture, PCR (*rrl. flaB, gyrB*), PFGE	n.a	CS	V

Reference	Location	Study scale	Data sources	Leptospirosis diagnosis methods	Case definitions described	Study design	Spatial/Temporal analysis
Widiastuti et al. (2016)	Indonesia	Sub-national	Survey and notification	Culture, PCR (*rpoB*)	n.a	CS	V
Cipullo & Dias (2012)	Brazil	Sub-national	Notification	n.d	N	CS	V+E
Fonzar & Langoni (2012)	Brazil	Sub-national	Survey and notification	MAT	N	CS	V
Della Rossa et al. (2016)	Thailand	Sub-national	Survey and notification	Culture + PCR (*lipL32, B-actin, rrs, secY*)	N	CS	V+E+M
Biscornet et al. (2017)	Seychelles	Sub-national	Survey	Culture, PCR (rrs), MLST (*adk, icdA, lipL23, lipL41, rrs2, secY*)	Y	CS	V+M
Hurd et al. (2017)	Germany	Sub-national	Survey	Culture, PCR (*hap1*)	n.a (animal); N (human)	CS	V
Pijnacker et al. (2016)	Netherlands	National	Passive surveillance	Culture, IgM-IgG ELISA	Y	CS	V
Sumanta et al. (2015)	Indonesia	Sub-national	Survey and notification	Lateral flow	n.a	CS	V+E

Abbreviations: n.d, not described; n.a, not applicable (as study used molecular detection); Study design: CS, cross-sectional; CC, case-control; PC, prospective cohort; TS = time-series; MAT, microscopic agglutination test; MSA, microscopic serum agglutination; Spatial/temporal analysis: V, visualisation; E, exploration; M, modelling; TM, temporal modelling

Table B-3 Summary of studies on mapping human leptospirosis (N=56)

Study area	Outcome(s)	Data source	Reference
Regional (n=1)			
South America	Incidence map	Notification	Schneider et al. (2017)
National (n=23)			
Denmark	Incidence maps	Notification	van Alphen et al. (2015)
Nicaragua	Incidence maps, risk maps	Notification	Schneider et al. (2012)
Sri Lanka	Incidence maps	Notification	Robertson et al. (2012)
American Samoa	Seroprevalence maps, predictive seroprevalence maps	Serological survey	Lau et al. (2012a)
American Samoa	Seropositivity maps	Serological survey	Lau et al. (2012b)
Palau	Incidence map	Notification	Stevens et al. (2011)
China	Incidence map, suitability map	Notification	Zhao et al. (2016)
Thailand	Risk maps	Notification	Suwanpakdee et al. (2015)
Mexico	Case distribution map, suitability map	Notification	Sanchez-Montes et al. (2015)
American Samoa	Seropositivity maps	Serological survey	Lau et al. (2012c)
Fiji	Seroprevalence map	Serological survey	Lau et al. (2016)
Futuna Island	Incidence map	Notification	Massenet et al. (2015)
Germany	Incidence map	Notification	Jansen et al. (2005)
Australia	Distribution map (serovar)	Notification	Slack et al. (2007)
China	Incidence map	Notification	Shi et al. (1995)
Netherlands	Kernel density map, incidence map, residual incidence map	Notification	Rood et al. (2017)
Thailand	Seroprevalence map	Serological survey	Gonwong et al. (2017)
Fiji	Predicted probability infection maps, hotspots maps	Serological survey	Mayfield et al. (2018a)
Colombia	Cluster map	Notification	Gutierrez and Martinez-Vega (2018)
Brazil	Predictive risk maps	Notification	Baquero and Machado (2018)
Fiji	Predictive risk (seroprevalence) maps	Survey	Mayfield et al. (2018b)
China	Disability-adjusted life-years (DALY) distribution maps	Notification	Dhewantara et al. (2018)
French Guiana	Case distribution map	Hospital admission report (notification)	Le Turnier et al. (2018)
Sub-national (n=32)			
Rio Grande do Sul, Brazil	Incidence maps	Notification	Schneider et al. (2015)
Rio Grande do Sul, Brazil	Incidence maps	Notification	Barcellos et al. (2003)
Queensland, Australia	Incidence maps (serovar-specific)	Notification	Lau et al. (2015)
Coffee-triangle region, Colombia	Incidence maps	Notification	Garcia-Ramirez et al. (2015)
Indonesia	Distribution map	Notification	Sulistyawati et al. (2016)
Rio de Janeiro, Brazil	Incidence map, distribution map	Investigation (active surveillance)	Barcellos and Sabroza (2000)
Rio de Janeiro, Brazil	Distribution map	Investigation (active surveillance)	Barcellos and Sabroza (2001)
Rio de Janeiro, Brazil	Smoothed Kernel density distribution map	Notification	Tassinari et al. (2004)

Study area	Outcome(s)	Data source	Reference
Rio de Janeiro, Brazil	Distribution map	Notification	Tassinari et al. (2008)
Pau da Lima communities, Salvador, Brazil	Smoothed Kernel density of seropositivity	Notification	Reis et al. (2008)
Sao Paolo, Brazil	Incidence map	Notification	Soares et al. (2010)
Aracaju, Brazil	Kernel density map	Notification	de Melo et al. (2011)
Semarang, Indonesia	Distribution map	Notification + survey	Sunaryo and Widiastuti (2012)
Rio de Janeiro, Brazil	Incidence maps	Notification	Gracie et al. (2014)
Pau da Lima communities, Salvador, Brazil	Risk maps	Cohort	Hagan et al. (2016)
Petailing district, Malaysia	Risk maps	Notification	Hassan and Tahar (2016)
Bantul district, Indonesia	Risk maps	Notification	Widayani et al., (2016)
Curitiba, Brazil	Distribution map, risk maps	Notification	Dozsa et al., (2016)
Belem, Para, Brazil	Distribution map, risk maps	Notification	Goncalves et al. (2016)
Rio de Janeiro, Brazil	Kernel smoothed density (incidence) map (based on empirical Bayes estimate)	Notification	Chaiblich et al. (2017)
Lake Victoria Basin Region, Kenya	Kernel smoothed density (risk) map	Serological survey	Cook et al. (2017)
Phrae Province, Thailand	Incidence map	Notification	Herbreteau et al. (2006)
Sao Paolo, Brazil	Incidence map	Active hospital-based surveillance	Ko et al. (1999)
Koprivnica-Krizevci, Croatia	Incidence map	Cohort (active hospital-based surveillance)	Mišić-Majerus (2014)
Kamphaeng Phet, Thailand	Incidence map (serovar)	Cohort (active hospital-based surveillance)	Myint et al. (2007)
Australia	Distribution map	Notification	Slack et al. (2006)
Trinidad & Tobago	Kernel map of standardized incidence rate (SIR)	Notification	Vega-Corredor and Opadeyi (2014)
Iran	Incidence map, risk maps	Notification	Mohammadinia et al. (2017)
Malaysia	Distribution map, Kernel density map, incidence map	Notification	Mohd Radi et al. (2018)
Indonesia	Distribution map	Notification	Rahayu et al. (2018)
India	Predicted infection maps, hotspots map	Cohort (active hospital-based surveillance)	Deshmukh et al. (2019)
Côte d'Ivoire, Africa	Distribution map anti-*Leptospira* antibodies	Serum repository	Koffi et al. (2018)

Table B-4 Summary of studies on mapping animal infection and both animal and human infection data

Study area	Outcome(s)	Animal hosts	Data source	Reference
Animal infection (n=32)				
National (n=4)				
USA	Distribution map, predictive probability MAT-positive maps	Dogs	Medical records	White et al. (2017)
Switzerland	Distribution map	Dogs	Laboratory database	Major et al. (2014)
Thailand	Uroprevalence map		Uroprevalence survey	Suwancharoen et al. (2016)
Netherlands	Distribution map (serovar)	Dogs	Laboratory database	Hartman (1984)
Sub-national (n=28)				
USA	Seropositivity map	Dogs	Medical records	Gautam et al. (2010)
Kansas and Nebraska, USA	Case-control location map	Dogs	Medical records	Raghavan et al. (2012)
Kansas and Nebraska, USA	Distribution map	Dogs	Medical records	Raghavan et al. (2011)
Kansas and Nebraska, USA	Prevalence map	Dogs	Medical records	Raghavan et al. (2013)
KwaZulu-Natal, South Africa	Case-control location map	Livestock (cattle)	Serological survey	Hesterberg et al. (2009)
North California, USA	Seropositivity map	Dogs	Medical records	Ghneim et al. (2007)
USA	Case-control location map, cluster map	Dogs	Medical records	Ward et al (2004)
North California, USA	Distribution map	Dogs	Medical records	Hennebelle et al. (2013)
Oregon, USA	Seropositivity map	Dogs	Medical record, survey	Grayzel & DeBess (2016)
Vila Pantanal, Curitiba, Parana, Brazil	Seropositivity map, clusters map	Dogs	Serological survey	Bier et al. (2012)
Vancouver, Canada	Seropositive map, risk map	Rodents	Serological survey	Himsworth et al. (2013)
Vila Pantanal, Curitiba, Parana, Brazil	Seropositive map, risk map	Dogs	Serological survey	Bier et al. (2013)
Brejo Paraibano, Brazil	Distribution map (serovar), prevalence map, Kernel density map	Horse	Serological survey	Filho et al. (2014)
Sete Lagoas, Minas Geras, Brazil	Serostatus for anti-leptospiral distribution	Livestock (dairy cattle)	Serological survey	Nicolino et al. (2014)
Niamey, Niger	Suitability map of rodents	Rodents	Serological survey	Dobigny et al. (2015)
Lyon, France	Seropositivity map	Rodents	Serological survey	Ayral et al. (2015)
Sao Paolo, Brazil	Serostatus for anti-leptospiral distribution map	Dogs	Serological survey	da Silva et al. (2006)
Queensland, Australia	Seroprevalence maps	Livestock (cattle, pigs)	Serological survey	Elder et al. (1986)
Queensland, Australia	Seroprevalence maps	Livestock (cattle, pigs)	Serological survey	Elder & Ward (1978)
Parana, Brazil	Kernel density map	Livestock (cattle)	Serological survey	Hashimoto et al. (2015)
Veal Renh and Kaev Selma, Cambodia	Trapping locations map	Rodents	Animal survey (rodent)	Ivanova et al. (2012)
Miyazaki Prefecture, Japan	Distribution map	Rodents	Animal survey	Koizumi et al. (2008)
Pernambuco state, Brazil	Prevalence map, distribution map	Livestock (sheep)	Serological survey	Machado et al. (2016)

Study area	Outcome(s)	Animal hosts	Data source	Reference
Minas Gerais, Brazil	Distribution map (serovar), seropositivity map, risk map	Dogs	Animal survey (dog)	Magalhães et al. (2006)
Adamawa, Cameroon	Seroprevalence map	Livestock (cattle)	Serological survey	Scolamacchia et al. (2010)
Ontario, Canada	Seropositivity map	Wildlife	Wild animal survey	Shearer et al. (2014)
Tohoku, Japan	Seropositive map, disease cluster map	Livestock (dairy cattle)	Bulk milk survey (serological survey)	Miyama et al. (2018)
Teresina, Brazil	Seropositive map	Dogs	Serological survey	Silva et al. (2018)
Human-animal infection (n=9)				
National (n=9)				
Thailand	Seroprevalence maps	Livestock (buffaloes, cattle, pigs)	Human and livestock passive surveillance programs	Chadsuthi et al. (2017)
Seychelles	Distribution maps	Rodents, dogs, cats	Cohort (human) and animal sampling	Biscornet et al. (2017)
Netherlands	Distribution map (autochthonus and imported cases)	Dogs	Notification (human and animal)	Pijnacker et al. (2016)
Tanzania	Serogroup distribution map	Rodents	Survey and animal sampling	Assenga et al. (2015)
Luzon, Philippines	Serogroup distribution map (human and rats)	Rodents	Human passive surveillance and animal sampling	Villanueva et al. (2014)
Maringa, Parana, Brazil	Distribution map	Dogs	Animal sampling	Fonzar & Langoni (2012)
Sao Paolo, Brazil	Distribution map	Dogs	Notification	Cipullo & Dias (2012)
Sindon and Jeron village, Boyolali, Indonesia	Distribution map	Rodents	Animal sampling, notification (human)	Widiastuti et al. (2016)
Tha Wang Pha and Pua, Nan, Thailand	Distribution map	Rodents	Animal sampling, medical records (human)	Della Rossa et al. (2016)
Lower Saxony, Germany	Muskrats smoothed prevalence map (empirical Bayes estimates)	Rodents	Animal sampling and notification (human)	Hurd et al. (2017)
Indonesia	Distribution map (human), seropositivity map (rodent)	Rodents	Animal sampling and notification (human)	Sumanta et al. (2015)

Table B-5 Summary of reviewed studies that explored spatial patterns or spatial autocorrelation of leptospirosis (N=34)

Country	Spatial scale	Objectives	Methods	Reference
Human leptospirosis (n=20)				
Thailand	National	To analyse spatial-temporal pattern of leptospirosis; to test the association of flooding and animal census data on leptospirosis incidence	Getis Ord local G	Suwanpakdee et al. (2015)
American Samoa	National	To detect spatial clustering of seropositive and seronegative cases	Kulldorf's Bernoulli spatial scan statistics, semivariogram	Lau et al. (2012a)
Sri Lanka	National	To detect spatial-temporal clusters of cases during outbreak of suspected leptospirosis	Kulldorf's Poisson space-time scan statistics	Robertson et al. (2012)
Brazil	Sub-national	To identify spatial clusters of outbreaks; to estimate the effect of socioeconomic with prevalence of *Leptospira* antibodies	Kulldorf's spatial and space-time scan statistics	Tassinari et al. (2008)
Malaysia	Sub-national	To identify hot spot, cold spot and spatial outlier; to identify spatial risk factors for leptospirosis	Getis Ord local G	Hassan & Tahar (2016)
Brazil	Sub-national	To identify the role of environmental and socioeconomic factors on leptospirosis	Moran	Goncalves et al. (2016)
Brazil	Sub-national	To test spatial autocorrelation during epidemic and endemic period, to identify environmental and socioeconomic determinants associated with the occurrence of leptospirosis at different geographical scale	Moran	Gracie et al. (2014)
Brazil	Sub-national	To analyse spatial pattern of cases	Global Moran, local Moran	Soares et al. (2010)
Indonesia	Sub-national	To identify disease pattern and risk factors leptospirosis in Yogyakarta from 2011 to 2013	Average nearest neighborhood, Moran	Suryani et al. (2016)
Indonesia	Sub-national	To identify spatial pattern of cases	Kulldorf's spatial scan statistics (Multinomial model)	Sulistyawati et al. (2016)
Barbados	National	To examine the space-time clustering of leptospirosis	Knox	Bennett & Everard (1991)
Kenya	Sub-national	To investigate seropositivity and associated risk factors among slaughterhouse workers	Moran's I	Cook et al. (2017)
Futuna Island	National	To describe epidemiology of leptospirosis, to test the link of rainfall and leptospirosis cases, to map incidence, and to identify spatial clusters	Kulldorf's Poisson space-time scan statistics	Massenet et al. (2015)
Iran	Sub-national	To compare effectiveness of fixed and adaptive kernels in modelling human leptospirosis using GWR	Moran's I	Mohammadinia et al. (2017)
Netherlands	National	To map and to investigate spatial variation in morbidity of leptospirosis, to quantify the role of biotic and abiotic environmental factors on the incidence of leptospirosis	Moran's I, Local Indicators of Spatial Association (LISA)	Rood et al. (2017)
Thailand	Sub-national	To investigate the environmental factors associated with human leptospirosis incidence	Moran's I statistic	Della Rossa et al. (2016)
Brazil	Sub-national	To identify risk factors associated with human infection	Spatial scan	Cipullo & Dias (2012)
Malaysia	Sub-national	To compare spatial-temporal pattern of leptospirosis before and after outbreak	Average Nearest Neighborhood, global Moran's I, LISA	Mohd Radi et al. (2018)
India	Sub-national	To describe the epidemiology of leptospirosis and examine the role of climatic factors on leptospirosis incidence	Kulldorf's Poisson spatial scan statistics	Deshmukh et al. (2019)

Country	Spatial scale	Objectives	Methods	Reference
Fiji	National	To assess hotspots and coldspots of predicted probability leptospirosis infection	Getis-Ord Gi* test	Mayfield et al. (2018a)
Colombia	National	To examine the the association of climatic variability with spatiotemporal clusters of leptospirosis	Kulldorf's space-time permutation	Gutierrez & Martinez-Vega (2018)
Animal leptospirosis (n=13)				
USA	National	To identify space and space-time clusters of seroreactivity on dogs to MAT over the country during 2000–2007	Kulldorf's Poisson space-time scan statistics	Gautam et al. (2010)
USA	Sub-national	To identify clustering among cases and controls locations	Cuzick-Edwards *K*th neighbor test	Raghavan et al. (2012)
USA and Canada	National	to determine clustering of leptospirosis cases among dogs	Kulldorf's Poisson space-time scan statistics	Ward (2002)
Brazil	Sub-national	To detect spatial clustering of seropositive and seronegative in herds	Kulldorf's Bernoulli spatial scan statistics	Nicolino et al. (2014)
Canada	Sub-national	to identify spatial clusters of high and low rate on *L.interogans* infection among trapped Norway rats	Kulldorf's Bernoulli spatial scan statistics	Himsworth et al. (2013)
USA	Sub-national	to identify global and local area clustering of cases in space, time, and space-time on dogs with Leptospira	Cuzick-Edwards *K*th neighbor, Kulldorf's Bernoulli spatial scan statistics, Poisson space time permutation	Hennebelle et al. (2013)
Canada	Sub-national	To examine spatial clustering of infected dogs; to assess risk factors	Empirical Bayes Index Modification Moran's I statistic, empirical semivariogram, Binomial spatial scan statistic	Alton et al. (2009)
Brazil	Sub-national	To assess the risk factor of seropositivity on dogs and to identify its spatial distribution	Kulldorf's Poisson spatial scan statistics	da Silva et al. (2006)
Cameroon	Sub-national	To identify spatial distribution of herd prevalences, to test spatial clustering of Leptospira seropositive herds	Cuzick-Edwards' k-nearest neighbour	Scolamacchia et al. (2010)
USA	Sub-national	To assess dogs' urban vs. rural address locations and different land cover types from two disparate land cover datasets, within 2500 m as potential risk factors for canine leptospirosis in Kansas and Nebraska.	Empirical variogram	Raghavan et al. (2011)
USA	Sub-national	To test if varying spatial extents (MAUP) changed the types and statistical significance of environmental risk factors of canine leptospirosis derived from land cover/land use datasets.	Empirical variogram	Raghavan et al. (2013)
Indonesia	Sub-national	To examine distribution pattern and clustering of *Leptospira* bacteria in rats, water, soil	Kulldorf's spatial scan statistics	Sumanta et al. (2015)
Japan	Sub-national	To detect spatial clustering of *L. Hardjo* seropositivy in dairy herds	Kulldorf's spatial scan statistics	Miyama et al. (2018)
Human-animal infection (n=1)				
Germany	Sub-national	To investigate the spatial pattern of leptospirosis in muskrats and association with human infection	Global Moran's I, Geary's C test, semi-variogram, Kulldorf's Poisson spatial scan statistics, flexibly shaped spatial scan test (FleXScan).	Hurd et al. (2017)

Table B-6 Summary of studies on quantifying risk and modelling on leptospirosis

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
						Exploration		Modelling		
					Mapping	Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Human infection										
Suwanpakde et al. (2015)	Thailand	2010-2012	National	To examine the correlation of spatial-temporal of leptospirosis incidence and flooding	Y	Y	N	Y	N	Negative binomial (NB) regression model, univariate analysis, Z test, multivariate analysis, variance inflation factor, stepwise selection
Schneider et al. (2015)	Brazil	2008-2012	Sub-national	To identify potential drivers of leptospirosis considering the One Health approach	Y	N	N	Y	N	Multivariable regression, negative binomial regression (NB), univariate analysis, Variance inflation factors, two-way interaction, deviance performance, zero-inflated negative binomial (ZINB), chi-squared, Vuong statistics, Akaike information criteria, Poisson regression

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
						Exploration		Modelling		
					Mapping	Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Lau et al. (2016)	Fiji	September - December 2013 (4 months)	National (Island country)	To characterize the epidemiology and risk factors for human leptospirosis in Fiji	Y	N	N	Y	N	Multivariable logistic regression model, multilevel hieararchical model, Intracluster correlation coefficients, Hosmer-Lemeshow test, AUC, Akaike information criterion, Bayesian information criterion
Lau et al. (2012a)	American Samoa	May-July 2010	National (Island country)	To estimate leptospirosis seroprevalence at geographic locations based on environmental factors, produce a predictive disease risk map for American Samoa, and assess the accuracy of the maps in predicting infection risk	Y	Y	Y	Y	Y	Logistic regression, multivariable logistic regression model, spatial autocorrelation, semi-variograms, Akaike information criterion, AUC
Lau et al. (2012b)	American Samoa	May-July 2010	National (Island country)	To identify risk factors associated with infection	Y	N	N	Y	N	Chi-square, Fischer exact test, univariate analysis, multivariable logistic regression model
Robertson et al. (2012)	Sri Lanka	2005-2010	National	To characterize risk factors of leptospirosis; to examine the role of rainfall in the outbreak	Y	Y	N	Y	N	Cross-correlation function, log-linear regression, space-time scan statistic, Monte-Carlo randomization, logistic regression

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
						Exploration		Modelling		
					Mapping	Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Sanchez-Montes et al. (2015)	Mexico	2000-2010	National	To determine the potential leptospirosis distribution	Y	N	N	Y	Y	Ecological Niche Model (ENM)/Maxent model, Genetic Algorithm for Rule-set Production (GARP), chi-square, recursive partitioning analysis, classification and regression tree, non-parametric regression
Schneider et al. (2012)	Nicaragua	2008-2012	National	To stratify the risk and identify “critical areas” for leptospirosis outbreaks in Nicaragua, and to perform an exploratory analysis of potential “drivers”	Y	N	N	Y	N	Pearson correlation, t-test, one-way ANOVA, multinomial logistic model. Poisson regression, binary logistic, lagged cross-correlation analysis
Zhao et al. (2016)	China	2010-2014	National	To identified environmental and socioeconomic factors associated with leptospirosis; forecast potential risk area of leptospirosis	Y	N	N	Y	Y	Ecological Niche Model (ENM)/Maxent model; logistic regression, receiver operating characteristic

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
					Mapping	Exploration		Modelling		
						Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Gracie et al. (2014)	Brazil	1996-1999	Sub-national	To assess the relationships among various environmental and socioeconomical factors and leptospirosis incidence using different geographical scales and units of analysis	Y	Y	N	Y	N	spatial autocorrelation, non-parametric Spearman's rank correlation
Barcellos et al. (2000)	Brazil	February-March 1996	Sub-national	To characterized environmental conditions associated with leptospirosis	Y	N	N	Y	N	ANOVA
Barcellos et al. (2001)	Brazil	February-March 1996	Sub-national	to analyze the spatial distribution of leptosirosis cases based on the location of defined risk factors	Y	N	N	Y	N	Chi-squared
Dozsa et al. (2016)	Brazil	2014	Sub-national	to investigate the regions with highest risk of leptospirosis and flooding in the city of Curitiba	Y	Y	N	Y	N	semivariogram, kriging

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
					Mapping	Exploration		Modelling		
						Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Hagan et al. (2016)	Brazil	2003-2007	Sub-national	to identify risk factors and to quantify the role on leptospirosis; to examine the spatial-temporal distribution of random effects to assess the unexplained variation in the pattern	Y	N	N	Y	N	generalized estimating equations, generalized additive model, Akaike information criterion, Stochastic Partial Differential Equations; Integrated Nested Laplace Approximation (INLA), deviance information criterion, multivariable mixed effect models
Reis et al. (2008)	Brazil	2003-2004	Sub-national	To evaluate the association of environmental and socioeconomic variables with the risk of acquiring Leptospira antibodies; to estimate the effect of demographic, socioeconomic, household and workplace-related factors on the prevalence of *Leptospira* antibodies.	Y	N	N	Y	N	Chi-square, Wilcoxon rank sum test, Kernel density estimation, Generalized Additive Models, Poisson regression, Bayesian inference, standard non-informative, multivariate analysis, univariate analysis, Spearman correlation coefficient
Soares et al. (2010)	Brazil	1998-2006	Sub-national	To identify potential ecological and social components of Leptospira transmission	Y	Y	N	Y	N	Spearman correlation

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
						Exploration		Modelling		
					Mapping	Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Suryani et al. (2016)	Indonesia	2011-2013	Sub-national	To explore the spatial distribution of leptospirosis case and risk factors	Y	Y	N	Y	N	Bivariate analysis
Tassinari et al. (2008)	Brazil	1997-2002	Sub-national	To evaluate the spatial and temporal influence of rainfall and spatial influence of socioeconomic and environmental characteristics on the risk of a leptospirosis case belonging to a cluster vs. noncluster	Y	Y	N	Y	N	Voronoi tassellation, Bartlett's test, spatial scan statistics, space-time scan statistics, generalized linear mixed model, logistic multilevel analysis, Variance partition coefficient (VPC), Akaike's corrected information criterion
Widayani et al. (2016)	Indonesia	2009-2011	Sub-national	To determine local and global risk factors for leptospirosis, to develop vulnerability map of leptospirosis	Y	Y	N	Y	Y	Geographical Weighted Regression (GWR)
Goncalves et al. (2016)	Brazil	2007-2013	Sub-national	To identify spatial correlations between social and environmental risk factors and leptospirosis in Belém in the State of Pará from 2007 to 2013	Y	Y	N	Y	N	Chi-square, kriging, spatial autocorrelation

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
					Mapping	Exploration		Modelling		
						Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Cook et al. (2017)	Kenya	2011-2012	Sub-national	To investigate seropositivity and associated risk factors among slaughterhouse workers	Y	Y	N	Y	N	Multilevel logistic regression, correlation analysis, multilevel mixed effect regression model, Akaike information criterion, variance inflation factors, intraclass correlation coefficient, Moran's I
Ledien et al. (2017)	Cambodia	2007-2009	Sub-national	To examine best remotely-sensed flooding indicators for better predict leptospirosis incidence	Y	N	N	Y	N	Chi-square test, generalized linear model (GLM), logistic regression model, Akaike information criteria (AIC), Area Under Cover (AUC), boosted regression tree (BRT), cross-validation
Vega-Corredor et al. (2014)	Trinidad Tobago	1998-2008	National (Island country)	To assess the spatial variation in risk of leptospirosis associated with hydrological factors	Y	N	N	Y	Y	non-parametric global Poisson regresssion, Geographically Weighted Poisson Regression, Akaike information criterion
Gonwong et al. (2017)	Thailand	2007-2008	National	To understand the distribution of leptospirosis incidence in young Thailand population	Y	N	N	Y	N	Spearman Correlation

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
					Mapping	Exploration		Modelling		
						Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Mohammadinia et al. (2017)	Iran	2009	Sub-national	To compare effectiveness of fixed and adaptive kernels in modelling human leptospirosis using GWR	Y	Y	N	Y	N	Geographical Weighted Regression (GWR), Inverse Diverse Weighting (IDW), Kernel, Spatial autocorrelation test (Moran's), Jarque-Bera statistics, Variance inflation factor, Akaike Information Criterion, Bayesian Information Criterion, Cross Validation, Bisquare-Gaussian weighting function
Rood et al. (2017)	Netherlands	1995-2012	National	To investigate spatial variations in leptospirosis incidence and to identify associations with environmental variables	Y	Y	Y	Y	Y	Simultaneous Auto Regression (SAR), Akaike information criterion (AIC), spatial autocorrelation test in the residuals
Radi et al. (2018)	Malaysia	2014	Sub-national	To investigate spatial-temporal pattern of leptospirosis associated with major outbreak	Y	Y	Y	Y	N	Average Nearest Neighborhood, Global Moran's I, LISA, Kernel density, geographical weighted regression, Poisson GLM
Desmukh et al. (2018)	India	2015-2016	Sub-national	To describe the epidemiology of leptospirosis and examine the role of	Y	N	Y	Y	N	Kriging, Kernel density, Poisson spatial scan statistics, Time-series Poisson regression

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
					Mapping	Exploration		Modelling		
						Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
				climatic factors on leptospirosis incidence						
Mayfield et al. (2018b)	Fiji	2013	National	To determine drivers of leptospirosis transmission under different scenarios of environmental and livestock exposures	Y	N	N	Y	Y	Spatial Bayesian Networks
Boquero et al. (2018)	Brazil	2000-2016	National	To model spatiotemporal pattern of morbidity and lethality, to examine the effects of environmental and socioecomic factors linked with leptospirosis	Y	N	Y	Y	Y	Besag, York, Mollie (BYM), INLA, Pearson correlation
Mayfield et al. (2018a)	Fiji	2013	National	To compare the performance of GWLR model with standard aspatial regression; by using GWLR, to described the eco-epidemiology of leptospirosis and identify potential interventions	Y	N	Y	Y	Y	geographically logistic weighted regression (GWLR), Getis-Ord G*
Animal infection										

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
					Mapping	Exploration		Modelling		
						Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Ghneim et al. (2007)	USA	1998-2000	Sub-national	To investigate landscape and land use aspects that link with canine leptospirosis	Y	N	N	Y	N	Chi-square test of homogeneity, unconditional logistic regression model
Raghavan et al. (2011)	USA	2002-2009	National	To determine the association of land cover characteristics and dogs infection	Y	N	Y	Y	N	Multivariable logistic regression model, variance inflatation factor, Akaike information criterion, chi-square goodness-of-fit, ROC, spatial autocorrelation, empirical variogram of residuals and spatial envelopes
Raghavan et al. (2013)	USA	2002-2009	National	To identify the effect of spatial extents (buffer) on the risk factors for canine leptospirosis	Y	N	Y	Y	N	Multivariable logistic regression model, variance inflatation factor, Akaike information criterion, chi-square goodness-of-fit, ROC, spatial autocorrelation, empirical variogram of residuals and spatial envelopes

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
						Exploration		Modelling		
					Mapping	Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Raghavan et al. (2012)	USA	2002-2009	National	To investigate urban characteristics that associated with canine leptospirosis	Y	N	Y	Y	N	Multivariable logistic regression model, variance inflatation factor, Akaike information criterion, chi-square goodness-of-fit, ROC, spatial autocorrelation, empirical variogram of residuals and spatial envelopes
Ward et al. (2004)	USA	1997-2002	Sub-national	To identify environmental risk factors for canine leptospirosis	Y	N	N	Y	N	Logistic regression, stepwise analysis, classification tables
White et al. (2017)	USA	2000-2014	National	To identify environmental and socioeconomic factors associated with canine leptospirosis; to produce predictive maps	Y	N	N	Y	Y	Boosted Regression Tree (BRT)
Bier et al. (2013)	Brazil	2009-2010	Sub-national	To identify spatial distribution of seroreagent in dogs; to identify risk factors of canine leptospirosis	Y	N	N	Y	N	Generalized additive model, Monte-Carlo simulation, Akaike's information criterion
Bier et al. (2012)	Brazil	2010	Sub-national	To identify spatial pattern and risk factors associated with dogs leptospirosis	Y	N	N	Y	N	Decision tree analysis, training-testing, confusion matrix, Kappa index

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
					Mapping	Exploration		Modelling		
						Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Himsworth et al. (2013)	Canada	2011-2012	Sub-national	To characterize the prevalence and distribution of L. interrogans amongst Norway rats and the degree to which season and population characteristics influence the ecology of this bacterium	Y	Y	N	Y	N	Logistic regression, multiple logistic regression, Spearman's rank correlation, Akaike's information criterion, generalized linear model
Alton et al. (2009)	Canada	1998-2006	Sub-national	To describe the epidemiology of canine leptospirosis, to assess factors associated with infections, to detect cluster of canine infection	Y	Y	N	Y	N	Logistic regression, Akaike information criterion (AIC), chi-squared goodnees-of-fit, generalized linear mixed models, Penalized Quasi-likelihood, Empirical Bayes Index Modification of Moran's I, semivariogram, spatial scan test

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
					Mapping	Exploration		Modelling		
						Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Elder et al. (1986)	Australia	1972-1983	Sub-national	To assess the environmental factors associated with bovine leptospirosis	Y	N	N	Y	N	Linear regression, quadratic regression model, Mallow's Cp statistics
Elder and Ward (1978)	Australia	1973-1976	Sub-national	To investigate trends in the spatial distribution of L. pomona and L. hardjo infection in bovine; to test association of rainfall and *Leptospira* prevalence	Y	N	N	Y	N	Spearman rank correlation
Ivanova et al. (2012)	Cambodia	2008-2009	Sub-national	To test the role of climate, vegetation, and habitat on rodents infection rate	Y	N	N	Y	N	Generalized linear models (GLM), Akaike information criterion (AIC)
Biscornet et al. (2017)	Seychelles	2014-2015	National	To describe the burden and epidemiological links between animal and human infection, to investigate the biotic and abiotic determinants of transmission	Y	N	N	Y	N	Generalized Linear Model (GLM), Fisher's exact test

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
					Mapping	Exploration		Modelling		
						Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Miyama et al. (2018)	Japan	2014-2015	Sub-national	To estimate seroprevelance and risk factors of Hardjo infection in dairy herds	Y	N	Y	Y	N	Univariate analysis, GLM, Hosmer-Lemeshow test, Akaike information criterion (AIC)
Silva et al. (2018)	Brazil	2014	Sub-national	To examine anti-Leptospira antibodies in dogs, distribution and risk factors	Y	N	N	Y	N	Univariate analysis, Logistic regression, Chi-square, Fischer exact, Monte Carlo test, Goodman test
Major et al. (2014)	Switzerland	2003-2012	National	To describe the epidemiology of canine leptospirosis, to assess the effect of climatic factors on incidence	Y	N	N	Y	N	Linear regression
Both human & animal infection										
Chadsuthi et al. (2017)	Thailand	2010-2015	National	To identify the cross-correlation of serovars amongst species and/or regions; to investigate seropositivity with regard to species and regions	Y	N	N	Y	N	GLM with binomial function, Spearman with Banferroni adjustement, logistic regression, Akaike information criterion, Chi-squared

Reference	Study site	Data Period	Study scale	Objectives	Spatial analytical method					Statistical methods
					Mapping	Exploration		Modelling		
						Disease global clustering tests (first-order)	Spatial autocorrelation tests (second-order, local test)	Model parameter estimates	Spatial prediction	
Hurd et al. (2017)	Germany	2007-2009	National	To investigate the spatial pattern of leptospirosis in muskrats and association with human infection	Y	Y	N	Y	N	Poisson regression models, spatial autocorrelation tests
Della-Rossa et al. (2016)	Thailand	2003-2012	Sub-national	To identify environmental factors linked with leptospira infection in rodents and human	Y	Y	N	Y	N	Generalized Linear Model (GLM), Akaike information criterion, negative binomial, spatial autocorrelation

Note: Y = Yes; N = No;

Table B-7 Summary environmental and socioeconomic predictors used on the risk modelling studies

Reference	Study site	Covariates				Findings
		Environment	Climate	Socioeconomic	Demographical	
Human infection						
Suwanpakde et al. (2015)	Thailand	3,4				Flooding was not directly associated with leptospirosis; differents drivers (e.g., agriculture and animal farming) might have contributed to the variation in space-time pattern of incidence across regions
Schneider et al. (2015)	Brazil	1,2,6,9	3	2,3		Four possible drivers were associated with leptospirosis incidence: landscape, Neossolo Litolitico soil type, and rice and tobacco production
Lau et al. (2016)	Fiji	1,2,4,5,6,9	3	2,3	1-5,7	Seroprevalence was 19.4%; serovar Pohnpei was the dominant serovar. Based on statistical tests, gender, ethnicity, community type, water availability, work location, poverty, lived <100m from river, pigs in community, high cattle density, high rainfall intensity, were linked with the presence of *Leptospira* antibodies
Lau et al. (2012a)	American Samoa	1-9	1	1,3	2,3,5	Leptospirosis was associated with environmental (soil type, altitude, vegetation, piggeries) as well as individual-level (gender, job) factors. Predictive maps accuracy was 84.5%

Reference	Study site	Covariates				Findings
		Environment	Climate	Socioeconomic	Demographical	
Lau et al. (2012b)	American Samoa	2-4,6,7	1	1,3	2,3,5	Living at lower altitude and having higher number of piggeries around the home is associated with infection
Robertson et al. (2012)	Sri Lanka	1,6	1	1,2		Proportion of farms <0.2ha and average distance to rivers within <400m are associated with leptospirosis prevalence. No significant spatial autocorrelation identified in residuals
Sanchez-Montes et al. (2015)	Mexico		1,3			The cases were more closely related with temperature than precipitation. The cases were widespread through central and southern Mexico
Schneider et al. (2012)	Nicaragua	1,2,4,9	1	1-3	4	Four variables as the most important: percentage of Cambisol and Andosol soil type, minimum precipitation, average rainfall in the two months with more precipitation, and percentage of rural population
Zhao et al. (2016)	China	1,4,6	1,3	1,3		Annual mean temperature (Bio1) and annual total precipitation (Bio12) were the two most important variables governing the geographic distribution of leptospirosis in China. Seven provinces in China identified as high-risk areas for leptospirosis

Reference	Study site	Covariates				Findings
		Environment	Climate	Socioeconomic	Demographical	
Gracie et al. (2014)	Brazil	1,3,5,7,8		1	4	At municipal level, the connection of poverty, sanitation and leptospirosis were evident while at state level, environmental factors were showed significant associations. Flooding was the best predictor for leptospirosis at the local level
Barcellos et al. (2000)	Brazil	3,5,7,8		1,3		Access to water, waste collection services, and sewer system were associated with leptospirosis risk
Barcellos et al. (2001)	Brazil	3,8		1		The incidence rate inside the flood risk area were two-fold higher than outside; incidence rate decreased with increasing distance from waste accumulation sites
Dozsa et al. (2016)	Brazil	3				Leptospirosis cases were higher in the area with highly intense flood events
Hagan et al. (2016)	Brazil	1,2,4,7,8		3	1-5,7	Environmental factors related to topology such as household elevation and inadequate sewage drainage systems increased the risk of transmission in the slum microenvironment
Reis et al. (2008)	Brazil	1,2,4,7,8		3	1-4,7	Risk factors for acquiring *Leptospira* antibodies were associated with exposures in the household environment. *Leptospira* transmission was due to the interaction of factors associated with climate, geography and urban poverty
Soares et al. (2010)	Brazil	5,7	1	1,3	4	The incidence and lethality rates correlated with the socioeconomic conditions

Reference	Study site	Covariates				Findings
		Environment	Climate	Socioeconomic	Demographical	
Suryani et al. (2016)	Indonesia	3,5-8			3,5	The various risk factors like mudpuddle, water ditches, flood history, waste refusal, occupational, and skin lesions were potential risk factors for leptospirosis in Yogyakarta city
Tassinari et al. (2008)	Brazil	3,5,7	1	1,3	1,2,4	Rainfall was a significant risk determinant for leptospirosis cases belonging to a cluster vs. non-cluster event. Threshold of mean daily rainfall >4 mm was significantly associated (OR 3.71; 95% CI 1.83–7.51) with leptospirosis cluster events
Widayani et al. (2016)	Indonesia	1,3		2,4	2	At local scale, flood risk, health facility, proportion of residential area and age 25-50yrs were associated with higher risk of leptospirosis; at global level, proportion of paddy field was the main risk factors
Goncalves et al. (2016)	Brazil	2,3,5,7,8				The highest concentrations of the disease were in the Guamá and Jurunas neighborhoods in lower lying areas near canals and poor environmental conditions
Cook et al. (2017)	Kenya	4,5,6			1,3,5	The likelihood of leptospirosis infection was determined by personal hygiene factors. Water sources might play role in leptospirosis tranmission
Ledien et al. (2017)	Cambodia	1,2,6	1	1	1,2	Modified Normalized Difference Vegetation Index (MNDWI) could be used as proxy for flooding and predict leptospirosis incidence in Cambodia

Reference	Study site	Covariates				Findings
		Environment	Climate	Socioeconomic	Demographical	
Vega-Corredor et al. (2014)	Trinidad Tobago	2,6,9	1			Rainfall, imperfect soil drainage and topographic wetness were significantly associated with the spatial variation in leptospirosis incidence.
Gonwong et al. (2017)	Thailand	1				Higher seroprevalence was found in the north and south regions contrary to reported morbidity and potentially associated with environments such as forested and rural areas
Mohammadinia et al. (2017)	Iran	1,2	1,2,3			Adaptive kernel performed appears to be superior compared to fixed model for modelling leptospirosis in Gilan Province.
Rood et al. (2017)	Netherlands	1,6,9		1,2	1	Leptospirosis incidence was linked with soil characteristics, land-use, and spatial configurations
Radi et al. (2018)	Malaysia	1,3,6,8	1,2,3	1	1,2,3,7	Living near to water bodies increased risk of infection. Disease was clustered after flooding and associated with garbage collection sites and meteorological factors.
Desmukh et al. (2018)	India		1,2,3			Relative humidity in the month and rainfall in the previous month was the determinants of leptospirosis incidence in a given month
Mayfield et al. (2018b)	Fiji	1,4,5	1	1,3	3,4	Commericial dairy farm, presence of pig, and poverty rate could explain the variation of predicted risk (seroprevalence) in urban and rural areas.

Reference	Study site	Covariates				Findings
		Environment	Climate	Socioeconomic	Demographical	
Boquero et al. (2018)	Brazil	8,9	1,3	1,3	4	Soil moisture, precipitation, poverty, and proportion of urban population associated with spatiotemporal relative risk of leptospirosis morbidity
Mayfield et al. (2018a)	Fiji	1,4,6	1	3		GWLR was useful technique for predicting spatial heterogeneity of risks and leptospirosis infection. GWLR was more efficient than common logistic regression and can address non-stationarity.
Animal infection						
Ghneim et al. (2007)	USA	1,7	1			Hydrographic density was positively linked with infection in dogs
Raghavan et al. (2011)	USA	1				Dogs lived in urban areas were more likely to acquire *Leptospira* infection
Raghavan et al. (2013)	USA	1				Risk factors varied as the spatial extents around case/control locations increased
Raghavan et al. (2012)	USA	1,4,5		1,3		Poverty status among people in 18–64 years age group, houses that lack plumbing facilities, and proximity to public parks, college/universities, and newly urbanized areas were risk factors for canine leptospirosis in Kansas and Nebraska
Ward et al. (2004)	USA	1,4,5,7,8	1		1,2	Dogs in periurban areas were at greater risk of leptospirosis
White et al. (2017)	USA	1,4	1,3	3	1,2	Suburban areas or areas with deciduous forest, precipitation and temperature were predictors for positive MAT results

Reference	Study site	Covariates				Findings
		Environment	Climate	Socioeconomic	Demographical	
Bier et al. (2013)	Brazil	1,2,3,4,5,7,8			1,2,5,7	Animal, owner, and environmental factors correlated with leptospirosis risk in the areas
Bier et al. (2012)	Brazil	3,4,7,8			5,7	The occurrence of sewer, rats, rubbish and access to street determine seropositivity of dogs
Himsworth et al. (2013)	Canada		1		2,6	Clusters of high and low *L. interrogans* prevalence were detected and associated with weight, fat, and bite wounds
Alton et al. (2009)	Canada	1			1,2,7	Dogs in urban areas were more likely to have higher risk than dogs in rural areas. No disease cluster have been detected.
Elder et al. (1986)	Australia	1,4,9	1,2,3			The main ecological determinants vary for each serovar-specific infection. *L pomona* prevalence determined by low relative humidity, Typic Torrerts clays, the presence of feral pigs and the mean maximum temperature. While. *L. hardjo* infections closely related with presence of beef cattle, mean minimum temperature, alkaline soils, grey Typic Torrert, and the absence of Typic Pellustert clays.
Elder and Ward (1978)	Australia		1			A negative correlation between rainfall categories and *L. pomona* antibodies in beef cattle, total cattle and pigs. No significant correlation between the prevalence of *L. hardjo* antibodies in cattle and rainfall categories.

Reference	Study site	Covariates				Findings
		Environment	Climate	Socioeconomic	Demographical	
Ivanova et al. (2012)	Cambodia	1,2	1		1,2	Wet season, rain-fed fields, and proximity to forest increased the Leptospiral infection on rodents
Biscornet et al. (2017)	Seychelles	1	1		6,7	Higher prevalence of Leptospira in rats was found during the humid season and in urban areas. Genotype data informed that rats are not the primary reservoir for human infection.
Miyama et al. (2018)	Japan	4,10				Larger herd, cattle introduction and intensive farming areas were associated with leptospirosis in dairy herds
Silva et al. (2018)	Brazil	1,3,4,5,7,8,9	1	3	1,2,3,4,7	Dogs with access to the street and resided in anthropized areas were at high risk. Low income of dog owners was associated with risk of leptospirosis in dogs.
Major et al. (2014)	Switzerland		1,3			Seasonal pattern of canine leptospirosis was associated with temperature and rainfall.
Both human & animal infection						
Chadsuthi et al. (2017)	Thailand	1			7	The distribution of serovars across Thailand's regions were found to be similar in pattern for cattle but not for buffaloes. In humans, the serovar distribution in the south differed from other regions. In comparison with the central region, higher seropositivy was associated with northern, northeastern, and southern regions.

Reference	Study site	Covariates				Findings
		Environment	Climate	Socioeconomic	Demographical	
Hurd et al. (2017)	Germany	2	1,3	1		No relationships between muskrats, leptospirosis prevalence and human cases. Temperature was a good predictor for muskrats infection
Della-Rossa et al. (2016)	Thailand	1,2,6		1		Temporally, different environmental factors played a role in infection in rodent and humans. Associations between rodents and human infections remained unclear.

Code for covariates:

Environment: Land use/land cover (1), slope/elevation (2), flood (3), reservoirs (4), housing/sanitation/WASH (5), hydrological (6), sewerage system (7), waste disposal (8), soil type/pH (9), farms/biosecurity (10)

Climate: rainfall (1), relative humidity (2), temperature (3)

Socioeconomic: population (1), agricultural production/output (2), poverty/income (3), health system (4)

Demographical: age (1), gender (2), occupation (3), education/literacy (4), KAP/behaviour (5), morphological (animal) (6), ethnicity (human) or breed/species (animal) (7)

Table B-8 Characteristics of studies that used RS data for leptospirosis epidemiology (N=25)

No.	Reference(s)	Study area	Leptospirosis data	Study scale	Environmental/Socioeconomic data retrieved from RS technology				Environmental data from other sources	Source(s)	Key findings
					Physical environmental/ climatic data	Source(s)	Socio-economic data	Source(s)			
	Human leptospirosis (n=16)										
1	Schneider et al. (2015)	Brazil	Confirmed human leptospirosis data (notification)	Sub-national	Hydrology, altitude	USGS-EROS HYDRO1k, Digital Elevation Model (DEM) Global 30-Arc Second Elevation (GTOPO30)	-	-	Temperature, rainfall	WorldClim	Altitude-slope interaction and precipitation showed to be significantly related to higher number of cases of leptospirosis in the univariate analysis. None of these variables has significant association with leptospirosis case count in the final model
2	Gracie et al. (2014)	Brazil	Suspected and confirmed human leptospirosis data (notification)	Sub-national	Land use, altitude	Landsat 7	-	-	-	-	Leptospirosis incidence rate was positively correlated with urban land-use.
3	Lau et al. (2016)	Fiji	Human Leptospira seroprevalence (MAT-based survey)	National	Land use/cover, elevation, soils, roads, hydrology	n.d			Temperature, rainfall	n.d	MAT seropositivity was associated with distance between home and the closest river or major creek (<100m) and maximum rainfall in the wettest month.
4	Lau et al. (2012a)	American Samoa	Human Leptospira seroprevalence (MAT-based survey)	National	Altitude, vegetation type, soil type	USGS-National Elevation Dataset (NED) (7.5-minute Digital Elevation Model (DEMs))	-	-	-	-	Living below the median altitude of a village (OR 1.58, 95%CI 1.00-2.49), living in clay loams soils (OR 2.72; 1.08-6.85), and agricultural areas (OR 2.09; 1.12-3.89) were associated with Leptospira seropositivity
5	Lau et al. (2012b)	American Samoa	Human Leptospira seroprevalence (MAT-based survey)	National	Altitude	USGS-National Elevation Dataset (NED) Digital Elevation Model	-	-	-	-	In univariate model, living below median altitude of a village was associated with Leptospira seropositivity (OR 1.53; 95%CI 1.03-2.28). Different environmental exposures were differently linked with each serovars infection

No.	Reference(s)	Study area	Leptospirosis data	Study scale	Environmental/Socioeconomic data retrieved from RS technology				Environmental data from other sources	Source(s)	Key findings
					Physical environmental/ climatic data	Source(s)	Socio-economic data	Source(s)			
6	Zhao et al. (2016)	China	Confirmed human leptospirosis data (notification)	National	Land cover, pig density	GlobCover Land Cover v2.3 (ENVISAT MERIS), Gridded Livestock of the World (FAO)	Population density	Gridded human population density data	Annual mean temperature, temperature seasonality, annual precipitation and precipitation seasonality	WorldClim	Based on Maxent model, annual mean temperature (Bio1) and annual total precipitation (Bio12) were the most influential factors driving the spatial distribution of human leptospirosis in China
7	Sunaryo & Widiastuti (2012)	Indonesia	Human leptospirosis cases (notification)	Sub-national	Land use	Quickbird	-	-	-	-	Leptospirosis cases were found in irregular settlement (e.g., high density with poor infrastructures and sanitation) and in low vegetation index (-0.38-0.095). Remote sensing can be used to identify environmental risk factors of leptospirosis.
8	Reis et al. (2008)	Brazil	Human Leptospira seroprevalence (MAT-based survey)	Sub-national	Topographic, location open sewage and rainwater drainage systems	Aerial photograph	-	-	-	-	The risk of acquiring *Leptospira* antibodies was associated with environmental conditions including living in flood-risk areas with open sewers (prevalence ratio [PR] 1.42, 95%CI 1.14–1.75) and near to accumulated waste (1.43, 1.04–1.88)
9	Hagan et al. (2016)	Brazil	Human Leptospira seroprevalence (MAT-based survey)	Sub-national	Elevation	Aerial photograph					Lower household elevation was an environmental risk factor for infection
10	Suwanpakdee et al. (2015a)	Thailand	Suspected and confirmed human leptospirosis	National	Flood coverage	RADARSAT-1, RADARSAT-2, COSMO-	-	-	-	-	Flooding was not a direct risk factor for leptospirosis incidence

No.	Reference(s)	Study area	Leptospirosis data	Study scale	Environmental/Socioeconomic data retrieved from RS technology				Environmental data from other sources	Source(s)	Key findings
					Physical environmental/ climatic data	Source(s)	Socio-economic data	Source(s)			
			data (notification)			SkyMed-4,THEOS					
11	Goncalves et al. (2016)	Brazil	Suspected and confirmed human leptospirosis data (notification)	Sub-national	Land use (canals), altitude	SPOT 5	-	-	-	-	The highest concentrations of the disease in the Guamá and Jurunas neighborhoods in lower lying areas near canals.
12	Vega-Corredor et al. (2014)	Trinidad Tobago	Confirmed human leptospirosis data (notification)	National	Wet Index (derived from upslome flow accumulation and topographic slope	Digital Elevation Model (DEM)	-	-	-	-	Rainfall, imperfect drainage soil and topographic wetness index affect the transmission of human leptospirosis
13	Mohammadinia et el. (2017)	Iran	Confirmed human leptospirosis data (medical records)	Sub-national	Elevation, slope, NDVI	Digital Elevation Model (DEM)-SRTM, MODIS	-	-	-	-	The adaptive kernel performed superior to a fixed one; Bisquare was selected as weighting function that concludes more reliable results in comparison to Gaussian; no clear conclusion on the effect of environmental variables on leptospirosis risks
14	Ledien et al. (2017)	Cambodia	Cohort survey	Sub-national	Near Infrared Red (NIR), NDVI, EVI, NDWI, NDII, MNDWI, altitude	MODIS Terra MOD09A1, DEM-SRTM	Population density	National census (100m spatial resolution)	-	-	MNDWI is good flooding risk indicator that can support early warning system for leptospirosis
15	Rahayu et al. (2018)	Indonesia	Notification data (case definition did not describe)	Sub-national	Land use, River, Road, contour, altitude, soil texture, flood history, tidal flood, vegetation, waste disposal, rainfall	Quickbird					Based on risk scoring approach, three types of vulnerable zones of leptospirosis transmission was identified in Demak. High-risk zone was characterized by dense housing close to river and paddy field.
16	Boquero et al. (2018)	Brazil	Notification	National					Soil moisture, precipitation, temperature	TerraClimate	Soil moisture, precipitation, poverty and the proportion of urban households associated with the spatiotemporal risk pattern of leptospirosis

No.	Reference(s)	Study area	Leptospirosis data	Study scale	Environmental/Socioeconomic data retrieved from RS technology				Environmental data from other sources	Source(s)	Key findings
					Physical environmental/ climatic data	Source(s)	Socio-economic data	Source(s)			
	Animal leptospirosis (n=9)										
1	Raghavan et al. (2011)	USA	PCR-tested canine leptospirosis data (notification)	National	Land cover/Land use	USGS NLCD 2001 Land Cover. Kansas Gap Analysis Program (GAP) (Landsat ETM+ and DEM)	-	-	-	-	Canine leptospirosis incidence in Kansas and Nebraska were higher in medium intensity developed urban areas.
2	Raghavan et al. (2013)	USA	PCR-tested canine leptospirosis data (notification)	National	Land cover/Land use	USGS NLCD 2001 Land Cover. Kansas Gap Analysis Program (GAP) (Landsat ETM+ and DEM)	-	-	-	-	Risk factors are varies as the spatial extents around case/control locations increased
3	Raghavan et al. (2012)	USA	PCR-tested canine leptospirosis data (notification)	National	Water-bodies features, strealm flowline, flood risk, wetland areas, soil-hydrologic (flooding and ponding frequency, drainage class of soils)	USGS National Hydrography Dataset (NHD), USDA Natural Resources Conservation Service (NRCS) Soil Survey Geographic database (Web Soil Survey), FWS National Wetland Inventory datasets	-	-	-	-	Infection in dogs caused by the proximity to water features, hydrologic density and regularly flooded areas within 2.5km of dog's homes
4	Ghneim et al. (2007)	USA	PCR-tested canine leptospirosis data (notification)	National	Land use, hydrological features	USGS NLCD 2001 Land Cover. Kansas Gap Analysis Program (GAP) (Landsat ETM+ and DEM), USGS National Hydrography Dataset (NHD)	-	-	-	-	At closer spatial range from the dogs' homes (radius ≤ 0.5 km) hydrographic density was positively associated with cases; while at larger distances (radius ≥ 5 km) leptospirosis cases were correlated with percent of wetlands or public open area

No.	Reference(s)	Study area	Leptospirosis data	Study scale	Environmental/Socioeconomic data retrieved from RS technology				Environmental data from other sources	Source(s)	Key findings
					Physical environmental/ climatic data	Source(s)	Socio-economic data	Source(s)			
5	Dobigny et al. (2015)	Niger	PCR-tested Leptospira-infected Norway rats	Sub-national	Land cover	SPOT satellite imagery	-	-	-	-	Suitable areas for Leptospira-carrying rodent species in Niamey clearly correspond to intra-city agricultural zones, especially those along the Niger River and the Gountou Yéna wadi
6	Ward et al. (2004)	USA	Canine leptospirosis diagnosed by MAT	Sub-national	Hydrological features, wetland, land use	USDA Natural Resources Conservation Service (NRCS) Soil Survey Geographic database (Web Soil Survey), FWS National Wetland Inventory datasets	-	-	-	-	Dogs in periurban areas are at greater risk of leptospirosis
7	White et al. (2017)	USA	Canine leptospirosis diagnosed by MAT	National	Land cover, precipitation and temperature	USGS NLCD 2011 Land Cover dataset, PRISM Spatial Climate dataset	-	-	-		The variation in canine leptospirosis risk in specific counties and regions of the USA appears to be mainly influenced by environmental (precipitation, temperature) and land use factors (deciduous forest, shrubland, scrubland, and low density developed land)
8	Ivanova et al. (2012)	Cambodia	Rodents and shrews infection tested by PCR	Sub-national	Land cover (NDVI), slope, elevation	SPOT 5 satellite imagery, SRTM-DEM	-	-	-	-	Rodents lived in low-slope locations, paddy fields, and near to to forested areas is likely to be infected
9	Silva et al. (2018)	Brazil	Dogs (seropositivity tested by MSA)	Sub-national	Land use	Landsat-7/ETM+	-	-	-	-	Higher seropositive dogs were found in the anthropized area and during wet season

n.d = not defined

Appendix C. Chapter 5 Supplementary information

Table C-1 Temporal distribution of reported leptospirosis incidence in four regions in China by province, 2005–2015

Region	Province	Number of reported cases (Cases per 100 000 population)											Total No of cases (% confirmed)*	Annual IR
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015		
A	Guangdong	65 (0.07)	69 (0.08)	64 (0.07)	83 (0.09)	60 (0.06)	59 (0.06)	59 (0.06)	43 (0.04)	53 (0.05)	30 (0.03)	34 (0.03)	619 (53)	0.06
	Guangxi	72 (0.15)	66 (0.14)	62 (0.13)	86 (0.18)	66 (0.14)	56 (0.12)	28 (0.06)	36 (0.08)	24 (0.05)	28 (0.06)	19 (0.04)	543 (40)	0.10
	Hainan	7 (0.08)	5 (0.06)	4 (0.05)	4 (0.05)	4 (0.05)	3 (0.03)	4 (0.05)	5 (0.06)	3 (0.03)	6 (0.07)	2 (0.02)	47 (11)	0.05
	Sub-total	144 (0.10)	140 (0.09)	130 (0.08)	173 (0.11)	130 (0.08)	118 (0.07)	91 (0.06)	84 (0.06)	80 (0.05)	64 (0.05)	55 (0.03)	1,209 (45)	0.07
B	Jiangsu	13 (0.02)	6 (0.01)	7 (0.01)	5 (0.01)	1 (0.00)	1 (0.00)	4 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	37 (54)	0.00
	Zhejiang	14 (0.03)	8 (0.02)	53 (0.11)	9 (0.02)	6 (0.01)	17 (0.03)	8 (0.01)	2 (0.00)	6 (0.01)	7 (0.01)	8 (0.01)	138 (43)	0.02
	Anhui	25 (0.04)	18 (0.03)	56 (0.09)	55 (0.09)	32 (0.05)	47 (0.08)	24 (0.04)	19 (0.03)	9 (0.01)	18 (0.03)	7 (0.01)	310 (8)	0.05
	Fujian	40 (0.11)	26 (0.07)	33 (0.09)	43 (0.12)	53 (0.15)	49 (0.13)	45 (0.12)	47 (0.12)	59 (0.16)	54 (0.14)	53 (0.14)	502 (47)	0.12
	Henan	0 (0.00)	3 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (0)	0.00
	Jiangxi	89 (0.21)	54 (0.13)	58 (0.13)	61 (0.14)	47 (0.11)	27 (0.06)	30 (0.07)	17 (0.04)	19 (0.04)	17 (0.04)	2 (0.00)	421 (5)	0.09
	Hubei	38 (0.07)	22 (0.04)	54 (0.09)	97 (0.17)	17 (0.03)	19 (0.03)	15 (0.03)	9 (0.02)	6 (0.01)	6 (0.01)	13 (0.02)	296 (11)	0.05
	Hunan	74 (0.12)	92 (0.15)	150 (0.24)	79 (0.12)	39 (0.06)	41 (0.06)	33 (0.05)	41 (0.06)	30 (0.05)	36 (0.05)	41 (0.06)	656 (16)	0.09
	Chongqing	56 (0.20)	13 (0.05)	20 (0.07)	28 (0.10)	24 (0.08)	13 (0.05)	8 (0.03)	10 (0.03)	7 (0.02)	6 (0.02)	15 (0.05)	200 (10)	0.06
	Sichuan	792 (0.96)	155 (0.19)	218 (0.27)	237 (0.29)	203 (0.25)	255 (0.31)	73 (0.09)	145 (0.18)	98 (0.12)	110 (0.14)	66 (0.08)	2352 (6)	0.26
	Guizhou	56 (0.15)	45 (0.12)	42 (0.11)	31 (0.08)	16 (0.04)	18 (0.05)	14 (0.04)	30 (0.09)	7 (0.02)	8 (0.02)	24 (0.07)	291 (12)	0.07
	Yunnan	114 (0.26)	130 (0.29)	135 (0.30)	109 (0.24)	87 (0.19)	109 (0.24)	77 (0.17)	82 (0.18)	110 (0.24)	226 (0.48)	129 (0.27)	1,308 (86)	0.26
	Sub-total	1,311 (0.18)	572 (0.09)	826 (0.13)	754 (0.12)	525 (0.08)	596 (0.09)	331 (0.05)	402 (0.06)	351 (0.06)	488 (0.08)	358 (0.06)	6,514 (28)	0.09
C	Beijing	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.01)	1 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (50)	0.00
	Shandong	1 (0.00)	2 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)	5 (0.01)	2 (0.00)	2 (0.00)	0 (0.00)	5 (0.01)	2 (0.00)	20 (65)	0.00
	Hebei	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)	1 (0.00)	3 (33)	0.00
	Shanxi	1 (0.00)	0 (0.00)	2 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (33)	0.00
	Inner Mongolia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100)	0.00
	Liaoning	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0)	0.00
	Jilin	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2(100)	0.00
	Shaanxi	0 (0.00)	0 (0.00)	1 (0.00)	0 (0.00)	2 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	4 (25)	0.00
	Sub-total	3 (0.00)	2 (0.00)	3 (0.00)	1 (0.00)	4 (0.00)	5 (0.00)	5 (0.00)	3 (0.00)	1 (0.00)	6 (0.00)	3 (0.00)	36 (55)	0.00
D	Gansu	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)	0 (0.00)	1 (100)	0.00
	Qinghai	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0)	0.00
	Xinjiang	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0)	0.00
	Sub-total	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)	0 (0.00)	1 (0.00)	0 (0.00)	4 (25)	0.00
Morbidity		1,458 (0.11)	714 (0.05)	959 (0.07)	930 (0.07)	659 (0.05)	719 (0.05)	427 (0.03)	490 (0.04)	432 (0.03)	559 (0.04)	416 (0.03)	7,763 (31)	0.05

* number of cases; per cent of reported laboratory-confirmed cases (in parenthesis)

Table C-2 Reported leptospirosis cases and confirmed cases (in per cent) by type of occupation, China, 2005–2015

Occupation	No. of reported cases (% confirmed cases)											Total (% confirmed cases)
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	
Farmer	1119 (7.5)	500 (28.2)	721 (24.5)	725 (21.8)	527 (23)	571 (26.6)	312 (36.2)	387 (31.5)	311 (49.2)	460 (55)	304 (54.3)	5937 (27.6)
Cadre	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (60)	3 (100)	8 (75)
Commercial service	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (87.5)	14 (85.7)	23 (87)
Fisherman	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (66.7)	1 (100)	4 (75)
Herdsman	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	0 (0.0)	2 (0.0)
Seaman	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	1 (100)
Medical/Nurse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)	2 (100)	4 (100)
Teacher/Student	246 (6.9)	115 (17.4)	135 (14.8)	99 (26.3)	76 (17.1)	48 (33.3)	29 (13.8)	28 (17.9)	16 (50)	17 (70.6)	17 (35.3)	826 (17.8)
Retiree	8 (0.0)	11 (54.5)	14 (57.1)	8 (62.5)	4 (50)	7 (71.4)	5 (100)	12 (66.7)	17 (70.6)	3 (66.7)	9 (66.7)	98 (60.2)
Other	82 (23.2)	88 (67)	81 (72.8)	89 (61.8)	46 (45.7)	89 (62.9)	73 (74)	63 (77.8)	90 (71.1)	51 (72.5)	57 (64.9)	809 (63)
Not working	10 (0.0)	2 (0.0)	7 (42.9)	8 (50)	6 (33.3)	3 (0.0)	4 (50)	1 (0.0)	2 (0.0)	4 (50)	4 (25)	51 (27.5)
TOTAL	1465 (8.2)	717 (31.7)	958 (27.9)	929 (26.8)	659 (24)	718 (31.9)	423 (42.1)	491 (37.4)	436 (54.3)	556 (57.7)	411 (56.7)	7763 (31)

Table C-3 Case fatality-rates (CFR) of leptospirosis across two regions in China, 2005–2015

Region	Province	Case fatality-rates (%)											Annual CFR	95% CI	
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015		Lower	Upper
A	Guangdong	4.69	2.99	6.06	5.95	1.69	0.00	1.75	0.00	1.92	0.00	0.00	2.28	0.88	3.67
	Guangxi	12.50	0.08	0.06	0.02	0.04	0.02	0.00	0.03	0.00	0.04	0.00	1.16	-1.06	3.38
	Hainan	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	CFR by region	8.39	5.15	6.02	4.07	3.05	0.83	1.12	1.16	1.27	1.56	0.00	2.97	1.41	4.52
B	Jiangsu	0.00	0.00	14.29	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.30	-1.25	3.84
	Zhejiang	14.29	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.14	0.00	1.31	-1.23	3.85
	Anhui	4.00	5.56	1.79	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.03	-0.13	2.19
	Fujian	0.00	0.00	0.00	4.55	1.89	0.00	0.00	0.00	1.69	0.00	0.00	0.74	-0.12	1.60
	Jiangxi	3.37	1.85	5.17	1.64	2.13	3.70	0.00	0.00	0.00	0.00	0.00	1.62	0.54	2.71
	Henan	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Hubei	10.53	4.55	1.85	2.06	5.88	0.00	0.00	0.00	0.00	0.00	7.69	2.96	0.78	5.14
	Hunan	8.11	3.26	7.33	2.53	2.56	2.44	3.03	4.88	0.00	0.00	0.00	3.10	1.47	4.73
	Chongqing	5.36	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.49	-0.47	1.44
	Sichuan	0.76	0.00	0.92	1.27	1.48	3.14	2.74	0.00	0.00	1.85	0.00	1.10	0.44	1.77
	Guizhou	17.86	11.11	23.81	6.45	6.67	0.00	7.14	6.67	42.86	25.00	0.00	13.41	5.77	21.06
	Yunnan	0.88	0.77	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.15	-0.05	0.35
	CFR by region	2.75	2.11	3.51	1.59	1.53	1.68	1.21	0.99	1.14	1.04	0.27	1.62	1.09	2.15

Note: No death cases reported from region C and D.

Table C-4 Temporal distribution of leptospirosis mortality in two regions in China, by province, 2005–2015

Region	Province	Number of reported death (per 100,000 population)											Total	Annual Mortality Rate
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015		
A	Guangdong	3 (0.03)	2 (0.02)	4 (0.04)	5 (0.05)	1 (0.00)	0 (0.00)	1 (0.01)	0 (0.00)	1 (0.01)	0 (0.00)	0 (0.00)	17	0.01
	Guangxi	9 (0.19)	5 (0.11)	4 (0.08)	2 (0.04)	3 (0.06)	1 (0.02)	0 (0.00)	1 (0.02)	0 (0.00)	1 (0.00)	0 (0.00)	26	0.05
	Total	12 (0.08)	7 (0.05)	8 (0.05)	7 (0.03)	4 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	0 (0.00)	43	0.02
B	Jiangsu	0 (0.00)	0 (0.00)	1 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1	0.001
	Zhejiang	2 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.02)	0 (0.00)	3	0.005
	Anhui	1 (0.02)	1 (0.02)	1 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3	0.005
	Fujian	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.05)	1 (0.03)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.03)	0 (0.00)	0 (0.00)	4	0.01
	Jiangxi	3 (0.07)	1 (0.02)	3 (0.07)	1 (0.02)	1 (0.02)	1 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	10	0.02
	Hubei	4 (0.07)	1 (0.02)	1 (0.02)	2 (0.03)	1 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.02)	10	0.02
	Hunan	6 (0.09)	3 (0.04)	11 (0.16)	2 (0.03)	1 (0.01)	1 (0.01)	1 (0.01)	2 (0.03)	0 (0.00)	0 (0.00)	0 (0.00)	27	0.04
	Chongqing	3 (0.10)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3	0.01
	Sichuan	6 (0.07)	0 (0.00)	2 (0.02)	3 (0.04)	3 (0.04)	8 (0.10)	2 (0.02)	0 (0.00)	0 (0.00)	2 (0.02)	0 (0.00)	26	0.03
	Guizhou	10 (0.29)	5 (0.14)	10 (0.29)	2 (0.03)	1 (0.03)	0 (0.00)	1 (0.03)	2 (0.06)	3 (0.09)	2 (0.06)	0 (0.00)	36	0.09
	Yunnan	2 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2	0.004
	Total	37 (0.06)	11 (0.02)	29 (0.05)	12 (0.01)	8 (0.01)	10 (0.02)	4 (0.01)	4 (0.00)	4 (0.01)	5 (0.01)	1 (0.00)	125	0.02
National Mortality		**49 (0.004)**	**18 (0.001)**	**37 (0.003)**	**19 (0.002)**	**12 (0.001)**	**11 (0.001)**	**5 (0.00)**	**5 (0.00)**	**5 (0.00)**	**6 (0.00)**	**1 (0.00)**	**168**	**0.001**

Note: No death cases reported from region C and D

Table C-5 Reported deaths due to leptospirosis based on case classification in China, 2005–2015

Case classification	Number of reported deaths											TOTAL
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	
Suspected	4	3	4	1	1	0	0	0	0	0	0	13
Clinically-diagnosed	40	12	31	16	10	10	3	3	2	4	0	131
Confirmed	5	3	2	2	1	1	2	2	3	2	1	24
TOTAL	**49**	**18**	**37**	**19**	**12**	**11**	**5**	**5**	**5**	**6**	**1**	**168**

Table C-6 Number of counties in China that reported leptospirosis each year and new counties that reported leptospirosis during 2005–2010 and 2011–2015

Region	Province	No. of counties that reported											t	P value*	No. of new counties	
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015			2005-2010	2011-2015
A	Guangdong	29	32	37	46	33	40	31	27	31	23	25	2.792	.021	31	11
	Guangxi	35	38	39	37	35	32	20	26	16	22	15	7.557	.000	38	7
	Hainan	5	4	4	3	3	1	4	5	3	4	1	-.077	.941	5	4
	Total	69	74	80	86	71	73	55	58	50	49	41			74	22
B	Jiangsu	9	6	7	5	1	1	4	0	0	0	0	2.467	.036	21	2
	Zhejiang	8	6	11	7	6	11	6	2	4	7	7	2.176	.058	14	5
	Anhui	8	8	10	11	8	9	9	6	5	8	6	2.514	.033	16	5
	Fujian	18	17	19	24	15	23	20	16	29	24	26	-1.413	.191	13	8
	Jiangxi	24	21	27	22	23	13	16	10	12	8	2	4.044	.003	24	5
	Henan	0	3	0	0	0	0	0	0	0	0	0	.905	.389	3	0
	Hubei	15	11	13	13	9	6	8	6	3	2	6	3.485	.007	18	2
	Hunan	29	40	49	32	23	28	18	23	17	18	21	3.220	.010	40	16
	Chongqing	20	10	9	13	11	10	6	7	5	6	4	3.467	.007	16	5
	Sichuan	69	43	46	40	34	38	20	28	26	30	27	3.228	.010	37	9
	Guizhou	23	15	16	14	8	14	7	13	5	5	11	2.593	.029	20	6
	Yunnan	12	9	9	8	9	8	8	8	8	14	11	-.498	.630	12	12
	Total	235	189	216	189	147	161	122	119	114	122	121			234	75
C	Beijing	0	0	0	1	1	0	0	0	0	0	0	1.430	.186	2	0
	Hebei	0	0	0	0	0	0	1	0	0	1	1	-2.714	.024	0	3
	Shanxi	1	0	2	0	0	0	0	0	0	0	0	1.324	.218	3	0
	Inner Mongolia	0	0	0	0	0	0	0	1	0	0	0	-1.108	.297	0	1
	Liaoning	1	0	0	0	0	0	0	0	0	0	0	.905	.389	1	0
	Jilin	0	0	0	0	0	0	2	0	0	0	0	-1.108	.297	0	2
	Shaanxi	0	0	1	0	2	0	0	0	1	0	0	.717	.492	3	1
	Shandong	1	2	0	0	1	5	2	1	0	0	0	.980	.353	5	6
	Total	3	2	3	1	4	5	5	2	1	1	1			14	13
D	Gansu	0	0	0	0	0	0	0	0	0	1	0	-1.108	.297	0	1
	Qinghai	0	0	0	1	0	0	0	0	0	0	0	.905	.389	1	0
	Xinjiang	0	0	0	1	0	0	0	1	0	0	0	-.129	.900	1	1
	Total	0	0	0	2	0	0	0	1	0	1	0			2	2
TOTAL (all region)		307	265	299	278	222	239	182	180	165	173	163	6.206	.000	324	112

*test of average number of counties reported between two periods: 2005–2010 and 2011–2015

Table C-7 Disability-adjusted life-years (DALYs) estimates of leptospirosis in China, by sex, age, and year

Characteristics		DALYs estimate											Total	Annual DALY
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015		
Female	0-9	0.71	1.90	81.92	0.71	1.42	0.47	0.47	0.00	0.00	0.71	0.47	88.81	8.07
	10-19	157.45	220.72	440.97	71.73	75.66	2.85	1.19	143.13	0.71	1.42	1.66	1,117.51	101.59
	20-29	192.84	201.93	72.57	68.89	67.94	3.56	3.09	3.32	3.80	8.55	3.32	629.83	57.26
	30-39	185.59	11.87	66.89	61.46	9.26	9.02	4.99	4.75	5.70	7.60	6.89	374.03	34.00
	40-49	21.14	10.69	107.78	58.51	88.92	53.25	9.26	10.45	10.45	9.97	7.12	387.55	35.23
	50-59	153.33	9.50	82.86	51.35	12.11	14.49	6.65	41.91	8.31	9.97	6.41	396.90	36.08
	60-69	29.42	3.09	4.51	6.41	25.47	36.65	4.27	5.46	5.22	7.84	4.27	132.63	12.06
	70-79	0.47	0.71	1.19	2.14	18.23	1.66	1.42	2.14	1.66	2.61	1.19	33.43	3.04
	80-89	0.00	0.00	0.24	0.47	0.00	0.00	0.00	0.24	0.47	0.47	0.47	2.37	0.22
	90+	0.00	0.00	0.24	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.24	0.47	0.04
	Total	740.96	460.41	859.17	321.69	299.03	121.96	31.35	211.41	36.34	49.16	32.06	3,163.54	287.59
Male	0-9	90.09	4.75	83.30	82.11	2.85	1.90	1.42	0.95	1.19	0.71	0.24	269.51	24.50
	10-19	839.13	306.58	377.76	94.99	16.15	9.50	153.83	75.30	78.93	4.27	3.56	1,960.01	178.18
	20-29	587.81	142.38	149.34	22.80	185.79	69.59	6.41	66.27	124.47	70.51	7.36	1,432.75	130.25
	30-39	261.28	75.65	276.79	181.31	17.34	22.09	10.69	11.16	6.89	167.17	8.07	1,038.44	94.40
	40-49	206.24	62.27	189.03	67.50	62.04	26.12	92.72	19.47	14.72	63.46	57.04	860.63	78.24
	50-59	172.58	121.69	229.99	133.90	56.36	117.17	17.34	14.25	13.54	46.75	16.15	939.71	85.43
	60-69	64.25	35.31	40.92	85.95	40.86	141.29	31.01	14.49	66.11	12.11	15.44	547.75	49.80
	70-79	3.32	20.76	4.27	39.17	3.56	4.75	3.32	5.46	3.80	2.61	4.75	95.80	8.71
	80-89	0.24	0.00	1.19	0.47	0.24	0.00	0.71	0.47	0.47	0.71	0.24	4.75	0.43
	90+	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.24	0.00	0.00	0.24	0.02
	Total	2,224.94	769.39	1352.60	708.21	385.19	392.42	317.47	207.83	310.37	368.33	112.85	7,149.59	649.96
DALYs (both sexes)		2,965.90	1,229.80	2,211.77	1,029.91	684.22	514.37	348.82	419.24	346.71	417.49	144.91	10,313.13	937.56

Table C-8 Years of life lost (YLL) estimates for leptospirosis in China, by sex, age, and year

Characteristics		YLLs											Total	Annual YLLs
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015		
Female	0-9	0.00	0.00	79.31	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	79.31	7.21
	10-19	143.68	215.02	435.03	69.36	72.34	0.00	0.00	141.71	0.00	0.00	0.00	1,077.14	97.92
	20-29	177.40	196.23	66.40	63.43	63.43	0.00	0.00	0.00	0.00	0.00	0.00	566.89	51.54
	30-39	155.90	0.00	52.17	48.64	0.00	0.00	0.00	0.00	0.00	0.00	0.00	256.71	23.34
	40-49	0.00	0.00	88.54	43.79	80.85	41.85	0.00	0.00	0.00	0.00	0.00	255.03	23.18
	50-59	138.13	0.00	68.61	37.10	0.00	0.00	0.00	33.36	0.00	0.00	0.00	277.20	25.20
	60-69	25.15	0.00	0.00	0.00	20.72	27.86	0.00	0.00	0.00	0.00	0.00	73.73	6.70
	70-79	0.00	0.00	0.00	0.00	17.28	0.00	0.00	0.00	0.00	0.00	0.00	17.28	1.57
	80-89	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	90+	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Total	640.26	411.25	790.06	262.32	254.62	69.71	0.00	175.07	0.00	0.00	0.00	2,603.29	236.66
Male	0-9	81.30	0.00	78.31	78.31	0.00	0.00	0.00	0.00	0.00	0.00	0.00	237.92	21.63
	10-19	788.78	286.39	353.77	74.33	0.00	0.00	147.66	69.36	76.32	0.00	0.00	1,796.61	163.33
	20-29	550.05	128.84	130.82	0.00	174.63	58.67	0.00	58.67	117.35	62.44	0.00	1,281.47	116.50
	30-39	210.22	54.51	251.62	153.76	0.00	0.00	0.00	0.00	0.00	154.35	0.00	824.46	74.95
	40-49	174.18	39.95	161.72	39.95	40.90	0.00	78.95	0.00	0.00	39.95	44.69	620.29	56.39
	50-59	138.14	101.03	197.45	99.23	36.17	92.71	0.00	0.00	0.00	30.60	0.00	695.33	63.21
	60-69	48.58	26.05	27.86	70.99	24.24	124.90	22.46	0.00	52.10	0.00	0.00	397.18	36.11
	70-79	0.00	18.15	0.00	34.66	0.00	0.00	0.00	0.00	0.00	0.00	0.00	52.81	4.80
	80-89	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	90+	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Total	1991.25	654.92	1201.55	551.23	275.94	276.28	249.07	128.03	245.77	287.34	44.69	5,906.07	536.92
YLLs (both sexes)		2,631.51	1,066.17	1,991.61	813.55	530.56	345.99	249.07	303.10	245.77	287.34	44.69	8,509.36	773.58

Table C-9 Years of life lost (YLLs) estimates for leptospirosis in China, by region, sex, and age group during both periods, 2005–2010 and 2011-2015

Region	Age group	2005–2010			2011–2015			2005–2015		
		Males	Females	Both sexes	Males	Females	Both sexes	Males	Females	Both sexes
A	0-9	0	0	0	0	0	0	0	0	0
	10-19	74.33	215.02	289.35	0	68.38	68.38	74.33	283.4	357.73
	20-29	484.64	123.68	608.32	61.45	0	61.45	546.09	123.68	669.77
	30-39	150.23	53.34	203.57	52.17	0	52.17	202.4	53.34	255.74
	40-49	248.32	126.54	374.86	0	0	0	248.32	126.54	374.86
	50-59	243.82	37.1	280.92	0	0	0	243.82	37.1	280.92
	60-69	21.6	0	21.6	22.46	0	22.46	44.06	0	44.06
	70-79	52.81	0	52.81	0	0	0	52.81	0	52.81
	80-89	0	0	0	0	0	0	0	0	0
	90+	0	0	0	0	0	0	0	0	0
	Total	1,275.75	555.68	1,831.43	136.08	68.38	204.46	1,411.83	624.06	2,035.89
B	0-9	237.92	79.31	317.23	0	0	0	237.92	79.31	317.23
	10-19	1,428.94	720.41	2,149.35	293.34	73.33	366.67	1,722.28	793.74	2,516.02
	20-29	558.37	443.21	1,001.58	118.34	58.67	177.01	676.71	501.88	1,178.59
	30-39	519.88	203.37	723.25	102.18	0	102.18	622.06	203.37	825.43
	40-49	208.38	128.49	336.87	163.59	0	163.59	371.97	128.49	500.46
	50-59	420.91	206.74	627.65	30.6	33.36	63.96	451.51	240.1	691.61
	60-69	301.02	73.73	374.75	52.1	0	52.1	353.12	73.73	426.85
	70-79	0	17.28	17.28	0	0	0	0	17.28	17.28
	80-89	0	0	0	0	0	0	0	0	0
	90+	0	0	0	0	0	0	0	0	0
	Total	3,675.42	1,872.54	5,547.96	760.15	165.36	925.51	4,435.57	2,037.9	6,473.47
Total (A+B)		**4,951.17**	**2,428.22**	**7,379.39**	**896.23**	**233.74**	**1,129.97**	**5,847.4**	**2,661.96**	**8,509.36**

Table C-10 Years-lived with disability (YLD) estimates for leptospirosis in China, by sex, age, and year

Characteristics		YLDs											Total	Annual YLDs
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015		
Female	0-9	0.71	1.90	2.61	0.71	1.42	0.47	0.47	0.00	0.00	0.71	0.47	9.50	0.86
	10-19	13.77	5.70	5.94	2.37	3.32	2.85	1.19	1.42	0.71	1.42	1.66	40.37	3.67
	20-29	15.44	5.70	6.17	5.46	4.51	3.56	3.09	3.32	3.80	8.55	3.32	62.94	5.72
	30-39	29.69	11.87	14.72	12.82	9.26	9.02	4.99	4.75	5.70	7.60	6.89	117.32	10.67
	40-49	21.14	10.69	19.24	14.72	8.07	11.40	9.26	10.45	10.45	9.97	7.12	132.52	12.05
	50-59	15.20	9.50	14.25	14.25	12.11	14.49	6.65	8.55	8.31	9.97	6.41	119.70	10.88
	60-69	4.27	3.09	4.51	6.41	4.75	8.79	4.27	5.46	5.22	7.84	4.27	58.90	5.35
	70-79	0.47	0.71	1.19	2.14	0.95	1.66	1.42	2.14	1.66	2.61	1.19	16.15	1.47
	80-89	0.00	0.00	0.24	0.47	0.00	0.00	0.00	0.24	0.47	0.47	0.47	2.37	0.22
	90+	0.00	0.00	0.24	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.24	0.47	0.04
	Total	100.70	49.16	69.11	59.37	44.41	52.25	31.35	36.34	36.34	49.16	32.06	560.25	50.93
Male	0-9	8.79	4.75	4.99	3.80	2.85	1.90	1.42	0.95	1.19	0.71	0.24	31.59	2.87
	10-19	50.35	20.19	23.99	20.66	16.15	9.50	6.17	5.94	2.61	4.27	3.56	163.40	14.85
	20-29	37.76	13.54	18.52	22.80	11.16	10.92	6.41	7.60	7.12	8.07	7.36	151.28	13.75
	30-39	51.06	21.14	25.17	27.55	17.34	22.09	10.69	11.16	6.89	12.82	8.07	213.98	19.45
	40-49	32.06	22.32	27.31	27.55	21.14	26.12	13.77	19.47	14.72	23.51	12.35	240.34	21.85
	50-59	34.44	20.66	32.54	34.67	20.19	24.46	17.34	14.25	13.54	16.15	16.15	244.38	22.22
	60-69	15.67	9.26	13.06	14.96	16.62	16.39	8.55	14.49	14.01	12.11	15.44	150.57	13.69
	70-79	3.32	2.61	4.27	4.51	3.56	4.75	3.32	5.46	3.80	2.61	4.75	42.99	3.91
	80-89	0.24	0.00	1.19	0.47	0.24	0.00	0.71	0.47	0.47	0.71	0.24	4.75	0.43
	90+	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.24	0.00	0.00	0.24	0.02
	Total	233.69	114.47	151.05	156.98	109.25	116.14	68.40	79.80	64.60	80.99	68.16	1,243.52	113.05
YLDs (both sexes)		334.39	163.63	220.16	216.36	153.66	168.38	99.75	116.14	100.94	130.15	100.22	1,803.77	163.98

Table C-11 Geographical distribution of YLD, YLL, and DALY estimates during both periods in China, 2005–2010 and 2011–2015

	YLD		TOTAL YLD (2005-2015)	%change	YLL		Total YLL (2005-2015)	%change	DALY		Total DALY (2005-2015)	%change
	2005-2010	2011-2015			2005-2010	2011-2015			2005-2010	2011-2015		
Region A												
Guangdong	91.44	51.54	142.97	-43.64	629.51	83.91	713.42	-86.7	720.95	135.45	856.39	-81.21
Guangxi	91.20	31.59	122.78	-65.36	1201.92	120.55	1,322.47	-90.0	1,293.12	152.14	1,445.25	-88.23
Hainan	6.41	4.75	11.16	-25.90	0	0	0.00	0.0	6.41	4.75	11.16	-25.90
Total	189.04	87.87	276.92	-53.52	1831.43	204.46	2,035.89	-88.8	2,020.47	292.33	2,312.81	-85.53
Region B												
Jiangsu	7.60	0.95	8.55	-87.50	30.60	0	30.60	-100.0	38.20	0.95	39.15	-97.51
Zhejiang	24.94	7.12	32.06	-71.43	69.53	30.60	100.13	-56.0	94.47	37.72	132.19	-60.07
Anhui	54.62	18.29	72.91	-66.52	168.19	0	168.19	-100.0	222.81	18.29	241.10	-91.79
Fujian	56.76	61.51	118.27	8.37	106.46	26.05	132.51	-75.5	163.22	87.56	250.78	-46.35
Jiangxi	77.42	20.19	97.61	-73.93	487.59	0	487.59	-100.0	565.01	20.19	585.20	-96.43
Henan	0.71	0.00	0.71	-100.00	0.00	0.00	0.00	0.0	0.71	0.00	0.71	-100.00
Hubei	56.52	11.40	67.92	-79.83	387.76	44.69	432.45	-88.5	444.28	56.09	500.37	-87.38
Hunan	107.11	42.27	149.38	-60.53	1,239.91	131.98	1,371.89	-89.4	1,347.02	174.25	1,521.27	-87.06
Chongqing	35.86	10.92	46.79	-69.54	148.15	0.00	148.15	-100.0	184.01	10.92	194.94	-94.06
Sichuan	436.52	115.90	552.41	-73.45	900.02	213.52	1,113.54	-76.3	1,336.54	329.42	1,665.95	-75.35
Guizhou	42.75	17.81	60.56	-58.33	1,893.39	478.67	2,372.06	-74.7	1,936.14	496.48	2,432.62	-74.36
Yunnan	161.97	148.20	310.17	-8.50	116.36	0.00	116.36	-100.0	278.33	148.20	426.53	-46.76
Total	1,062.79	454.57	1,517.36	-57.23	5,547.96	925.51	6,473.47	-83.3	6,610.75	1,380.08	7,990.83	-79.12
Region C												
Beijing	0.47	0.00	0.47	-100.00	0	0	0.00	0	0.47	0.00	0.47	-100.00
Hebei	0.00	0.71	0.71	71.25	0	0	0.00	0	0.00	0.71	0.71	71.25
Shanxi	0.71	0.00	0.71	-100.00	0	0	0.00	0	0.71	0.00	0.71	-100.00
Inner Mongolia	0.00	0.24	0.24	24.00	0	0	0.00	0	0.00	0.24	0.24	24.00
Liaoning	0.24	0.00	0.24	-100.00	0	0	0.00	0	0.24	0.00	0.24	-100.00
Shandong	2.14	2.61	4.75	22.22	0	0	0.00	0	2.14	2.61	4.75	22.22
Jilin	0.00	0.47	0.47	47.50	0	0	0.00	0	0.00	0.47	0.47	47.50
Shaanxi	0.71	0.24	0.95	-66.67	0	0	0.00	0	0.71	0.24	0.95	-66.67
Total	4.27	4.28	8.55	0.06	0	0	0.00	0	4.27	4.28	8.55	0.06
Region D												
Gansu	0.00	0.24	0.24	23.75	0	0	0.00	0	0.00	0.24	0.24	23.75
Qinghai	0.24	0.00	0.24	-100.00	0	0	0.00	0	0.24	0.00	0.24	-100.00
Xinjiang	0.24	0.24	0.47	0.00	0	0	0.00	0	0.24	0.24	0.47	0.00
Total	0.47	0.47	0.95	0.00	0	0	0.00	0	0.47	0.47	0.95	0.00
TOTAL (A+B+C+D)	1,256.58	547.19	1,803.77	-56.45	7,379.39	1,129.97	8,509.36	-84.7	8,635.97	1,677.16	10,313.13	-80.58

Appendix D. Chapter 6 Supplementary Information

Table D-1 Yearly notified human leptospirosis cases, proportion of laboratory confirmed cases and number of counties that reported, 2005-2016

Year	No. of cases (n=8158)	Incidence rate (1/100,000)	% confirmed cases	No. of counties reported
2005	1465	0.11	8.2	307
2006	717	0.05	31.7	265
2007	958	0.07	27.9	299
2008	929	0.07	26.8	278
2009	659	0.05	24	222
2010	718	0.05	31.9	239
2011	423	0.03	42.1	182
2012	491	0.04	37.4	180
2013	436	0.03	54.3	165
2014	556	0.04	57.7	173
2015	411	0.03	56.7	163
2016	395	0.03	58.2	171

Appendix E. Chapter 7 Supplementary information

Table E-1. Data used in the study

Data	Description	Sources
Epidemiological data		
Human leptospirosis case in Upper Yangtze River Basin (UYRB) and Pearl River Basin (PRB)	Notification data (2005–2016) containing information on age, gender, code of county, county's coordinates, case classification (suspected, probable, confirmed).	China Center for Disease Control and Prevention
Environmental variables		
Precipitation	Gridded precipitation data (1-km x 1-km). Values were sampled at county-level using ArcGIS software.	WorldClim (https://www.worldclim.org/)
Land surface temperature (LST)	Raster data with 1-km spatial resolution. Monthly LST for each county for period of 2005–2016 is sampled using ArcGIS software. Values were sampled at county-level using ArcGIS software.	MODIS Terra, MODIS11A2 8-day, 1 km spatial resolution (https://modis.gsfc.nasa.gov/data/dataprod/mod11.php)
Normalized difference vegetation index (NDVI)	Monthly NDVI value for each county for period of 2005–2016 were sampled using ArcGIS software. The NDVI value ranges from -1 to 1.	MODIS Terra 13Q1 v006 Vegetation Indices 16-Day L3 Global, 250 meter spatial resolution (https://lpdaac.usgs.gov/products/mod13q1v006/)
Normalized difference water Index (NDWI)	Monthly NDWI value for each county for period of 2005–2016 were sampled using ArcGIS software. MNDWI calculated by using formula $(R_{GREEN}-R_{SWIR)} / (R_{GREEN} + R_{SWIR})$. The value of the index ranges from -1 to 1.	MODIS Terra MOD09A1.V6 8-day, 500 m spatial resolution (https://modis.gsfc.nasa.gov/data/dataprod/mod09.php)
Elevation	GTOPO30 Digital elevation model (DEM), 1-km (30-arc seconds) spatial resolution. Values are sample at county level using ArcGIS software	https://www.usgs.gov/centers/eros/science/usgs-eros-archive-digital-elevation-global-30-arc-second-elevation-gtopo30?qt-science_center_objects=0#qt-science_center_objects

Data	Description	Sources
Slope	Slope was calculated from the SRTM-DEM elevation data by using ArcGIS toolbox. The mean slope values for each county were sampled.	
Land cover	Land cover types for 2005 and 2015. Reclassified into 6 categories: cultivated land (1), forested land (2), grassland (3), waterbodies (4), artificial surfaces (5), and bare land	Data Center for Resources and Environmental Sciences, Chinese Academy of Sciences (RESDC) (http://www.resdc.cn/)
Hydrological features	Yangtze River Basin and Pearl River Basin boundaries and streams	HYDRO1k - USGS https://gcmd.nasa.gov/records/GCMD_HYDRO1k.html; World Bank. Major River Basins of the World https://datacatalog.worldbank.org/dataset/major-river-basins-world Gassert, F., T. Luo, T. Shiao, and M. Luck. 2013. "Yangtze River Basin Study." Working Paper. Washington, DC: World Resources Institute. https://www.wri.org/resources/data-sets/yangtze-river-basin-study
Livestock density (Pig and Cattle density)	Gridded pigs and cattle density with year of reference is 2010. Cell resolution 0.00833 (1-km x 1-km). Values are sample at county level using ArcGIS software.	FAO-GeoNetwork model of livestock density (GLW 2.01) (http://www.fao.org/geonetwork/srv/en/main.home)
Urban/rural	Raster data for urban or rural classification with a 5x5 km resolution.	A 5x5 km resolution rural/urban surface derived from the Global Rural-Urban Mapping Project (GRUMP), (http://sedac.ciesin.columbia.edu/data/set/grump-v1-urban-extents).
Socioeconomic variables		
Population	Annual population data by county (2005–2015) for incidence estimation. For spatial modelling, raster (gridded) population data (in people per hectare) of 2010 and 2015 for China at the resolution of 100 m were used.	China National Bureau of Statistics (http://www.stats.gov.cn/english/) WorldPop database (https://www.worldpop.org/project/categories?id=3).

Data	Description	Sources
Population density	Gridded (raster) population density map with 1-km spatial resolution based on UN WPP-Adjusted Population Density, v4.10 (2010, 2015)	Socioeconomic data and application centers (SEDAC) – Center for International Health Science Information Network (CIESIN) (http://sedac.ciesin.columbia.edu/data/set/gpw-v4-population-density-adjusted-to-2015-unwpp-country-totals-rev10/data-download)
Farmland/crop production	Raster data for crop production 2010 (in kg per ha) with 1-km spatial resolution. Values were sampled at county-level using ArcGIS software.	Resource and Environmental Science Data Center of the Chinese Academy of Sciences (http://www.resdc.cn)
Gross Domestic Product (GDP)	Raster map of 2010 Gross Domestic Product (GDP) of China with 1-km resolution. Values are sampled at county-level using ArcGIS software.	Global change research data publishing and repository (http://www.geodoi.ac.cn/weben/doi.aspx?Id=125)

Table E-2. Quarterly leptospirosis notifications in Upper Yangtze River Basin (UYRB) and Pearl River Basin (PRB), 2005–2010 and 2011–2016

Region	Characteristics		2005–2010						2011–2016				
			Q1	Q2	Q3	Q4	Total		Q1	Q2	Q3	Q4	Total
UYRB	Sex	Female	0	12	695	64	771		2	9	186	28	225
		Male	3	44	1510	166	1723		2	20	411	65	498
	Age group	Under 19 years	0	7	399	34	440		0	1	44	2	47
		≥ 19 years	3	49	1806	196	2054		4	28	553	91	676
	Occup	Non-farmer	0	13	380	36	429		3	5	67	9	84
		Farmer	3	43	1825	194	2065		1	24	530	84	639
	Total		**3**	**56**	**2205**	**230**	**2494**		**4**	**29**	**597**	**93**	**723**
PRB	gender	Female	18	58	150	52	278		10	39	62	31	142
		Male	46	140	355	98	639		29	68	206	111	414
	Age group	Under 19 years	6	30	109	18	163		0	13	39	6	58
		≥ 19 years	58	168	396	132	754		39	94	229	136	498
	Occup	Non-farmer	37	83	168	54	342		21	46	100	51	218
		Farmer	27	115	337	96	575		18	61	168	91	338
	Total		**64**	**198**	**505**	**150**	**917**		**39**	**107**	**268**	**142**	**556**

Abbreviations: URYB, Upper Yangtze River Basin; PRB, Pearl River Basin; Q, quarter.

Table E-3. Spearman's correlation between covariates, Upper Yangtze River Basin (UYRB)

	Prec	NDVI	MNDWI	LST	Elev	Slope	Landcov	Cattle	Pig	Urban	Crop	Pop	GDP
Precipitation	1												
NDVI	0.06	1											
MNDWI	0.26	-0.62	1										
LST	-0.48	0.04	-0.65	1									
Elevation	-0.28	0.51	-0.65	0.29	1								
Slope	-0.22	0.47	-0.43	0.11	**0.88***	1							
Land cover	-0.02	0.32	-0.38	0.09	0.71	0.62	1						
Cattle density	-0.23	0.10	0.17	-0.28	-0.10	-0.07	-0.13	1					
Pig density	0.12	-0.42	0.46	-0.22	-0.77	**-0.81***	-0.66	0.20	1				
Urban/Rural	0.03	0.41	-0.12	0.03	0.04	0.03	-0.26	0.04	0.06	1			
Crop production	0.11	-0.60	0.39	0.12	-0.70	-0.75	-0.63	-0.31	0.65	0.06	1		
Population density	0.005	-0.57	0.28	-0.07	-0.22	-0.21	0.10	0.009	0.12	**-0.82***	0.11	1	
GDP	0.05	-0.58	0.24	-0.0004	-0.19	-0.19	0.10	-0.12	0.06	-0.73	0.16	0.73	1

Abbreviations: Prec, precipitation; NDVI, normalized difference vegetation index; MNDWI, modified normalized difference water index; LST, land surface temperature; Elev, elevation; Landcov, land cover; Pop, population density; GDP, gross domestic product

Table E-4. Spearman's correlation between covariates, Pearl River Basin (PRB)

	Prec	NDVI	MNDWI	LST	Elev	Slope	Landcov	Cattle	Pig	Urban	Crop	Pop	GDP
Precipitation	1												
NDVI	-0.28	1											
MNDWI	0.15	-0.28	1										
LST	0.14	0.22	0.08	1									
Elevation	-0.67	0.40	-0.20	-0.17	1								
Slope	-0.23	0.53	-0.15	-0.09	0.66	1							
Land cover	0.02	-0.23	0.05	0.04	-0.004	-0.06	1						
Cattle density	-0.43	0.35	-0.20	-0.05	0.42	0.30	-0.09	1					
Pig density	-0.06	0.008	0.03	0.05	-0.17	-0.17	0.06	0.27	1				
Urban/Rural	0.36	-0.64	0.22	0.05	-0.47	-0.54	0.51	-0.41	-0.03	1			
Crop production	-0.10	-0.04	-0.01	0.07	-0.31	-0.47	-0.45	0.04	0.19	-0.11	1		
Population density	0.18	-0.47	0.17	0.05	-0.30	-0.36	-0.16	-0.16	-0.002	0.72	-0.16	1	
GDP	0.36	-0.69	0.22	0.06	-0.49	-0.59	0.44	-0.41	0.004	**0.94***	-0.08	0.63	1

Abbreviations: Prec, precipitation; NDVI, normalized difference vegetation index; MNDWI, modified normalized difference water index; LST, land surface temperature; Elev, elevation; Landcov, land cover; Pop, population density; GDP, gross domestic product

Table E-5. Results of non-spatial multivariable analysis between environmental, socioeconomic factors, and leptospirosis count, Upper Yangtze River Basin

	Coefficient	95% CI		P-value
		Lower	Upper	
Environment				
Precipitation	-0.00007	-0.0001	-0.00003	<0.001
LST	-0.065	-0.070	-0.06	<0.001
NDVI	-9.31	-9.60	-9.03	<0.001
NDWI	-7.04	-7.24	-6.83	<0.001
Cattle density	0.012	0.0125	0.0128	<0.001
Pig density	0.0036	0.003	0.004	<0.001
Land cover	-0.416	-0.431	-0.400	<0.001
Elevation	-0.0004	-0.0003	-0.0003	<0.001
Socioeconomic				
Crop production	-0.0002	-0.00022	-0.00021	<0.001
GDP	-0.001	-0.0002	-0.00021	<0.001
Urban	-4.801	-5.170	-4.432	<0.001
Quarter				
1	Ref			
2	-0.567	-0.697	-0.436	<0.001
3	0.380	0.254	0.505	<0.001
4	0.326	0.200	0.451	<0.001
Year				
2005-2010	Ref			
2011-2016	-0.035	-0.042	-0.028	<0.001
Constant	14.64	14.21	15.07	<0.001

Table E-6. Results of non-spatial multivariable analysis between environmental and socioeconomic factors and leptospirosis count, Pearl River Basin

	Coefficient	95% CI		*P*-value
		Lower	Upper	
Environment				
Precipitation	0.0003	0.0002	0.0004	<0.001
LST	-0.051	-0.056	0.047	<0.001
NDVI	2.911	2.759	3.064	<0.001
NDWI	0.442	0.377	0.507	<0.001
Cattle density	-0.027	-0.028	-0.026	<0.001
Pig density	0.002	0.002	0.003	<0.001
Land cover	-0.037	-0.039	-0.035	<0.001
Elevation	0.001	0.0011	0.0013	<0.001
Socioeconomic				
GDP	0.00003	0.0002	0.0004	<0.001
Quarter				
1	Ref			
2	0.066	-0.002	0.135	0.059
3	0.140	0.063	0.216	<0.001
4	-0.593	-0.650	-0.536	<0.001
Year				
2005-2010	Ref			
2011-2016	0.195	0.169	0.220	<0.001
Constant	2.863	2.676	3.050	<0.001

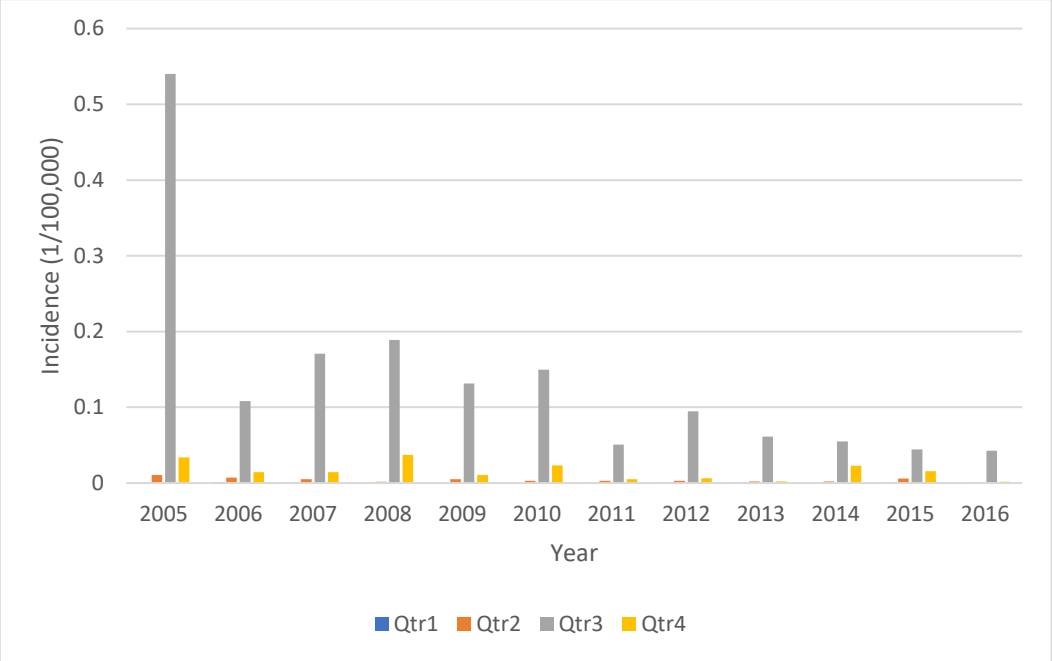

Figure E-1. Temporal variation of incidence of leptospirosis in UYRB, by quarter, 2005-2016.

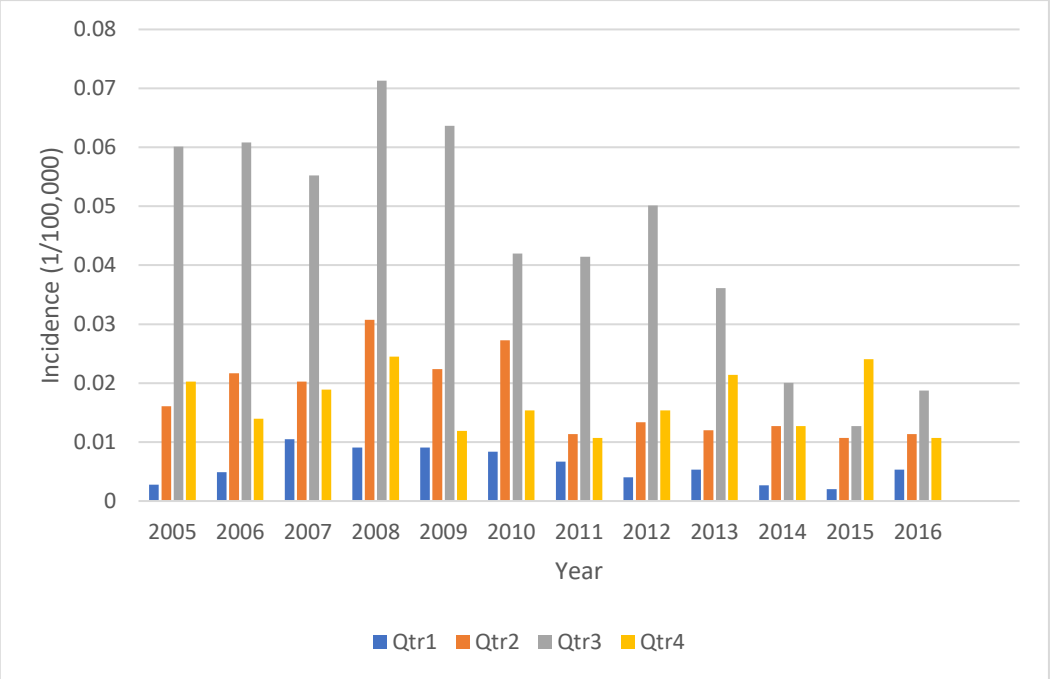

Figure E-2. Temporal variation of incidence of leptospirosis in PRB, by quarter, 2005-2016

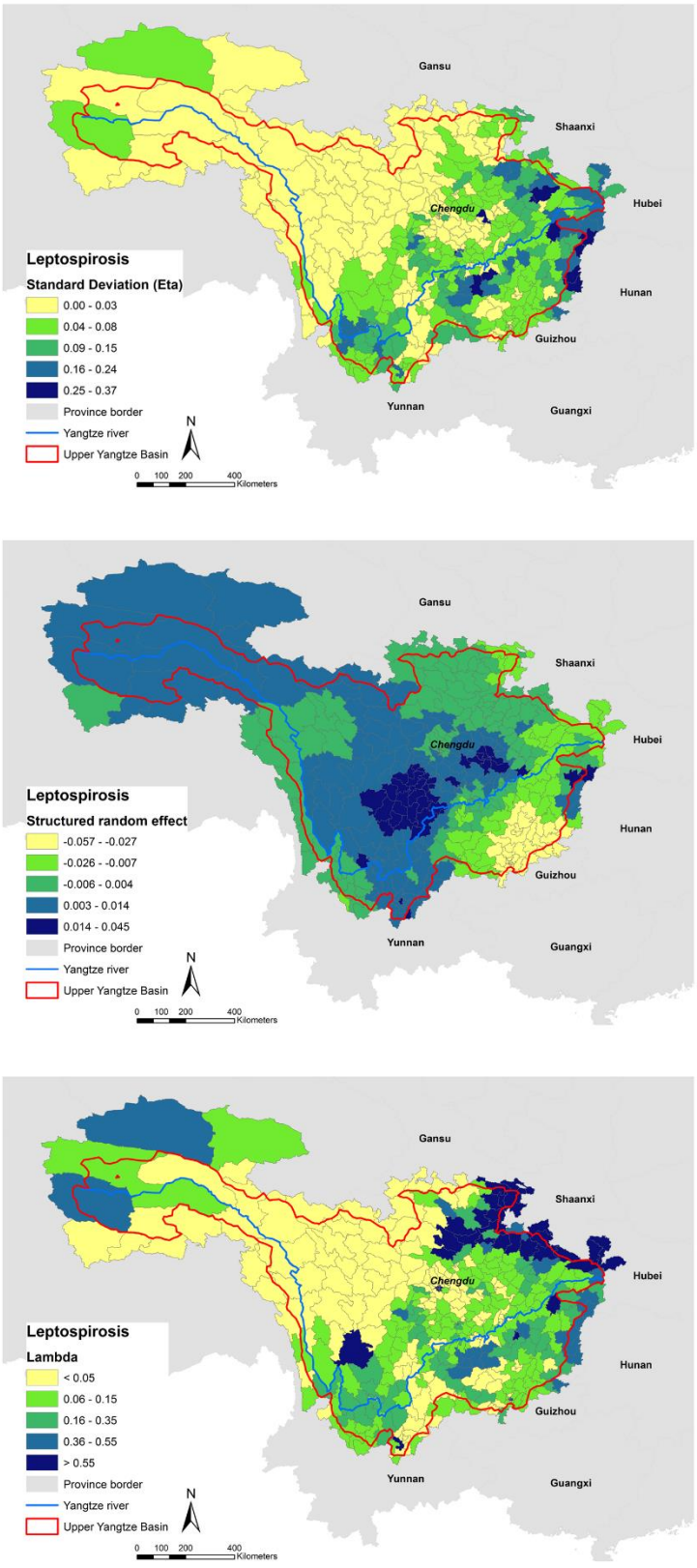

Figure E-3. Maps of standard deviation of predicted incidence of human leptospirosis (top), spatially-structured random effect (center), and probability of non-zero case of leptospirosis (bottom) in Upper Yangtze River Basin

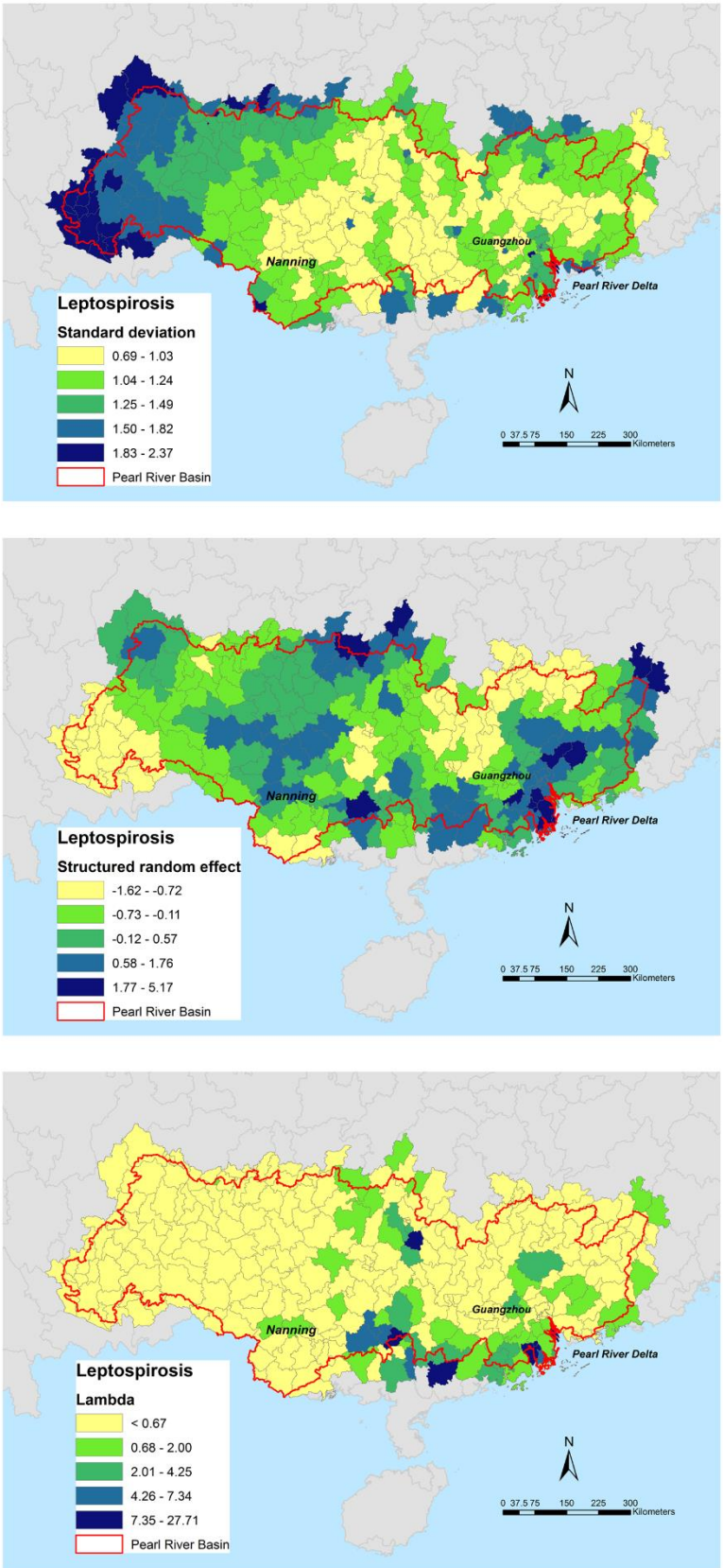

Figure E-4. Maps of standard deviation of predicted incidence of human leptospirosis (top), spatially-structured random effect (center), and probability of non-zero case of leptospirosis (bottom) in Pearl River Basin

BUGS code for the spatial ZIP-CAR model

```
model
{
for(i in 1:N){
O[i]~dpois(eta[i])
eta[i] <- zeros[i]*lambda[i]
zeros[i] ~ dbern(p[i])
logit(p[i]) <- alpha[1]+alpha[2]*cov1[i]+alpha[3]*cov2[i]+
…+alpha[16]*q2[i]+alpha[17]*q3[i]+alpha[18]*q4[i]+alpha[19]*year[i]+s[i]

log(lambda[i]) <-beta[1]+beta[2]*cov1[i]+beta[3]*cov2[i]+ …
+beta[16]*q2[i]+beta[17]*q3[i]+beta[18]*q4[i]+beta[19]*year[i]+s[i]

zdp[i] <- 1-p[i]+p[i]*exp(-lambda[i])
}
mzdp <- mean(zdp[])

s[1:N] ~ car.normal(adj[], weights[], num[], tau.s);
for (k in 1:sumNumNeigh){
weights[k] <-1
}

for (i in 1:z) {
beta[i] ~ dnorm(0,0.01)
alpha[i] ~ dnorm(0,0.01)
}

tau.s ~ dgamma(2,0.05)
sigma<-1/tau.s
}
```

Appendix F. Chapter 8 Supplementary information

Table F-1 Remotely-sensed indicators used in the study

Variables	Product	Temporal resolution	Spatial resolution	Descriptions
NDVI	MOD09A1	8-day	500 m	[NIR-Red]/[NIR+Red]
MNDWI	MOD09A1	8-day	500 m	[Green-SWIR]/[Green+SWIR]
LST	MOD11A2	8-day	1-km	Daylight temperature

Abbreviations: NDVI, normalized difference vegetation index; MNDWI, modified normalized difference water index; LST, land surface temperature.

Table F-2 Spearman correlation between explanatory variables in Mengla County, Xishuangbanna, Yunnan and Yilong County, Nanchong, Sichuan, China

Study site	Variables	Rainfall	RH	NDVI	LST	MNDWI
Mengla County	Rainfall	1.00				
	RH	0.311**	1.00			
	NDVI	-0.530**	-0.102	1.00		
	LST	0.553**	-0.170	-0.431**		
	MNDWI	0.634**	0.376**	-0.681**	0.345**	1.00
Yilong County	Rainfall	1.00				
	RH	-0.076	1.00			
	NDVI	0.452**	-0.343**	1.00		
	LST	0.725**	-0.445**	0.598**	1.00	
	MNDWI	-0.084	0.300**	-0.520**	-0.242**	1.00

Note: NDVI, LST, MNDWI indicate normalized difference vegetation index, normalized difference water index, modified normalized difference water index, respectively; * indicates $P < 0.05$; ** $P < 0.01$. No strong correlation ($r \geq |0.8|$) observed among variables in both counties.

Table F-3 Cross-correlation coefficients between leptospirosis cases and lagged climatic and remote sensed environmental variables

Lag	Mengla County					Yilong County				
	Rain	RH	NDVI	LST	MNDWI	Rain	RH	NDVI	LST	MNDWI
Lag 0	0.416*	0.264*	-0.285	0.248*	0.340*	0.144	0.124	0.006	0.085	-0.051
Lag 1	0.432*	0.082	-0.245*	0.419*	0.253*	0.227*	-0.002	0.245*	0.241*	-0.038
Lag 2	0.321*	-0.109	-0.256*	0.421*	0.163	0.544*	-0.069	0.283*	0.276*	0.039
Lag 3	0.077	-0.326*	-0.139	0.330*	-0.025	0.133	-0.020	0.130	0.245*	-0.064
Lag 4	-0.197*	-0.374*	0.009	0.108	-0.155	0.063	-0.129	0.074	0.231*	0.250*
Lag 5	-0.334*	-0.332*	0.172	-0.072	-0.240*	-0.050	-0.200*	-0.018	0.130	0.003
Lag 6	-0.430*	-0.286*	0.222	-0.317*	-0.323*	-0.130	-0.200*	-0.079	-0.043	-0.067
Lag 7	-0.406*	-0.147	0.278*	-0.411*	-0.324*	-0.169	0.051	-0.214*	-0.237*	0.048
Lag 8	-0.282*	0.083	0.201*	-0.355*	-0.167	-0.201*	0.087	-0.207*	-0.353*	0.103

Note: RH, NDVI and LST, MNDWI indicate relative humidity, normalized difference vegetation index, land surface temperature and modified normalized difference water index, respectively; * indicates $P < 0.05$.

Table F-4 Correlation analysis among lagged climatic and environmental factors and collinearity test of the final multivariable model for Mengla County, Yunnan

Variable	Spearman's rho		VIF	
	$Rainfall_0$	LST_0	$Rainfall_6$	LST_0
$Rainfall_6$		-0.549**		1.000
LST_0	-0.549**		1.000	

* indicates significant at $P < 0.05$; ** $P < 0.01$

Table F-5 Correlation analysis among lagged climatic and environmental factors and collinearity test of the final multivariable model for Yilong County, Sichuan

Variables	Spearman's rho			VIF		
	$Rainfall_1$	$NDWI_5$	LST_3	$Rainfall_1$	$NDWI_5$	LST_3
$Rainfall_1$	1.000			1.000		
$NDWI_5$	0.199*	1.000		1.277	1.000	
LST_3	0.468**	-0.153	1.000	1.041	1.041	1.000

* indicates significant at $P < 0.05$; ** $P < 0.01$

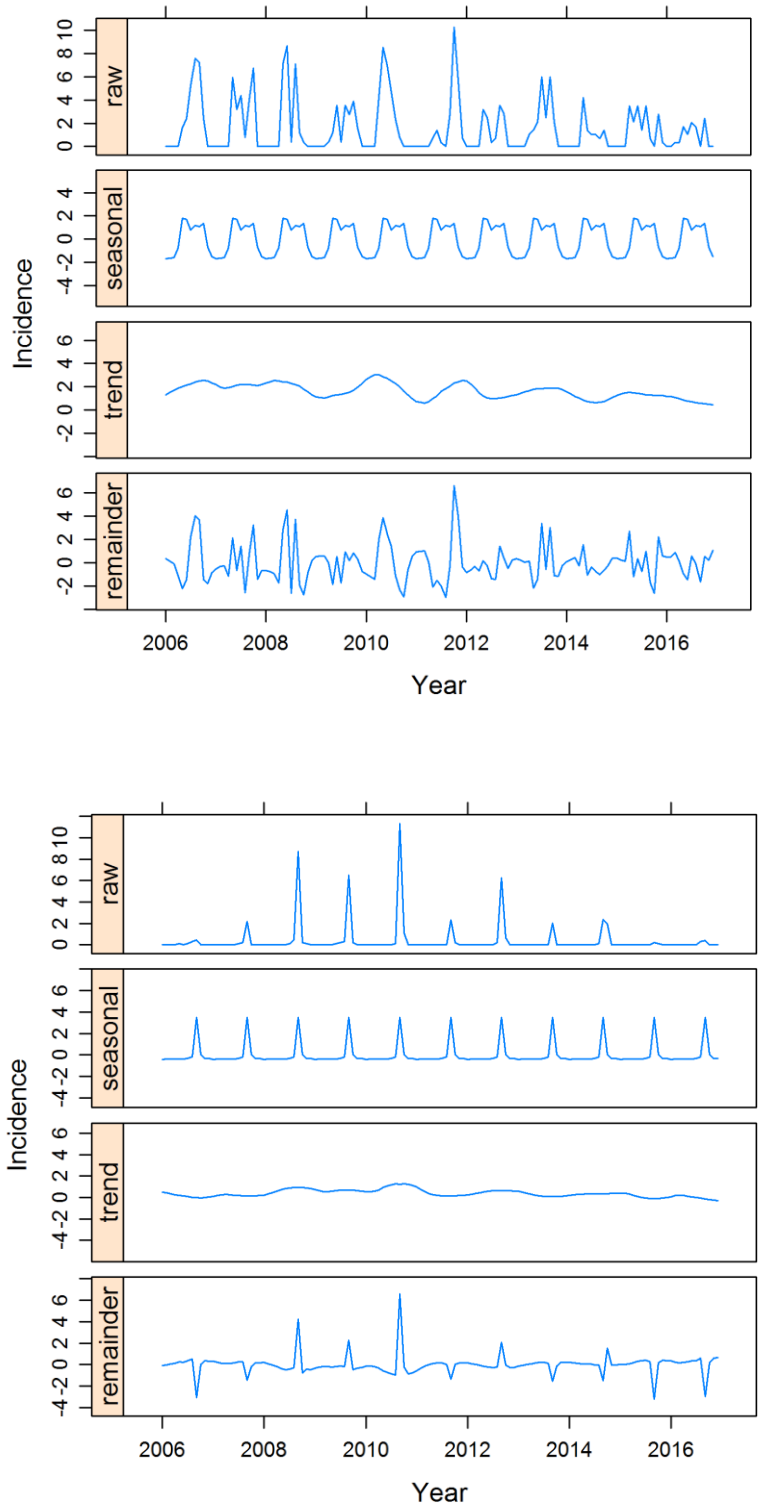

Figure F-1 Seasonal decomposition plot of leptospirosis cases in Mengla County, Xishuangbanna, Yunnan (left) and Yilong County (right), Nanchong, Sichuan, 2006–2016