Understanding complex drivers of infectious disease transmission dynamics

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Declaration

Statement of Own Work

I, Eleanor Rees confirm that the work presented in this thesis is my own. Where information has been derived from other sources, this has been indicated in the thesis. I have read and understood the school's definition of plagiarism and cheating given in the Research Degrees Handbook.

Eleanor Rees,
October 2022

Abstract

Infectious disease risk depends on both individual risk factors as well as the infectious state of the population, including current cases and immunity to disease from past exposure. For zoonotic diseases, this risk also includes the infectious state of the animal hosts. This is further complicated in diseases where there is an environmental disease reservoir, since external risk factors, such as extreme climatic events (e.g., flooding), can influence transmission risk and the timing and intensity of outbreaks. Furthermore, risk is influenced by behaviour of individuals and public health control measures. Infectious disease models can be used to simplify complex disease systems and help improve our understanding of transmission dynamics and population risk, as well as explore drivers of transmission.

An example of a complex disease system is leptospirosis, a neglected zoonotic disease. It is found in all regions of the world, but globally disease burden is highest in the Pacific region. The transmission of leptospirosis is complex, with human infection occurring either as a result of direct contact with infected animals (e.g., rodents and domestic animals), or indirectly via water or soil contaminated with urine of infected animals. As such, many different risk factors can shape the transmission dynamics. Leptospirosis is endemic in many Pacific island countries. For example, Fiji has regular outbreaks, and the frequency and intensity of outbreaks has been increasing in recent years. In this thesis, to explore the transmission of leptospirosis in Fiji, I used two different datasets: surveillance data from 2006-2017, and data from a large cross-sectional seroprevalence survey conducted in 2013.

Outbreaks of leptospirosis are often associated with heavy rainfall and flooding events. The climate in Fiji is also highly affected by El Niño-Southern Oscillation, which is a global climate phenomenon arising from changes in sea surface temperatures in the central and eastern tropical Pacific Ocean. However, the exact role of climate in driving outbreaks of leptospirosis has not been well quantified, particularly in the South Pacific. Therefore, using a Bayesian hierarchical mixed effects statistical modelling framework, I quantified the effects of different hydrometeorological indicators on leptospirosis incidence in Fiji, exploring these over both spatial and temporal scales. I found that total rainfall over six weeks, periods of negative sea surface temperature (i.e. La Niña events) and minimum temperature were all positively associated with leptospirosis cases. These results are an essential first step towards the development of a climate-based early warning system.

In addition, I used the cross-sectional seroprevalence study to estimate the duration of anti-

body persistence to leptospirosis. This has important epidemiological and clinical implications since it can provide insights into the frequency of reinfections and the level of under-reporting, as well as allow for improved interpretation of serosurveys for leptospirosis. Using a reverse catalytic model, I estimated the duration of antibody persistence to be around 7-8 years. Furthermore, using additional data on antibody kinetics, I estimated the most likely timing of infection. I found that most individuals who were seropositive in the 2013 serosurvey were likely to have been infected within the previous two years, which is consistent with surveillance data. This approach allows for richer, longitudinal information to be inferred from cross-sectional studies.

Given the disruption to the project from COVID-19 in 2020-21, and the accompanying importance of understanding coronavirus dynamics in 2020-21, I applied similar serocatalytic modelling methods to look at seasonal coronaviruses (CoV); my second disease case study. Seasonal human coronaviruses (HCoVs) have very different transmission patterns from leptospires, with human-human transmission being the primary transmission route. Using seroprevalence data from six studies covering four different circulating season HCoVs, I extended the reverse catalytic model to allow for a different force of infection (the rate at which susceptible individuals acquire infection and seroconvert) by age. The duration of antibody persistence was estimated to last around 1-4 years. This finding has clinical and epidemiological significance but was largely unknown for SARS-CoV-2 at the beginning of the pandemic. Since seasonal HCoVs have been circulating for longer than SARS-CoV-2, they may offer insights into the reinfection patterns of this group of viruses.

Finally, I explored how compartmental mechanistic models could be used to bring together climatic drivers and immunity dynamics within one disease framework, providing a more holistic understanding of transmission dynamics. I was particularly interested in diseases such as leptospirosis, which are zoonotic but also have an environmentally-persistent pathogen. Therefore, I systematically reviewed studies detailing models for a suite of environmentally persistent zoonotic diseases (20 diseases in total) and I identified model structures and methodologies that had previously been used. My review highlighted the need for more data-driven modelling of these diseases and for more models to include a holistic One Health approach which considers the human-animal-environment interface of transmission to inform disease prevention and control strategies.

Collectively, in this thesis, I show how a range of different data and methods can be used to enhance our understanding of infectious disease dynamics using mathematical and statistical modelling. I used a variety of methods specifically adapted to the setting and disease in question to provide insights into drivers and dynamics of transmission.

Acknowledgements

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Acronyms

AIC Akaike information criterion.

DALY disability-adjusted life years.

ELISA enzyme-linked immunosorbent assay.

ENSO El Niño Southern Oscillation.

ESS effective sample size.

EWARS early warning, alert, and response system.

FOI force of infection.

GLM generalised linear model.

GLMM generalised linear mixed model.

HCoVs human coronaviruses.

IgG Immunoglobulin class G.

IgM Immunoglobulin class M.

INLA Integrated Nested Laplace approximation.

LPS lipopolysaccharides.

MAT microscopic agglutination test.

MCMC Markov chain Monte-Carlo.

MERS-CoV Middle Eastern Respiratory Syndrome Coronavirus.

NOAA National Oceanic and Atmospheric Administration.

PCR polymerase chain reaction.

SARS-CoV-1 Severe Acute Respiratory Syndrome Coronavirus 1.

SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2.

SPEI Standardised Precipitation Evapotranspiration Index.

SPI Standardised Precipitation Index.

SST Sea surface temperature.

WAIC Widely Applicable information criterion.

WHO World Health Organization.

1

Introduction

1.1 Background

Infectious disease dynamics are typically non-linear since infection is a function of current cases and immunity following past exposure to infection. Mathematical and statistical modelling tools can be used to explore these drivers and dynamics of transmission and support decision-makers in understanding these complex disease systems. Mathematical models, also referred to as dynamic compartmental models, are a simplification of reality which uses mathematical language to describe the behaviour of disease transmission and can be used to test hypotheses and mechanisms of transmission. Traditionally, mathematical models have focused on single host, demographically-driven immunising infections, such as measles. However, for infectious diseases with more complex transmission pathways, for which infection confers non-sterilising immunity and where external factors may influence transmission, different methods must be used and adapted to account for this additional complexity. Statistical models describe the relationship between observed cases and explanatory variables, and are a useful tool in cases where the underlying risk factors and causal drivers of transmission are not well understood. For example, they can be used to explore extrinsic drivers of transmission such as climate variation and climate change.

Leptospirosis is an example of a disease with complex transmission pathways. It is a zoonotic disease with multiple animal reservoirs and circulating serovars. Infection does not provide life-long immunity, with reinfections known to occur. Furthermore, climatic factors, such as flooding events, combined with socio-economic vulnerability, drive transmission patterns. The burden of disease primarily occurs in resource-poor settings, and there remain many unan-

swered questions regarding the drivers and dynamics of transmission. Human seasonal coronaviruses (HCoV) are another example of diseases with complex transmission pathways, which are also understudied. As with leptospirosis, infection does not confer life-long immunity, with evidence of reinfection. In addition, infection pathways differ from leptospirosis as transmission primarily occurs via close contact between people, and therefore social and age-related patterns of transmission are important.

In this thesis, using both mathematical and statistical models, I explore the transmission dynamics of complex diseases, using leptospirosis and seasonal HCoVs as examples. This introduction provides background on both of these diseases, and how different mathematical and statistical modelling approaches can be used to address pertinent public health questions related to complex disease transmission dynamics.

1.2 Leptospirosis

Leptospirosis is a zoonotic bacterial disease found in all regions of the world with the highest prevalence found in tropical and subtropical regions [1–3]. Leptospirosis has a particularly high disease burden in resource-poor settings [4–7], and globally there are an estimated 1.03 million cases of leptospirosis per year, with approximately 58,000 deaths [1]. Leptospires, the bacteria that cause the clinical disease leptospirosis, are excreted through the urine of infected animals. Animals can either be incidental hosts (where typically they experience acute clinical disease and excrete bacteria via their urine for a limited amount of time) or reservoir hosts (where often they experience no clinical disease, but continue to excrete bacteria for months or even years) [2, 8]. The bacteria have been shown to survive and remain virulent in water and soil from a few days to several months under certain conditions [2, 9–13]. Virtually all mammalian species have been identified as hosts for leptospirosis, with notable examples including rodents, dogs and cattle [2, 14, 15]. Humans can become infected, either directly through contact with infected animals or tissue, or indirectly through water or soil contaminated by animal urine [6]; but human to human transmission is extremely rare [14]. Leptospires can enter the body through cuts and abrasions, or via mucous membranes (e.g., conjunctival or oral surfaces) [5, 8]. The leptospirosis transmission cycle is summarised in Fig. 1.1.

1.2.1 Clinical manifestation

In humans, most leptospirosis infections result in asymptomatic infection or self-limiting acute febrile illness, with the true frequency of asymptomatic infections being largely unknown. In those instances where infection results in clinical manifestation, 5-10% of patients experience severe or fatal disease, with multi-organ dysfunction [16]. The incubation period is usually 5-14 days after exposure but can vary from 2-30 days [16]. Clinical symptoms range from non-specific febrile illness, to jaundice, meningitis, and liver and renal failure [5, 6, 14, 17]. The variability of clinical manifestation, along with the need for a laboratory test for confirmation (discussed further below), means that cases of leptospirosis are often misdiagnosed and under-

reported. While animals often have no symptoms, leptospirosis infection in livestock can lead to reproductive failure (for example, abortion), decreased milk production, and systemic illness [2, 18]. This can cause significant economic losses. Therefore, this demonstrates that leptospirosis control is important for both animals and humans.

1.2.2 Risk factors and transmission routes of leptospirosis

Leptospirosis has complex transmission pathways, with many different animal hosts involved and environmental contamination occurring. As such, many different risk factors for infection and clinical disease exist and these can be broadly classified into three groups [4, 19–21] (Fig. 1.1):

1. Individual demographic and behavioural risk factors

   These include age, sex, occupation, recreational activity and contact with contaminated fresh water. Occupational risk factors include abattoir, sewage, and farm work [4, 20, 22, 23].

2. Community and environmental risk factors

   These include poor living conditions and limited access to sanitation (especially urban slums), rodent populations, animals living in the community and land-use [4, 20, 22].

3. Climatic risk factors

   Leptospirosis cases and outbreaks are more concentrated in tropical and subtropical regions, where temperature and humidity is higher, as they provide favourable climatic conditions for leptospire survival and transmission. In addition, outbreaks are often associated with heavy rainfall and flooding. This is discussed in more detail in section 1.2.3.

The factors driving transmission also vary considerably based on environmental setting. For example, in high-income countries recreational and water sports are more commonly associated with infection risk, as well as returning travellers, whilst occupation is more important in low-income settings [4, 19–21, 23]. Animal hosts are also likely to vary depending on setting, with rodents considered to be more important drivers of transmission in urban areas, and farm animals being more significant in rural areas. Over the past decade reported outbreaks of leptospirosis have been on the rise [22, 24, 25], with outbreaks occurring in previously unaffected areas [26, 27]. Evidence suggests that this is driven by climate change and an increase in extreme weather events (particularly flooding), but also urbanisation, poverty and agricultural intensification [4, 20].

1.2.3 Role of climate on leptospirosis transmission

Leptospirosis is a climate-sensitive disease, with outbreaks of leptospirosis often occurring following heavy rainfall and flooding [4, 19, 20, 24, 26, 27]. There are several different reasons why extreme precipitation and flooding may increase leptospirosis risk. Firstly, heavy rainfall

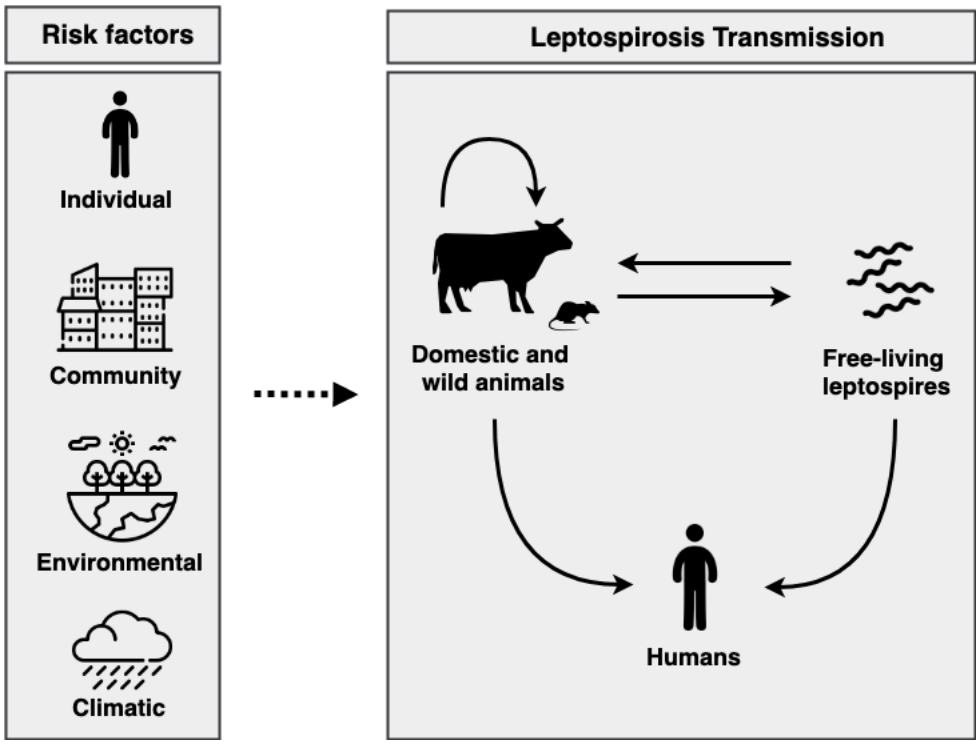

Figure 1.1: Transmission pathway and risk factors for leptospirosis. Leptospires are maintained in the environment by a wide variety of mammalian reservoir hosts. Humans can acquire leptospirosis through direct contact with infected animals or animal products, or by indirect contact with a contaminated environment. The cycle of transmission of leptospirosis is influenced by climatic risk factors (e.g., heavy rainfall and flooding), community risk factors (e.g., access to sanitation, housing infrastructure and animals in the community) environmental risk factors (e.g., land use) and individual risk factors (e.g., occupation and contact with contaminated water). This figure has been designed using resources from *Flaticon.com*.

provides a suitable environment for leptospire survival [9–12]. Studies have shown that leptospires are able to proliferate in water-logged soil, which mimics the post-flood environment, but not in soil or water alone [13]. Secondly, heavy rainfall and flooding causes humans to have more contact with contaminated water, and/or drinking water may become contaminated due to disruption in sanitation networks. Finally, flooding may disturb the natural habitat of rodents, resulting in closer contact with humans. Rainfall may also result in increased abundance of rodents, due to increased food sources and optimal reproductive conditions [28]. Furthermore, a previous study in New Caledonia showed that under wet and warm conditions there was a greater abundance of both rodent species and of *Leptospira* carriage, leading to increased environmental contamination and human exposure [29].

Leptospirosis transmission may also be influenced by temperature. Higher temperatures and humid environments have been shown to prolong *Leptospira* environmental survival [5, 10, 11]. Human behaviour also changes with temperature. Warmer temperatures may bring humans

in closer contact with the environment, for example through increases in recreational water activities or changes in agricultural activities.

Numerous studies have quantified the effect of climate on leptospirosis prevalence and incidence from different regions of the world, including New Caledonia, Fiji, Reunion Island, Brazil, Argentina, China and Thailand [30–40]. Many of these studies found that rainfall was associated with increased leptospirosis cases. However, the lags ranged from two weeks to eight months depending on setting. Several studies also identified a relationship with temperature, with increases in cases associated with higher temperatures, including in Reunion island, Thailand, Republic of Korea, and Santa Catarina state in Brazil [33, 34, 36, 39]. This association was not ubiquitous and this relationship was no observed in other regions (New Caledonia, Sao Paulo in Brazil, and India) [30, 32, 37].

A small number of studies also explored the role of inter-annual variation in climate, such as El Niño Southern Oscillation (ENSO), on leptospirosis incidence [30, 38, 41]. ENSO is an inter-annual cycle which arises from changes in sea-surface temperatures in the central and eastern tropical Pacific Ocean (Fig. 1.2). There are two distinct phases, El Niño and La Niña, and ENSO events occur every 2-7 years. ENSO influences the climate, including the timing and intensity of rainfall, in tropical Pacific Islands and elsewhere. Since the effects of ENSO vary globally, the relationship between leptospirosis incidence and ENSO is likely to vary depending on setting. One study explored the effect of ENSO on outbreaks of leptospirosis in New Caledonia [30], and found that La Niña phases were associated with leptospirosis outbreaks.

This climate sensitivity offers the opportunity for the development of climate-based early warning systems. This can allow public health practitioners to move away from passive disease surveillance and response, to more active disease prediction and prevention [42]. However, climate-based early warning systems require a good understanding of the climatic drivers and transmission mechanisms, as well as robust surveillance data. A previous study demonstrated how the sea surface temperature in El Niño Box 4 (a region in the Pacific Ocean) could be used to forecast leptospirosis outbreaks four months in advance in New Caledonia [30]. However, the implementation and real use of this model has not been documented.

1.2.4 Control measures

The complexity in transmission pathways for leptospirosis is a major challenge for control strategies, especially in remote and poorly resourced endemic areas. As previously described, the importance of risk factors varies based on setting, therefore, effective disease control relies on identification and interruption of the main exposure pathways (see Fig. 1.1). Although many control measures have been proposed, there is limited knowledge of their effectiveness, and many of these measures are expensive and difficult to implement. The different control measures can be classified into three broad categories:

1. Reducing burden of disease and infection in humans

   Increased public health messaging can reduce the risk of exposure and infection by high-

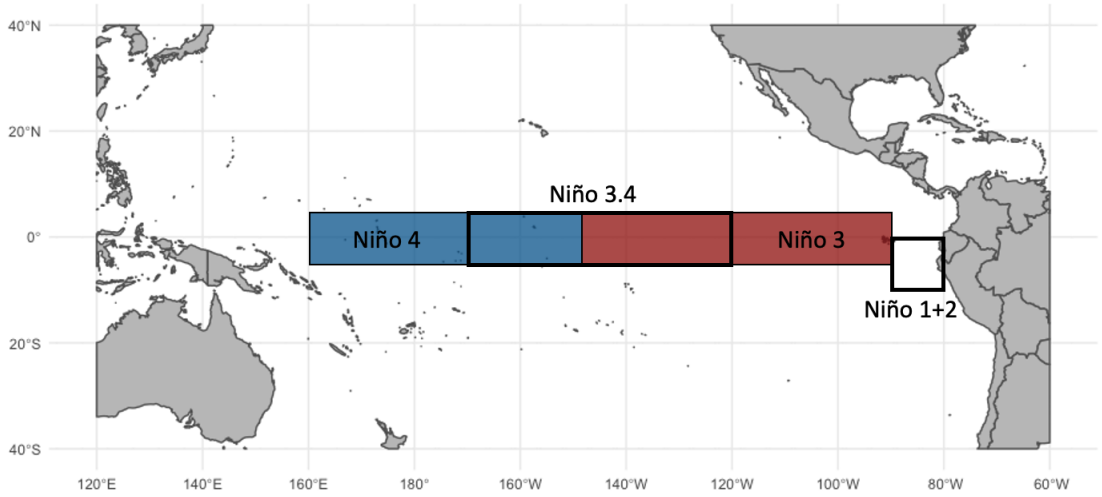

Figure 1.2: Niño index regions. Monitoring of El Niño Southern Oscillation (ENSO) typically focuses on anomalies in sea surface temperature (SST) in four regions of the equatorial Pacific Ocean (Niño 3.4, Niño 3, Niño 4 and Niño 1+2). El Niño events are characterised by SST anomalies above the threshold of +0.5°C, whilst La Niña events are characterised by SST anomalies below the threshold of -0.5°C. A three-month running mean, where anomalies exceed +0.5°C or -0.5°C for at least five consecutive months in the Niño 3.4 region is the Oceanic Niño Index (ONI), and this is the operational definition used by the National Oceanic and Atmospheric Administration (NOAA) for an El Niño or La Niña event [43]. The Niño 3.4 index and the ONI are the most commonly used indices to define an El Niño or La Niña event.

lighting risky behaviours (such as recreational activities in rivers, and keeping livestock close to dwellings), recommending the use of personal protective equipment during high risk activities, and the importance of seeking healthcare for symptoms [7, 44, 45]. Improved awareness is also important for clinicians, so that they increase clinical index of suspicion, have a low threshold for ordering laboratory tests, and start empirical treatment early for clinically suspected cases. Vaccines can also reduce human susceptibility, thus limiting effective transmission to humans. Current vaccines exist as killed whole-cell vaccines, and they have been used in high-risk occupation groups, or in response to floods and epidemics [14, 46], however, use of these vaccines is extremely limited. While results from vaccine studies have shown a reduction in cases, there are associated side-effects, and the vaccine only confers short-term serovar-specific prevention [46, 47]. Recent efforts have focused on developing subunit vaccine candidates which may be more efficacious [47]. Pre- and post-exposure antibiotic prophylaxis are also used to reduce clinical infection in high-risk groups, however, while reported efficacy is variable and it is not currently routinely recommended [7, 48, 49], it remains commonly used. Since no effective vaccine programmes in humans exist, at present prevention is key for reducing the burden of disease in humans.

2. Reducing burden of disease and transmission in animals

   Transmission in animals can either occur from the environment or from other animals. Possible control options in animals include vaccination, antibiotic therapy and rodent control [2]. Rodents are very difficult to control, in part due to their rapid reproduction rates [50], and there is limited evidence on the efficacy of rodent control with regards to reduction in leptospirosis cases. Furthermore, in countries such as Fiji where there are a number of different animal reservoirs, it is unlikely to be as successful. Vaccination is widely used in cattle, pigs, and dogs, particularly in high income countries. However, it is limited by the cost, availability, and relevance to the country and animal species. As described below, there is much heterogeneity in serovars, and the vaccine needs to include serovars specific to the region and animal species being targeted. Immunity from vaccination is thought to last up to one year [2]. Currently, due to the cost, animal vaccination is not available in many Pacific Island countries [7].

3. Reducing environmental contamination

   Environmental contamination by leptospires occurs from infected animals. Control options include limiting leptospire introduction into the environment by improved management of livestock and rodents; through improved drainage of animal waste and careful placement of animal pens to avoid water and soil contamination. In addition, improved flood control would reduce outbreak risk in residential and agricultural areas. Finally, improved housing infrastructure and sanitation would reduce contamination by rodent populations [7, 14]. However, these control options are expensive and can be difficult to implement.

A key challenge for understanding and controlling leptospirosis disease transmission is identifying, accounting for, and attributing variation in disease risk to multiple interacting components in a complex system. One Health recognises that there is an inter-connectedness between the health of people, animals and the environment we share, and highlights that an integrated, holistic approach is needed [51]. Therefore, effective control measures are likely to require a combination of approaches targeting human, animal and environmental health, and involving interdisciplinary collaborations [52].

1.2.5 Microbiology and classification of leptospires

The genus *Leptospira* is genetically highly heterogeneous, and knowledge of its genetic diversity remains incomplete. As such, the taxonomic classification of the genus *Leptospira* is evolving and changing. New methods in next generation sequencing have allowed for the identification of 68 named species [53, 54]. These are proposed to be organised in two clades and four subclades (P1, P2 (pathogenic group 1 and group 2) and S1, S2 (saprophytic group 1 and group 2)) which relates with the pathogenicity level of the species [53–55].

Historically, leptospires were classified into serovars based on the heterogeneity of surface expressed lipopolysaccharides (LPS). This led to the identification of 25 serogroups and more than

300 serovars [8, 47]. However, this serological taxonomy does not correlate well with the genetic taxonomy, and some serogroups contain many different bacterial species [21]. Nevertheless, this serological taxonomy remains in use today. Different serovars have been found to be associated with certain animal species (e.g., Hardjo [*Leptospira borgpetersenii* serovar Hardjo and *Leptospira interrogans* serovar Hardjo] is frequently associated with cattle, and *Leptospira interrogans* serovar Icterohaemorrhagiae and *Leptospira borgpetersenii* serovar Ballum are frequently associated with rodents), yet these distinctions are not definitive, and there is a lot of heterogeneity in serovars, even in small island nations [15, 21, 47]. For example, American Samoa, a small island nation with a population of approximately 55,000 people, has several different circulating serovars [56]. Since the animal species that may carry these serovars are different, the transmission routes to humans, and therefore risk factors may be different for each serovar.

1.2.6 Host immune response following infection

The immune response following *Leptospira* infection is largely mediated by the humoural response [46, 57]. The antibodies produced during infection are predominantly directed against the surface exposed LPS. Therefore, the immunity generated during infection is limited to the infecting serovar, or homologous serovars. The acute phase of infection typically lasts for 3-8 days and is associated with leptospiraemia (Fig. 1.3). The immune stage then follows, and levels of anti-*Leptospira* Immunoglobulin class M (IgM) antibodies are detectable, followed by Immunoglobulin class G (IgG) antibodies [14, 58]. IgM and IgG can continue to be detected at low levels for months, and even years following infection [17, 59]. Infection does not appear to be fully immunising, with previous studies demonstrating that reinfection does occur [60–63]. However, the duration of protective immunity conferred following *Leptospira* infection is largely unknown. Typically, reinfections occur with a different *Leptospira* serogroup, and reinfection appears to result in milder clinical disease [60, 61]. This suggests some degree of cross-reactive protective immunity between serovars. However, severe disease following reinfection with the same serovar has been reported [63].

1.2.7 Diagnostic testing

There are numerous laboratory tests for the diagnosis of leptospirosis [5, 14, 16, 17, 64–68] and these are summarised in Table 1.1. However, the diagnosis of leptospirosis remains a challenge, particularly in low- and middle-income countries. Firstly, it requires clinicians to suspect leptospirosis, and, since symptoms can resemble other acute febrile illnesses such as malaria and dengue fever, it is often misdiagnosed or untreated. Secondly, the laboratory tests are not always available, and there is variable sensitivity and specificity, and so accurate and timely diagnosis remains a challenge. Together, these lead to an under-reporting of leptospirosis [1, 14]. Broadly, the diagnostic tests can be categorised into: (i) polymerase chain reaction (PCR), which detects *Leptospira* DNA in the blood, (ii) isolation of leptospires in culture, and (iii) detection of specific antibodies (for example, the microscopic agglutination test (MAT) or the enzyme-

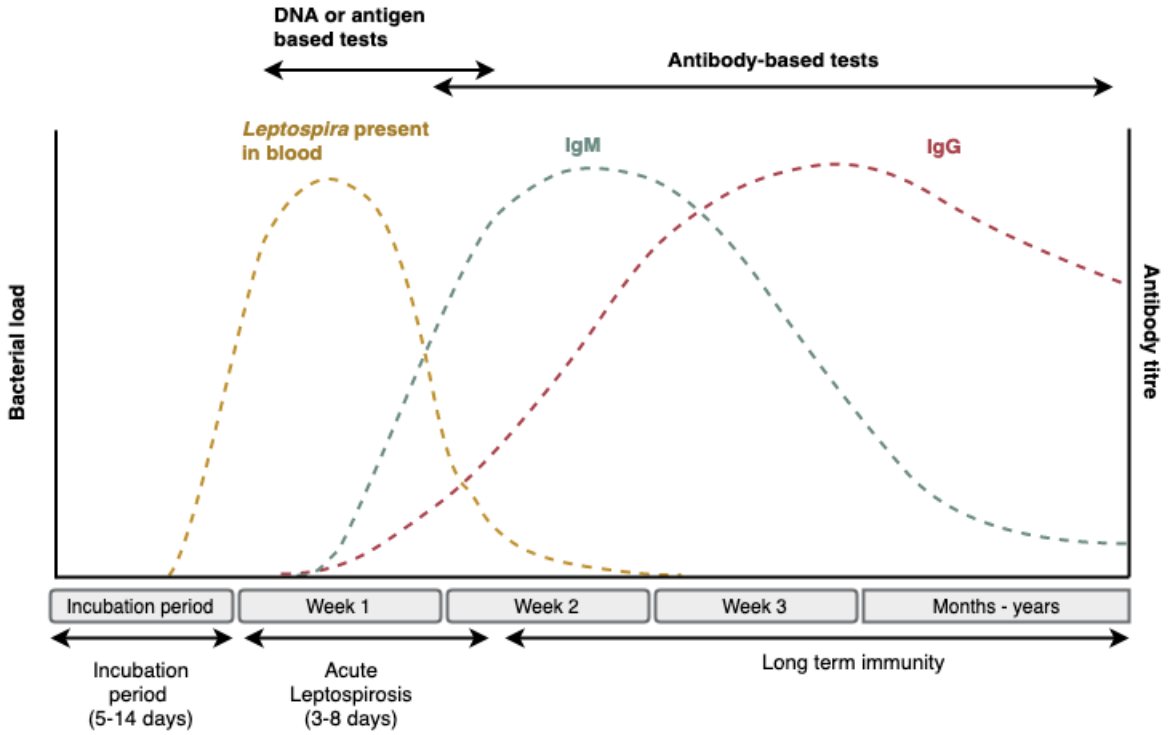

Figure 1.3: Schematic representation of the levels of *Leptospira* in the blood and titres of anti-*Leptospira* Immunoglobulin class M (IgM) and Immunoglobulin class G (IgG) antibodies following *Leptospira* infection, and the implications this has for the timing and suitability of diagnostic tests. The yellow line indicates the presence of leptospiral antigen and DNA in the blood; the blue line indicates the titre of anti-*Leptospira* IgG antibodies; the red line indicates the titre of the anti-*Leptospira* IgM antibodies. Figure developed using information from multiple sources [16, 58, 64].

linked immunosorbent assay (ELISA)). The time at which tests can be conducted varies, as shown in Fig. 1.3. If the antibody-specific tests are done too early, this can lead to false-negatives as antibody levels have not yet risen. If blood for the DNA or antigen-based tests is taken too late, or following administration of antibiotics, this can also cause false negatives. Cross-reactivity and previous infections can also lead to false positives from antibody-based tests. Finally, there is considerable heterogeneity in the rise and timing of the peak antibody titre between individuals [59, 69], as well as the waning of antibody response, making antibody titres difficult to interpret.

1.2.8 Leptospirosis in Fiji and the South Pacific

Fiji, a nation in the South Pacific Ocean, comprises over 330 islands and is classified by the United Nations as a small island developing state [74] (Fig. 1.4). The two biggest islands are Viti Levu (where most of the population resides) and Vanua Levu, and together they make up 87% of the total land area in Fiji. The population size in 2017 was 884,887 [75], and it is estimated that

90% of the population in Fiji are coastal dwellers [76]. Indigenous Fijians (iTaukei) and Indo-Fijians (Fijians of Indian descent) account for 57% and 35% of the population, respectively. The largest administrative units are Divisions (Central, Western, Northern and Eastern) followed by Provinces (14 in total).

A systematic review found that Oceania had the highest per capita leptospirosis morbidity (150.68 cases per 100,000 per year), mortality (9.61 deaths per 100,000 per year) [1], and disability-adjusted life years (DALY) in the world [77]. This may be an under-estimate of the true burden of disease, as access to testing is limited in Fiji and elsewhere in the Pacific, and cases are likely to be misdiagnosed [4, 22], as discussed above. The case definitions for suspected, confirmed, and probable cases in Fiji are shown in Fig. 1.5.

Leptospirosis is endemic in Fiji and has been identified as one of the four priority climate-sensitive diseases of major public health concern [78]. In addition to endemic transmission, frequent outbreaks of leptospirosis occur, usually following flooding events. The frequency and intensity of outbreaks in Fiji appear to be increasing. In 2012, two severe flooding events led to the largest outbreak of leptospirosis reported in the Pacific region at that time, with several hundred cases and 44 deaths. There were 576 suspected cases in 2012, however, Togami *et al.* [79] estimated the total suspected number of cases to be as high as 1,217 (314 probable or confirmed). More recently, outbreaks are larger in size with over 3,500 cases reported so far in 2022. In addition, the number of reported deaths has increased, although case fatality is lower with higher survival rates from intensive care reported (personal communication with local health ministry).

Previous serosurveys conducted in Fiji have suggested that the number of reported cases is likely to be much lower than the number of true infections occurring. A serological survey conducted in Fiji in 2013 included 2,152 participants across 81 communities from the three main islands, and the overall seroprevalence in Fiji was estimated to be 19.38% [22]. *Leptospira interrogans* serovar Pohnpei was the most common serovar circulating in Fiji, accounting for 84.2% of positive MAT tests. Another serosurvey conducted in 1982 [76] tested 300 individuals from Fiji, and 55.3% of individuals were found positive using the MAT. In addition to human testing, five animal serological surveys have been conducted in Fiji [15, 80–83]. In total, 11 different animal species in Fiji have been identified as hosts for leptospirosis, with 19 different serovars circulating. This shows that leptospirosis is common in a wide range of animals in Fiji, with prevalence found to be as high as 85% in horses and 73% in cattle [81]. Given the number of different animal hosts and circulating serovars, it is likely that there are a number of different transmission routes, and these differ across the country depending on setting (e.g., urban, peri-urban and rural).

A number of risk factors associated with leptospirosis infection have been identified in Fiji. These include individual risk factors (e.g., working outdoors, male sex and iTaukei ethnicity), community risk factors (e.g., lack of treated water at home, living in rural areas, high poverty rate, living less than 100m from a major river, pigs in the community and high cattle density), and climatic factors (high maximum rainfall in the wettest month) [22, 84]. Further analysis of

the seroprevalence data showed there is significant heterogeneity in risk factors between ethnic groups and residential setting, and that multiple animal species are thought to be important in Fiji [85]. For example, for iTaukei, contact with rodents and mongooses were strongly associated with leptospirosis. While for Indo-Fijians household exposure to livestock was more important with very few reported contact with rodents or mongooses. In urban settings, exposure to livestock was associated with infection. This is hypothesised to be a result of closer contact between animals and humans in urban areas compared with rural areas [85]. Furthermore, significant geographical variation in the relative importance of different environmental and sociodemographic factors has been shown within Fiji, despite its small geographical size [86].

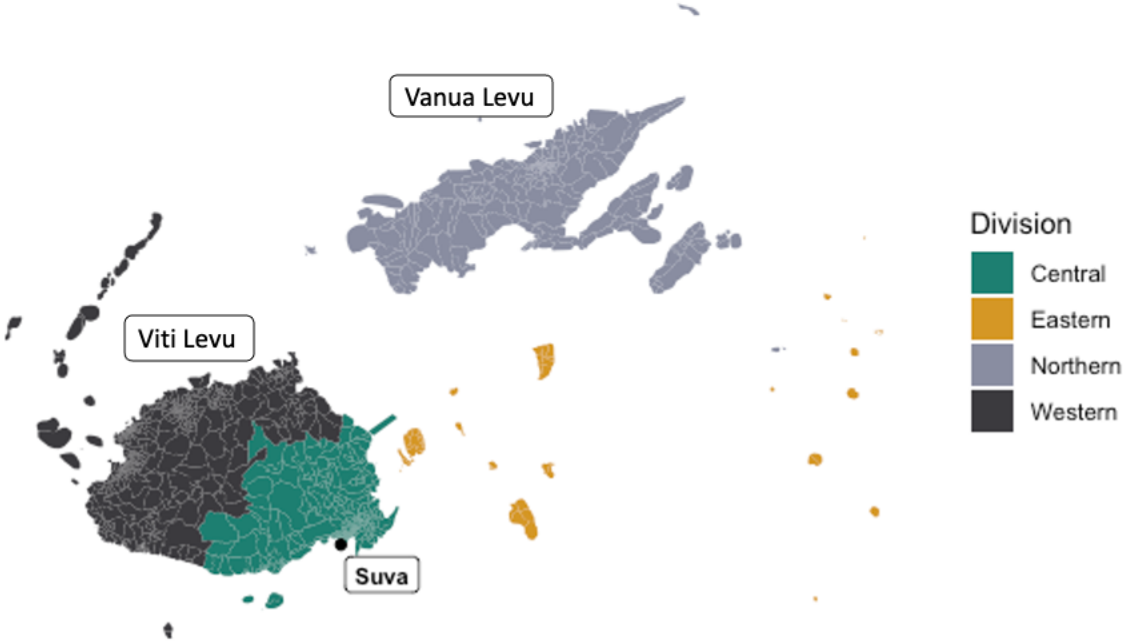

Figure 1.4: Map of divisions within Fiji. There are four divisions in Fiji: Central, Eastern, Northern and Western. The capital city Suva is located in the Central division. The two biggest islands are Viti Levu and Vanua Levu.

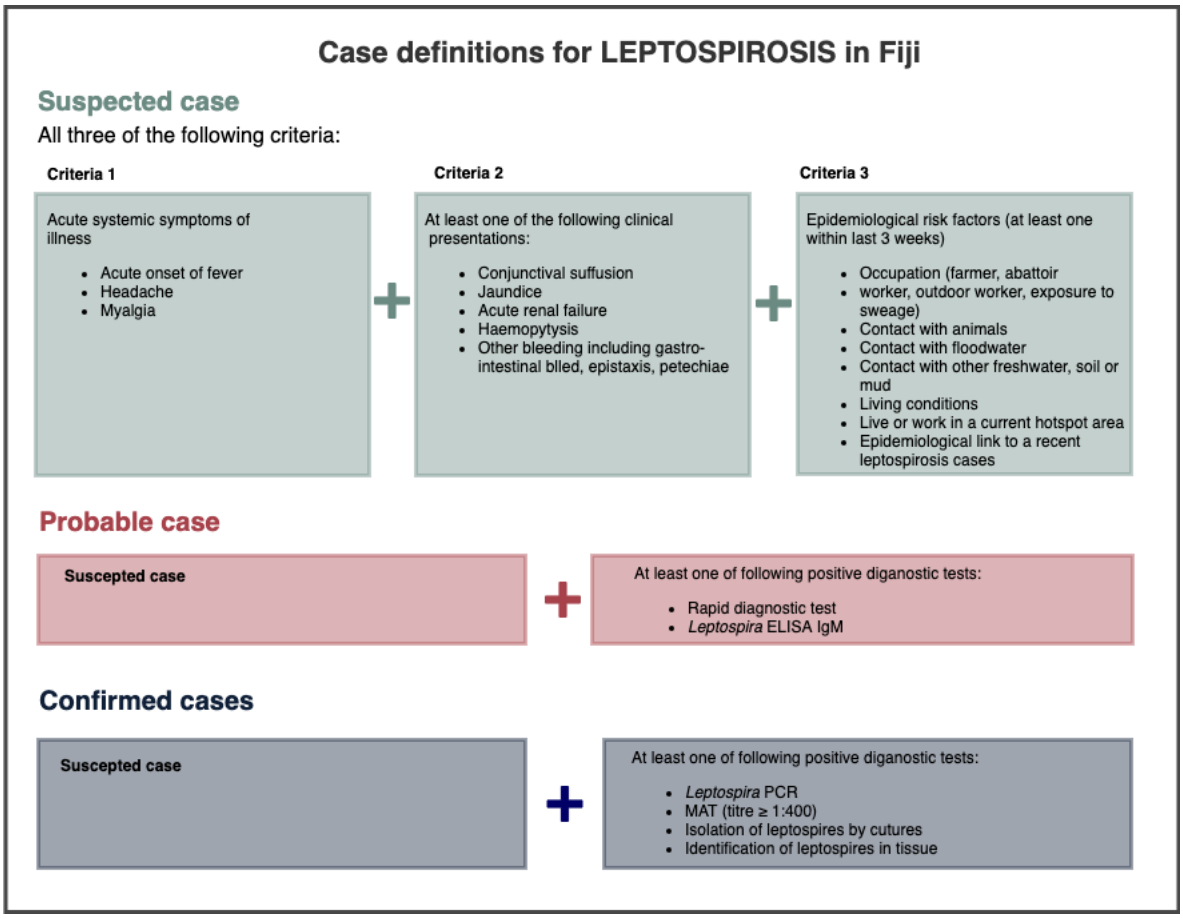

Figure 1.5: Case definitions for suspected, probable, and confirmed cases in Fiji. MAT, microscopic agglutination tests; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction. As of December 2015, none of the confirmatory tests were available in Fiji. Adapted from [66].

Table 1.1: Summary, advantages and disadvantages of the various diagnostic techniques used for the detection of leptospirosis [14, 16, 58, 64, 68, 70–72]. Partially reproduced from [73]. MAT, microscopic agglutination test; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; IgG, Immunoglobulin class G; IgM, Immunoglobulin class M; CSF, cerebrospinal fluid.

Diagnostic test	Description	Advantages	Disadvantages
MAT	Patient serum is incubated with live antigen leptospires. Agglutination then occurs, which is detected using dark-field microscopy. Live antigen leptospires are diluted sequentially, and the highest dilution in which 50% agglutination occurs is recorded. IgG and IgM antibodies can be detected using dark field microscopy.	• 'Gold standard' test, due to high specificity and ability to distinguish between serogroups	• Requires maintenance of a panel of live leptospires • It can be time consuming and difficult to interpret the results • Requires the correct selection of *Leptospira* serovars on the panel • Cross-reaction between different serogroups may occur • It can only be performed at certain reference laboratories • May be negative in the first 5-7 days
ELISA	Detection of antibodies (usually IgM) in patient serum using a broad-spectrum of antigens expressed by pathogenic *Leptospira* spp..	• More sensitive than MAT during the acute phase of the illness, and therefore may detect infection earlier than the MAT • It is easy to perform and results are rapidly available	• Not serovar-specific and detects both pathogenic and non-pathogenic *Leptospira* spp. • Sensitivity and specificity variable • May still get negative results during the early stages of infection
PCR	Amplification of specific parts of *Leptospira* DNA from serum, plasma or urine.	• Provides rapid diagnosis before antibodies have risen to detectable levels	• Expensive to perform and may provide false positives • Not serogroup specific
Culture	Blood, CSF, urine or tissue are inoculated in culture medium, and leptospire growth is measured using dark field microscopy.	• Provides definitive diagnosis	• Leptospires are slow growing, and so long turn around times • Low sensitivity
Rapid diagnostic test	Several different tests, which provide rapid detection of IgM (such as indirect hemagglutination test, latex agglutination assays, lateral flow assays and IgM Dipstick assays).	• Easy to perform and requires minimal equipment • Cost-effective • Provides rapid results	• Not serogroup specific • Variable sensitivity and specificity • Requires confirmation via a reference test such as MAT for definitive diagnosis

1.3 Seasonal human coronaviruses (HCoVs)

The second disease case study in this thesis is Seasonal human coronaviruses (HCoVs), another example of a complex disease system. Seasonal HCoVs are a common cause of acute respiratory infections. Infection usually results in mild or asymptomatic disease; although infection has been shown to be associated with more severe outcomes (such as pneumonia, bronchiolitis and croup), particularly in the very young, the elderly and immunocompromised individuals [87, 88]. They tend to be co-detected with other respiratory infections and are thought to be responsible for 15-30% of respiratory infections each year [89, 90]. Globally, approximately 10% of upper and lower respiratory tract infections in hospitalised children are caused by seasonal HCoVs [91–93].

Coronaviruses are enveloped viruses with a single-strand RNA genome [89]. There are four circulating seasonal human coronaviruses: two alpha coronaviruses (HCoV-NL63 and HCoV-229E) and two beta coronaviruses (HCoV-OC43 and HCoV-HKU1). HCoV-OC43 and HCoV-229E were first identified in the 1960s, but HCoV-NL63 and HCov-HKU1 were not identified until 2004 and 2005 respectively, as a result of heightened interest in HCoVs following the emergence of Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1) in 2002 [89, 93–96]. Coronaviruses are composed of four structural proteins, including spike, envelope, membrane and nucleocapsid proteins. The spike protein is composed of two subunits: S1 which contains the receptor-binding domain and is responsible for binding to host cell receptors, and S2 which mediates viral and host cell membrane fusion and cell entry [97, 98].

Seasonal HCoVs are endemic in human populations and have a global distribution. There is marked seasonality in temperate sites (with the exception of China), with cases more commonly occurring in winter months, whilst in tropical sites and China transmission tends to be less seasonal [99, 100]. Seasonal HCoVs are primarily transmitted from human to human via respiratory particles, close personal contact, and indirect transmission through fomite contact. Transmission is higher in children and adolescents [101], most likely due to the close social contact patterns between these groups and lack of pre-existing immunity [98]. First infection with seasonal HCoVs has been found to occur in early childhood, with HCoV-NL63 and HCoV-229E seroconversion occurring on average before 3.5 years [102].

1.3.1 Emerging human Coronaviruses

Three human beta coronaviruses have emerged in the last 20 years which can cause much more severe disease in humans. SARS-CoV-1 emerged in 2002 and spread rapidly before being contained in 2003, resulting in over 8,000 cases and 774 deaths [103]. Conversely, Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) emerged in 2012, and continues to cause sporadic outbreaks, but has not shown sustained community transmission [104]. Finally Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in 2019 [89]. SARS-CoV-2 was declared a pandemic by the World Health Organization (WHO) on 11th March 2020 [105], and has had a devastating impact, resulting in over 500 million cases and 6.2 million reported

deaths globally as of June 2022 [106].

1.3.2 Host immune response following seasonal HCoV infection

Given the mild clinical disease and low case fatality rate, relatively little research has been conducted on seasonal HCoVs, and as such relatively little is known about the adaptive and innate immune response following seasonal HCov infection. Following exposure to seasonal HCoVs, naive B-cells specific to the spike protein differentiate either into plasma cells that produce strain-specific cross-reactive antibodies, or memory B-cells. Upon subsequent exposure to HCoVs or SARS-CoV-2, these memory B-cells generate antibodies to mitigate infection [98]. Experimental and natural infection studies have shown that approximately one week post infection antibodies begin to rise rapidly, reaching a peak after two weeks, and then returning to baseline levels by four months to one year [107–109]. Furthermore, a positive correlation was found between antibody levels following infection and severity of clinical manifestation and viral shedding, with more severe cases associated with substantial rises in antibody titres post-infection [108]. There is some evidence that cellular immunity may also have a role in SARS-CoV-1, MERS-CoV and SARS-CoV-2 infection, and therefore it may also be involved in seasonal HCoVs, however questions remain regarding the exact role and importance [110–113]. Together, the antibody-mediated immunity and cell-mediated immunity form the adaptive immune response, which ideally results in longer term protection.

1.3.3 The duration of immunity following seasonal HCoV infection

The duration of immunity to seasonal coronaviruses is largely unknown. Two human challenge studies found evidence that reinfection could occur within a year [107, 114]. Evidence from cohort and community-based surveillance studies are mixed. Several studies found evidence that reinfections occur within one year [115–118]. Two of these studies also observed reinfections with the same strain within one year [117, 118], and this usually resulted in less severe symptoms with the second infection [117]. In contrast, a three-year cohort study found that reinfection within a year only occurred with a different strain [116]. This study also found that there were only eight reinfection events (from 216 confirmed first infections), which may suggest longer lasting immunity. Finally, although Edridge *et al.* [115] reported reinfection within one year, the average reinfection time was found to be 30 months. However, care should be taken with the interpretation of cohort and community-based surveillance studies as background exposure rates are not known and this will influence the reinfection patterns observed.

1.3.4 Cross-reactivity and cross-protection between HCoVs and SARS-CoV-2

A systematic review found some evidence of cross-reactivity that occurred within alpha strains (HCoV-229E and HCoV-NL63) and beta strains (HCoV-OC43 and HCoV-HKU1), but minimal reactivity between alpha coronaviruses and beta coronaviruses [94]. However, it is not clear how cross-reactivity equates to cross-protection. In addition, there is evidence of the presence

of pre-existing antibodies against SARS-CoV-2 in uninfected individuals, suggesting cross reactivity between SARS-CoV-2 and other HCoVs, particularly in children and adolescents [119, 120]. This has been proposed as a hypothesis to explain why in general children, who have higher HCoV infection rates, experience less severe disease as a result of COVID-19 infection [98].

1.4 Tools for investigating infection transmission drivers and dynamics

There are many different types of computational models that can be used to understand the drivers and transmission dynamics of infectious diseases. It is possible to distinguish between phenomenological (i.e. statistical) and mechanistic (i.e. transmission dynamic), and the decision regarding which model to use depends upon the question of interest. Statistical models aim to understand how variables are associated with each other, not why they behave that way. These models can be particularly useful when the causal relationships underlying disease transmission are not yet fully understood [121]. In contrast, mechanistic models aim to understand how parameters and variables impact other variables, and they can allow for the inclusion of explicit hypotheses about the biological mechanisms driving transmission [122, 123]. Keeling and Rohani [122] defined a good model to be both suited to its purpose (that is, as simple as possible, but no simpler) and parameterizable by available data. Models are limited by a balance between predictive accuracy (ability to reproduce observed patterns of infection), transparency (clarity of the role and impact of the model and its components) and flexibility (ability to be adapted to new situations) [122]. In this thesis I explore two types of infectious disease models, statistical models and compartmental mechanistic models (including both "SIR" ("Susceptible Infected Recovered") compartmental models and catalytic models), and further details regarding these models is provided below.

1.4.1 Statistical models

Statistical models can be used to describe the relationship between observed cases (response variable) and explanatory variables and this can allow for extrinsic drivers of disease transmission to be explored. For climate-sensitive diseases, such as leptospirosis, these models can be particularly useful to investigate climate drivers and can be used to explore multiple different risk factors and quantify the risk. Statistical models can either be classified as fixed effect, where all the parameters are fixed, or mixed effect, which contain both fixed and random effects [124]. These random effects can account for unobserved or unaccounted for heterogeneity in the model. An example of a statistical model is the generalised linear model (GLM), which is a flexible generalisation of ordinary linear regression, and its extension, the generalised linear mixed model (GLMM) which includes both fixed and random effects. These models can be formulated within a Bayesian framework, which can quantify the uncertainty (discussed further below).

1.4.2 Application of statistical models for leptospirosis

Numerous previous studies have used statistical models to understand leptospirosis epidemiology and risk factors, and in particular, the role of climate on leptospirosis cases. The results of many of these studies have been discussed in section 1.2.3, "Role of climate on leptospirosis transmission".

There have been a range of different models used, including spatial, temporal and spatio-temporal models. A recent systematic review published in 2018 identified 51 studies which modelled the relationship between various risk factors (i.e. environmental risk factors such as land use and flood risk, and climatic risk factors such as precipitation) and leptospirosis incidence and prevalence in humans, animals, or both [35]. Many different data sources were used in these models. Several spatial models used cross-sectional seroprevalence data [31, 35]. The advantage of seroprevalence data is the provision of a cross-sectional representation of the spatial risk factors, which can be useful for understanding the role of environmental risk factors, such as the presence of floodplains. However, it does not capture temporal risk factors, and so is less suited to exploring the role of climate and acute events (e.g., flooding) on leptospirosis cases. Other models use routine surveillance data, which is limited by the surveillance systems and testing and reporting practices established in the given setting and is subject to fluctuations in these practices over time. Since leptospirosis burden is often high in under-resourced settings, surveillance data in many countries can be limited, particularly given these countries may also experience coinciding outbreaks of other diseases such as dengue, which have similar clinical manifestations. To avoid the limitations with surveillance data, some studies instead focussed on hospital admissions [125], which is likely to accurately capture the most severe cases. However, given that leptospirosis is often asymptomatic or mildly symptomatic, hospital admissions will only capture a fraction of the true cases. It is known that some serovars are associated with higher pathogenicity, and that the transmission processes may likely vary due to animal host associations. Therefore hospital admissions may not be representative of all risk factors. Finally, one study instead explored the syndromic surveillance system [126], the early warning, alert, and response system (EWARS), which was developed by the WHO to improve disease outbreak detection. The study demonstrated an association between six EWARS syndromic conditions that are commonly associated with leptospirosis, typhoid and/or dengue, and meteorological data (seasonality and rainfall). They suggest that it may be possible to predict outbreaks of climate-sensitive diseases using EWARS data, allowing time to adjust diagnostic capabilities and treatments.

1.4.3 Compartmental mechanistic models

Compartmental "SIR" models

One of the most common dynamic transmission models is the mechanistic compartmental "SIR" model, where a population is divided up into compartments based on their transmission status [123, 127]. One of the simplest forms of this model is the ""SIR" model (Fig. 1.6). These

models are often deterministic, in which the same results are always obtained from a given set of parameters, and the rate of flow between these compartments is typically determined by a series of ordinary differential equations.

$$\frac{dS(t)}{dt} = -\lambda(t)S(t) = -\beta S(t)I(t) \tag{1.1}$$

$$\frac{dT(t)}{dt} = \lambda(t)S(t) - \gamma I(t) \tag{1.2}$$

$$\frac{dR(t)}{dt} = \gamma I(t) \tag{1.3}$$

The number of susceptible individuals who are newly infected per unit time is the product of the force of infection (λ) and the number of susceptible individuals at time *t, S(t)*. If we assume random mixing, the force of infection (λ) can be replaced by the product of β, which is the rate at which two individuals come into effective contact per unit time, and *I(t)*, which is the number of infectious individuals at time *t*. Individuals are assumed to remain infectious for a constant amount of time, and γ is the rate at which individuals recover and become immune. This simple model makes several simplifying assumptions, such as that random mixing occurs, that individuals are infected for the same duration of time, and that they are equally infectious. These models can be extended to address these assumptions.

Depending on the disease system, compartmental models can be divided into further compartments, for example, including a latent period (time between the infection event and infectiousness) or additional age categories, or in the case of zoonotic diseases, the inclusion of both humans and animal reservoirs [128, 129]. A schematic representation of a leptospirosis compartmental is shown in Fig. 1.7, which includes humans, animals and the environmental leptospires.

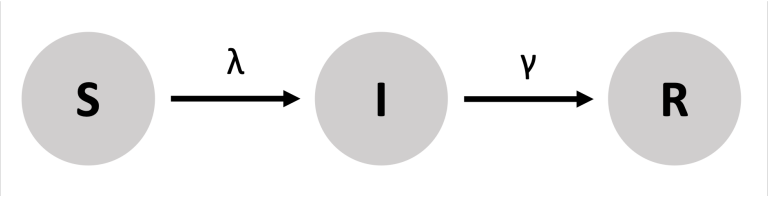

Figure 1.6: Schematic of a Susceptible (S) - Infected (I) - Recovered (R) compartmental model. λ: force of infection; γ: rate at which individuals move from the infected to recovered compartment.

Application of compartmental "SIR" models for leptospirosis

There have been a number of compartmental "SIR" models developed and used to explore leptospirosis transmission dynamics. These have been systematically reviewed in Chapter 5 and so

will only briefly be discussed here. The majority of previous compartmental leptospirosis models have been theoretical (i.e. exploring thresholds for disease elimination or endemic equilibrium), with only a handful of studies calibrating or fitting their model to data [130–136]. Most studies chose to focus on particular elements of the transmission pathway, and only two studies considered the whole transmission system [133, 137]. Chadsuthi *et al.* [133] fitted their transmission model to human case data from Thailand, along with local climate information. They found that a model in which the transmission rate depended on both flooding and temperature best explained the human data observed. This study highlights that by incorporating information on the transmission processes, as well as the role of climate, can allow for a greater understanding of the transmission dynamics. This can allow for more accurate predictions of outbreaks and an improved understanding of the interventions most likely to be successful. Overall, however, most of the studies did not consider the environmental reservoir within their models despite being a major source of transmission to humans. Furthermore, the role of climate on transmission was rarely considered. This highlights the need for more data-driven modelling, and for more models which consider the full transmissions process within a One Health framework.

Catalytic models

Another type of compartmental model is the catalytic model [123, 138]. The catalytic model differs from the mechanistic compartmental "SIR" model as instead of explicitly describing the transmission between individuals (i.e. expressing the force of infection in terms of the number of infectious individuals and a transmission parameter), the catalytic model assumes that individuals are infected at a constant rate. They were first proposed by Muench [139], and the term catalytic stems from the similarity to the processes that drive chemical reactions. In its simplest form, the catalytic model assumes that the population is divided into two states, "susceptible", *s(a)* and "infected", *z(a)*, and individuals are infected at a given rate per year, the force of infection (FOI), λ. Once infected, individuals recover and remain immune. If a disease is fully immunising, as is the case for pathogens like measles, then seroprevalence would be expected to accumulate over time, and therefore with age. However, for diseases which are not fully immunising, such as leptospirosis and seasonal HCoVs, individuals serorevert, and this is marked by the progressive loss of protective antibodies over time. The catalytic model can be extended to allow for waning immunity and for previously infected individuals to become susceptible once more (reverse catalytic model; Fig. 1.8). The rate at which antibody prevalence declines over time can be estimated as the waning rate, ω. The expressions for both the catalytic and reverse catalytic model are shown below.

The catalytic model follows individuals from birth and assumes that there is a life-long constant FOI, λ, which is independent of age (a) and calendar year.

The differential equations for the catalytic model are as follows:

$$\frac{ds}{da} = -\lambda s(a) \tag{1.4}$$

$$\frac{dz}{da} = \lambda s(a) \tag{1.5}$$

Where *a* is age, *s(a)* is the proportion susceptible and *z(a)* is the proportion ever infected.

The differential equations can then be solved, and the rate of change in the proportion of individuals who are infected *z(a)* with age can be written as follows:

$$z(a) = 1 - e^{-\lambda a} \tag{1.6}$$

where λ is the FOI and *a* is age and assumes that all individuals are born susceptible, *z(0) = 0*.

The reverse catalytic model assumes that antibody prevalence declines over time, at a rate ω. The expression for the proportion of individuals age a who are seropositive, *z(a)*, in the reverse catalytic model is as follows:

$$z(a) = \frac{\lambda}{\lambda + \omega}(1 - e^{-a(\lambda+\omega)}) \tag{1.7}$$

where λ is the FOI, ω is seropositivity waning rate and *a* is age, and *z(0) = 0*. Both models assume the mortality rates for susceptible and infected individuals are the same.

The assumption that the FOI is the same for all age groups and over time may not always hold true. For example, for respiratory infections, the FOI may be higher in younger age groups due to increased intensity in social contacts in these age groups. Likewise, the FOI may change over time, either due to large outbreaks or the introduction to interventions such as vaccination. Therefore, to account for these, numerous studies have adapted the catalytic model to allow for age and time-varying FOI [123, 140, 141]. Generally, catalytic models are fitted to cross-sectional seroprevalence data broken down by age, as this can provide information on the populations who have evidence of prior exposure.

Application of catalytic models for leptospirosis and seasonal HCoV

Although there are many examples of catalytic models applied to infectious diseases (including measles [142], rubella [143], malaria [140], trachoma [141] and dengue [144]), a literature search did not reveal any previous studies applying this class of model to leptospirosis. Furthermore, to the best of my knowledge, there has been one previous study which applied catalytic models to seasonal HCoV. Huang *et al.* [94] presented a simple catalytic model combining data from six seroprevalence studies, which assumed no waning immunity and a constant FOI. This model was the starting basis of the analysis I present in Chapter 4.

1.4.4 Fitting models to data

Advances in computational capabilities and the field of infectious disease modelling have enabled the development of more complex models, and for these models to be fitted and informed with real world data. Model parameters can be estimated from data using a wide range of techniques. Bayesian methods are commonly used for model fitting, such as Markov chain Monte-Carlo (MCMC) [140,141], and these allow for the inclusion of external information from previous studies using prior distributions. This relies on Bayes theorem, where the posterior distribution, p(θ|data), is proportionate to the likelihood of the data given the model parameters θ (p(data|θ)) multiplied by the prior information on θ (p(θ)):

$$p(\theta|data) \propto p(data|\theta)p(\theta) \tag{1.8}$$

In this thesis I have assumed that surveillance data follows a Negative Binomial distribution. The Negative Binomial distribution can be used for count data which exhibit overdispersion as it relaxes the assumption of the Poisson distribution that the mean and variance are equal [145]. When fitting models to seroprevalence data I assumed that this data followed a Binomial distribution.

MCMC is a commonly used method to sample from the posterior distribution when the analytical form of that distribution is not known, and generates estimates of the parameter distributions. MCMC methods involve proposing initial parameter values and drawing samples from the approximate distribution. The parameters are updated based on the sample and accepted or rejected based on the likelihood. These parameters are then updated using an iterative process until the parameter estimates converge. Two of the most common MCMC sampling algorithms are Metropolis-Hastings and Gibbs sampling. An example of the Metropolis-Hastings is presented below:

1. An initial value of θ is chosen ($\theta_0 = \theta_{t-1}$) as the "current" sample
2. A new sample θ' is proposed from the "proposal distribution" $g(\theta'|\theta_{t-1})$
3. Accept or reject the proposed sample θ' with a probability:

$$P_{Accept} = min(1, \frac{p(\theta'|data)/g(\theta'|\theta_{t-1})}{p(\theta_{t-1}|data)/g(\theta_{t-1}|\theta')}$$

   If θ' is rejected, use the current sample as a new sample instead.

4. Steps 2 and 3 are repeated until convergence.

Gibbs sampling is a special case of the Metropolis-Hastings algorithm where proposals are always accepted with a probability of one. The Gibbs sampler draws iteratively from posterior conditional distributions, with each current draw depending on the previous draw [146]. One of the challenges with MCMC is assessing when the MCMC chains have converged, as one

needs to ensure that the full parameter space has been sampled. There are a number of different convergence diagnostics that can be used, such as the effective sample size (ESS) and the Gelman-Rubin diagnostic [147].

An alternative approach for Bayesian inferences is Integrated Nested Laplace approximation (INLA) [148]. INLA provides a computationally more efficient alternative to MCMC methods, by using numerical approximations of model parameters. This can be particularly useful when comparing multiple models, for example a range of different climatic variables with different lags.

When there are multiple candidate models, model selection criteria can be used to distinguish between different models. Information criterion aim to balance goodness of fit of the model with model complexity (number of parameters), and therefore aims to balance the risks of overfitting and underfitting [149]. The Akaike information criterion (AIC) is the most widespread information criterion, and is defined as,

$$AIC = -2L + 2k$$

Where k is the number of parameters within the model and L is the log-likelihood. The Widely Applicable information criterion (WAIC) is a generalised version of the AIC and is a Bayesian approach for estimating the out of sample expectation which uses the full posterior distribution [149, 150]. The WAIC is defined as,

$$WAIC(y,\theta) = -2(lppd - \sum_i var_\theta log p(y_i|\theta)$$

Where y is the observations, θ is the posterior distribution and lppd is the log-posterior-predictive-density.

Model performance can also be assessed using cross-validation. Cross-validation leaves out small chunks of observations, and then assesses the model's ability to accurately predict the observations that were left out, after training on all the other data. This is repeated with all the data, to obtain an estimate of out of sample accuracy. Often, only a single observation is left out, and this is referred to as the leave-one-out cross-validation (LOO-CV). However, this process can be computationally intensive, and therefore approximations exist, such as the Pareto-smoothed importance sampling (PSIS) cross-validation, also known as PSIS-LOO.

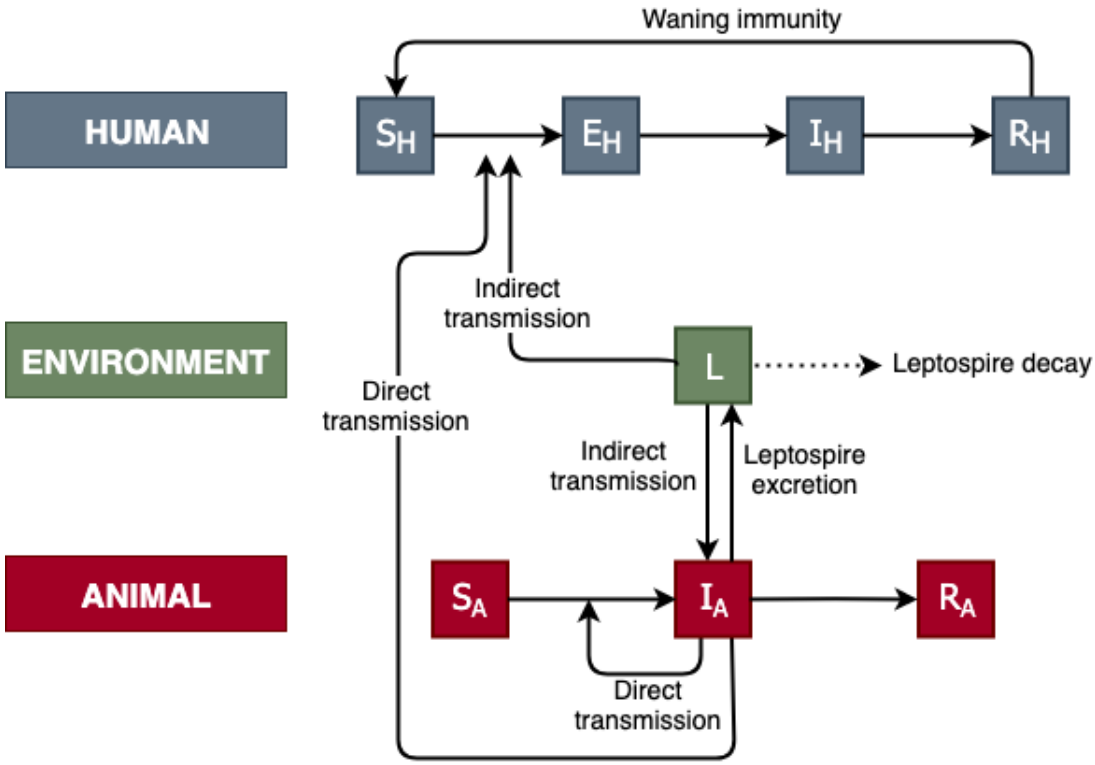

Figure 1.7: Schematic representation of a leptospirosis compartmental model. Humans can become infected either indirectly via the environment (L) or directly via an infected animal (S_A). Once infected, humans move from susceptible (S_H) to latently infected (E_H), to infected (I_H) and finally to recovered (R_H). Once recovered they lose immunity at a waning rate and return to the susceptible compartment, where they can once more become infected. Animals are infected either from the environment (indirect) or from another infectious animal (direct). Once infected they move from susceptible (S_A), to infected (I_A) and finally to recovered (R_A). This model assumes that there is no waning immunity due to the shorter animal lifespan. Infected animals release leptospires (L) into the environment. Once in the environment they decay based on a decay rate. While in reality there are many different animal hosts, this theoretical model is based on cattle given they are thought to be one of the predominant sources of infection to humans in Fiji.

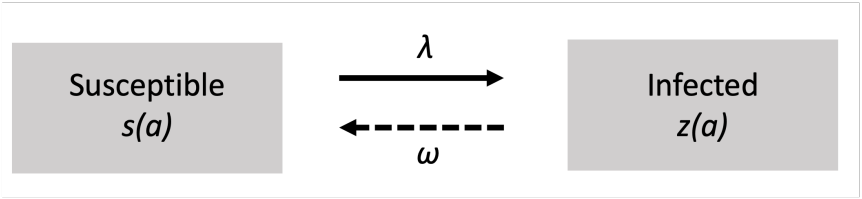

Figure 1.8: Schematic of a reverse catalytic model. λ, force of infection; ω, waning of immunity.

1.5 Aim

The overall aim of this thesis is to understand the complex drivers of infectious disease transmission dynamics using two different diseases as case studies, leptospirosis and seasonal HCoV.

This aim will be addressed with the following objectives:

1. Identify hydrometeorological indicators influencing leptospirosis incidence in Fiji and how these vary over geographical space and temporal scale, moving towards a climate-based early warning system for leptospirosis.
2. Understand the infection dynamics of leptospirosis by estimating the duration of antibody persistence from a large cross-sectional serosurvey, and estimate the most likely timing of infection.
3. Estimate the duration of antibody persistence and age-varying infection risk using serocatalytic models with data from six seroprevalence studies covering four seasonal HCoVs.
4. Identify existing compartmental models of zoonotic diseases with environmentally persistent pathogens to provide insights for the future development of compartmental transmission models which include the transmission process within a One Health framework.

1.6 Structure of this thesis

This thesis is written in a research paper style, where each analysis chapter takes the form of a scientific paper that has been published or is in the process of submission. This introductory chapter provides the relevant background for leptospirosis, seasonal HCoV, and the different mathematical models that can be applied to understand transmission drivers and dynamics. The thesis then contains four results chapters, which are described below, followed by an overall discussion. A summary of leptospirosis transmission and how Chapters Two and Three relate to this, is described in the schematic diagram Fig. 1.9.

Chapter One: Quantifying the relationship between hydrometeorological indicators and leptospirosis incidence in Fiji: a modelling study.

This chapter addresses objective one. It uses a Bayesian mixed-effects model to explore different climatic drivers (including rainfall, temperature and ENSO indicators) of leptospirosis outbreaks in Fiji from 2006-2017 using surveillance data. This paper also explores how these climatic drivers vary over temporal scale and over geographic space. The results provide a greater understanding of the role of climate in Fiji, allowing for more targeted public health approaches, as well as moving towards the development of a climate-based early warning system.

Chapter Two: Estimating the duration of antibody positivity and likely timing of *Leptospira* infection using data from a cross-sectional serological study in Fiji.

This chapter was published in PLOS NTD in 2022, Rees *et al.* [73], and addresses objective two. It describes a reverse catalytic model used to estimate the duration of *Leptospira* antibody persistence from a cross-sectional seroprevalence survey. This has important epidemiological and clinical significance since it can provide insights into the frequency of reinfections and the level of under-reporting, and allow for improved interpretation of leptospirosis serosurveys. In addition, this paper also estimates the most likely timing of infection from the serosurvey by bringing in longitudinal information on antibody kinetics. This provides new insights from serology data, and may be particularly useful in resource-limited settings.

Chapter Three: Estimating the duration of seropositivity of human seasonal coronaviruses using seroprevalence studies.

This chapter was published in Wellcome Open Research in 2021, Rees *et al.* [151], and addresses objective three. It describes a reverse catalytic model used to estimate the duration of seropositivity of seasonal HCoVs from six cross-sectional seroprevalence surveys covering the four different circulating seasonal HCoVs. This model was extended to allow for age-variation in risk. The results from this study provide insights into the transmission dynamics of seasonal HCoVs. Furthermore, the duration of antibody persistence and reinfection was largely unknown for SARS-CoV-2 at the beginning of the pandemic, therefore, since seasonal HCoVs have been circulating for much longer, they offered insights into the reinfection patterns of this group of diseases.

Chapter Four: Transmission modelling of environmentally persistent zoonotic diseases: a systematic review.

This chapter was published in Lancet Planetary Health in 2021, Rees *et al.* [152], and addresses objective four. This chapter details the results from a systematic review which critically appraises compartmental transmission models of zoonotic diseases with environmentally persistent pathogens. Previous studies that had modelled these complex pathogens were reviewed, with a particular focus on how the environmental reservoir was included and accounted for. In addition, the different model structures and the data that was used were highlighted. Key themes and best practices were identified, as well as areas for improvement.

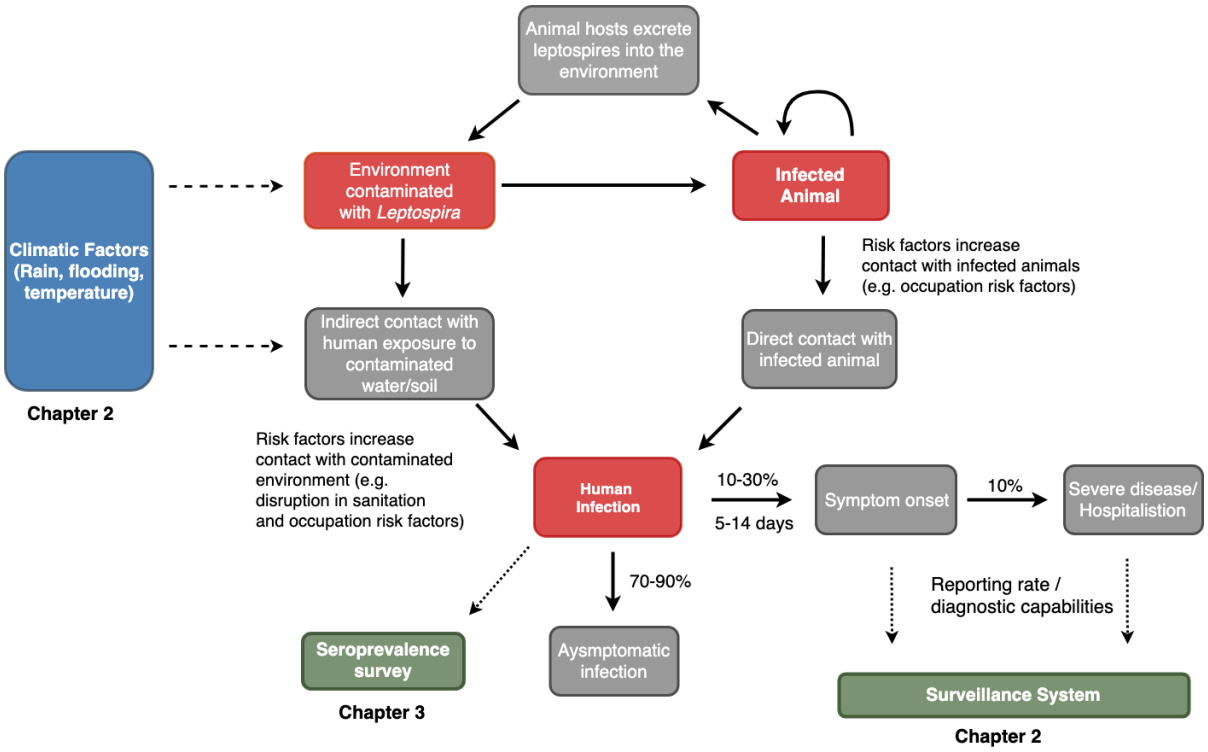

Figure 1.9: Schematic of transmission pathways and risk factors for leptospirosis including the way in which climate impacts transmission. Climatic factors (including rain, flooding and temperature) impact both the survival of the pathogen in the environment and indirect contact of humans with contaminated water or soil (e.g., flooding leads to disruption of sanitation networks). The role of climate on leptospirosis transmission is explored in Chapter two. Humans can also become infected by direct contact with a contaminated animal. Once infected, humans may be symptomatic or asymptomatic. Of those that are symptomatic, approximately 10% will develop severe disease and/or hospitalisation. Symptomatic individuals may be captured by the surveillance system, and this is dependent on whether someone reports to health care (which will depend on disease severity) and the diagnostic capabilities of the setting (including whether or not leptospirosis is clinically suspected). Leptospirosis surveillance data is used in Chapter two. Seroprevalence data instead captures individuals who have evidence of a past *Leptospira* infection, and so captures both asymptomatic and symptomatic individuals, and this data was used in Chapter three.

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2

Quantifying the relationship between hydrometeorological indicators and leptospirosis incidence in Fiji: a modelling study

Climate variables, such as precipitation and temperature, can modulate and increase the risk of leptospirosis transmission via multiple pathways [1, 2]. Climate can impact the pathogen itself, (i.e. providing suitable temperatures for survival in the environment) [3], but also can affect human exposure to infection [4]. This may be through heavy rainfall and flooding events bringing people and animals into contact with contaminated water, or due to human behavioural factors, such as heat-related changes in recreational and agricultural activities. In Fiji, leptospirosis is endemic, with outbreaks often occurring following heavy rainfall and flooding events. However, the relationship between climate and cases has not been well quantified. Therefore, the aim of this study was to explore the role of climate on leptospirosis incidence in Fiji using a Bayesian hierarchical mixed model framework. I also explored how these climate indicators varied over geographical space and temporal scale. I had access to daily case data and this offered the opportunity to explore the impact of aggregating cases to different temporal scales. Studies often use monthly case data since publicly available surveillance data and gridded climate products are often only available at this resolution. I explored the impact of using aggregated data on model outputs, and the implications of this for public health policy. Furthermore, understanding the climatic drivers of leptospirosis cases is a necessary first step towards the development of a climate-based early warning system, which could allow for more targeted public

health approaches.

The supplementary material of the paper is included as Appendix B.

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Surname/Family Name	Rees		
Thesis Title	Understanding complex drivers of infectious disease transmission dynamics		
Primary Supervisor	Adam Kucharski		

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2.1 Abstract

Background

Leptospirosis is a zoonotic disease which occurs globally, particularly in tropical and subtropical regions. Leptospirosis is endemic in Fiji, with cases occurring year round and frequent sporadic outbreaks. These outbreaks often coincide with periods of heavy rainfall and flooding. However, the relationship has not yet been well characterised in the South Pacific. In this study, we quantify the effects of different hydrometeorological indicators on leptospirosis incidence in Fiji, using a time series of weekly case data between 2006 and 2017 by division.

Methods and Findings

We used a Bayesian hierarchical mixed-model framework to explore the impact of different precipitation, temperature, and El Niño Southern Oscillation (ENSO) indicators on leptospirosis cases in Fiji over a 12-year period. We found that total precipitation from the previous six weeks was the best precipitation indicator, with increased total precipitation leading to increased leptospirosis incidence. La Niña periods (i.e., prolonged negative Sea Surface Temperature anomalies) were associated with increased leptospirosis risk. Finally, minimum temperature when included with the other variables was moderately associated with leptospirosis risk, with warmer temperatures resulting in increased risk. We found that the final model was better able to capture the outbreak peaks compared with the baseline model (which included seasonal and interannual random effects), particularly in the Western and Northern division, with climate indicators improving predictions 58.1% of the time.

Discussion

The results from this study identified key hydrometeorological and climatic factors influencing leptospirosis risk in Fiji. This information, combined with data on demographic and spatial risk factors of leptospirosis, could allow for a precision public health framework. This may allow for more effective public health preparedness and response, targeting interventions to the right population, place, and time. This study further highlights the need for enhanced surveillance data, and this study is a necessary first step and moves us towards the development of a climate-based early warning system.

2.2 Introduction

Leptospirosis is a zoonotic disease with an estimated 1.03 million cases, and 58,000 deaths reported globally each year [1]. It is found in all regions of the world, but the burden of disease is particularly high in Oceania and other resource-limited settings [2–4], and it is a major public health concern in many countries. It is caused by pathogenic spirochaete bacteria, of the genus *Leptospira* [5]. Leptospirosis typically presents as an acute febrile illness and symptoms can resemble other diseases, such as dengue and malaria, which often leads to misdiagnosis or underdiagnosis [5–9]. In some patients, more severe disease can occur and the case fatality rate of leptospirosis is estimated to be approximately 7% [1], although in settings with limited access to treatment and diagnosis it can be higher. Surveillance of leptospirosis is often limited, and many countries have limited capacity for diagnostic testing. Furthermore, the laboratory diagnosis of leptospirosis is challenging, and there is a lack of adequate diagnostic tests available for accurate and early diagnosis of leptospirosis [10, 11].

Leptospirosis transmission is driven by complex interactions between animals, humans and their environment. Hundreds of animal species have been identified as hosts for leptospirosis, including rodents, livestock, and domestic and wild animals [7, 12, 13]. Humans can become infected, either directly through contact with infected animals or tissue, or indirectly through water or soil contaminated by animal urine; but human-to-human transmission is extremely rare [5, 7, 8]. Once in the environment, bacteria can survive for weeks or even months in water or moist soil [5, 14–16]. As such, there are many different risk factors for leptospirosis, and these are context specific. Risk factors include occupational (such as agricultural workers and abattoir workers), lack of sanitation, poor living conditions, animals in the community and recreational exposures [4, 17–19].

Climatic factors have also been shown to increase leptospirosis risk, with outbreaks of leptospirosis often associated with extreme precipitation and flooding events [4, 18, 19]. Extreme precipitation and flooding bring humans into increased contact with the bacteria and their animal hosts, as well as disrupting public health infrastructure and sanitation networks. Furthermore, Leptospira can survive for longer periods in water and moist soil, and flooding prevents animal urine from being absorbed into the soil or evaporation. These outbreaks have been reported worldwide in geographically diverse areas, although they appear to be more common in tropical island nations and resource-poor settings [4, 19]. Temperature may also have a role in leptospirosis transmission since higher temperatures and humid environments have been shown to prolong Leptospira environmental survival [5, 13, 14]. Human interaction with the environment also increases with higher temperatures, leading to more exposure risk [4].

Large-scale climate patterns, such as the El Niño Southern Oscillation (ENSO), which is an inter-annual cycle involving changes in sea-surface temperatures in the central and eastern tropical Pacific Ocean, influences the timing and intensity of rainfall in the tropical Pacific islands and elsewhere. El Niño and La Niña are opposite phases of the ENSO, and on average ENSO events occur every four years. In Fiji, El Niño tends to be associated with drier and cooler

conditions than normal and can be associated with droughts in some parts of the country, whilst La Niña is associated with wetter than normal conditions. This leads to increased incidence of flooding, particularly if the La Niña event coincides with the wet season [20]. However, since Fiji lies in the transition zone, the impacts of ENSO are not always uniform and no two ENSO events are quite the same, although they tend to share typical characteristics. ENSO has been shown to be associated with leptospirosis outbreaks in New Caledonia [21]. The authors found that La Niña phases (cool Sea surface temperature (SST) anomalies in the Pacific Ocean) were associated with leptospirosis outbreaks, and they demonstrated how SST anomalies (a measure of ENSO) may be used as an early warning system in this setting. Tropical cyclones regularly occur in Fiji, usually during the wet season (November to April), and these can cause extensive damage and flooding [20, 22]. On average, 1-2 cyclones affect Fiji every season, and tropical cyclone activity has been shown to increase during El Niño phases, compensated by a decrease during La Niña phases [20, 22]. Due to climate change, Fiji is expected to experience more extreme rainfall events and rising temperatures. Furthermore, tropical cyclones are expected to be less frequent, but more intense in the future [23].

Leptospirosis disease burden is particularly high in Oceania, and a systematic review found that Oceania had the largest per capita leptospirosis morbidity (150.68 cases per 100,000 per year) and mortality (9.61 deaths per 100,000 per year) globally [2]. Leptospirosis is endemic in Fiji, with cases reported throughout the year. However, outbreaks of leptospirosis are reported most frequently during the rainy season (between January and March) [24]. In recent years the number of reported cases has been increasing, with large outbreaks occurring more frequently. This could either be due to a real increase in the number of cases, or improvements in testing capabilities and increased health awareness, particularly since the release of new leptospirosis guidelines in 2016. A previous seroprevalence study conducted in 2013 identified risk factors associated with leptospirosis cases in Fiji, including individual risk factors (working outdoors, male sex and iTaukei ethnicity) and community risk factors (lack of treated water at home, living in rural areas, high poverty rate, living less than 100m from a major river, pigs in the community and high cattle density) [17]. The seroprevalence study was further analysed and it was found that there was significant geographical variation in these sociodemographic and environmental drivers [25].

Despite the substantial disease burden, there still is limited quantitative evidence about the effects of precipitation, temperature and ENSO on leptospirosis cases in the Pacific region. This study aims to identify the most relevant hydrometeorological indicators and quantify the effect of these indicators at different spatial and temporal scales on leptospirosis incidence in Fiji. Together with the knowledge of demographic and spatial factors, this can support a precision public health approach, efficiently targeting interventions to the right populations at the most appropriate time and place. This will become increasingly important in the future as extreme weather events are expected to increase in frequency as a result of climate change, the effects of which are already being felt in this region.

2.3 Methods

2.3.1 Study location and setting

Fiji is an island nation in the South Pacific Ocean and is made up of over 330 islands. It is classified by the United Nations as a small island developing state [26] (Fig. 2.1). The population size was 884,887 in 2017 [27], and it is estimated that 90% of the population in Fiji are coastal dwellers [28]. Fiji is divided into four administrative divisions (Central, Western, Northern and Eastern). There are two main islands in Fiji, Viti Levu which is split between the Central and Western division and where approximately 80% of the population resides, and Vanua Levu in the Northern division. The capital, Suva, is located in the South East of the Central division, and has a population size of 94,088.

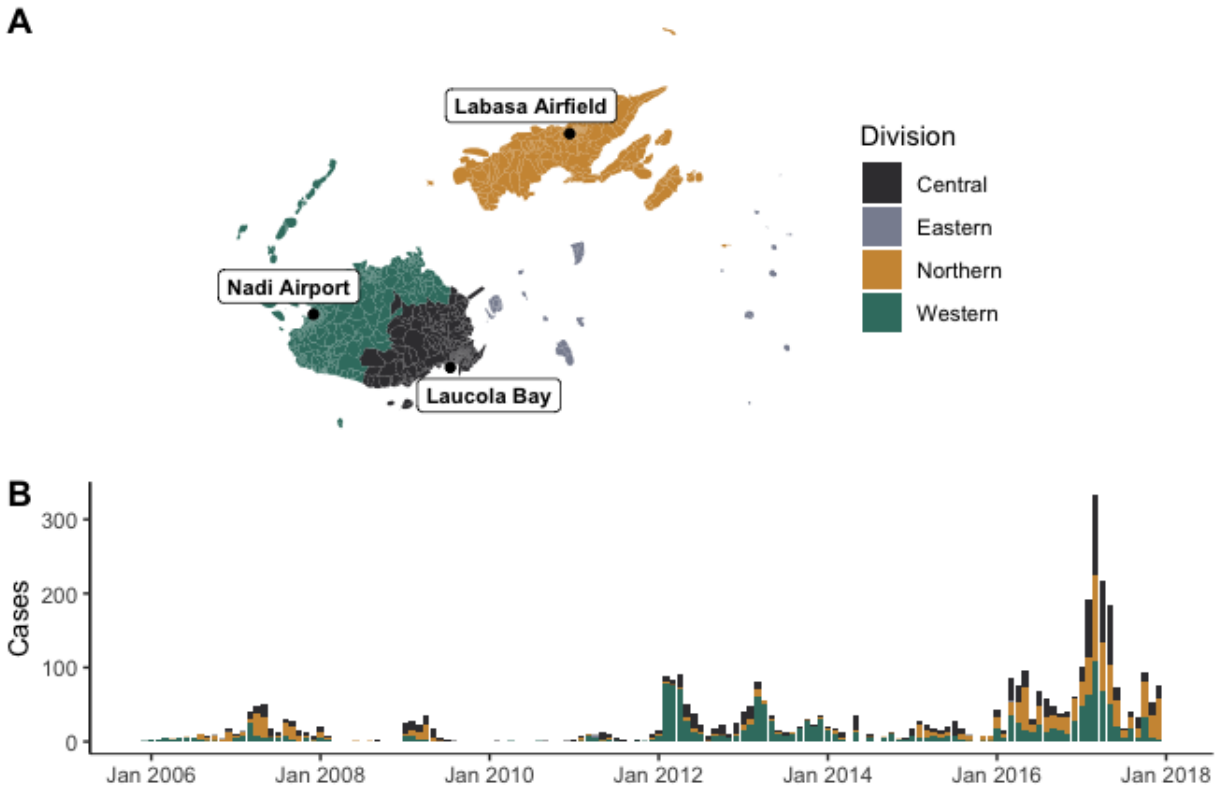

Figure 2.1: A. Map of divisions within Fiji. The location of the three meteorological stations used are labelled (Laucola Bay, Nadi Airport and Labasa Airfield). B. Monthly reported leptospirosis cases by division between 2006 and 2017 in Fiji.

2.3.2 Leptospirosis surveillance data

Leptospirosis is a notifiable disease in Fiji, and cases are reported through the Notifiable Diseases Surveillance System. Cases are defined as suspected, probable, and confirmed. Suspected cases are based entirely on clinical assessment and epidemiological risk factors. Probable and confirmed cases are based on a combination of clinical assessment, epidemiological risk factors and the results from diagnostic testing. The two most common diagnostic tests performed in Fiji are the anti-Leptospira immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA), which is only available from Mataika house in Suva, and rapid diagnostic tests, which are available in laboratories across Fiji. Cases which are positive using these tests are considered probable cases. Very few cases in Fiji are confirmed using confirmatory diagnostic tests. Further information can be found in the clinical guidelines [29]. Once an outbreak has been declared, it recommended that diagnosis is performed based on case definitions and clinical assessment to conserve testing capabilities [30].

In this analysis, ELISA-positive cases of leptospirosis reported between 2006 and 2017 were included. Where possible, date of sample collection was used. For 225 cases, the date of sample collection was unavailable, and the date received or date tested were used instead. These dates were then adjusted by the median number of days between date of sample collection and date received (four days) and the date of sample collection and date tested (16 days). Cases were aggregated into weekly (by ISO weeks) and monthly cases.

2.3.3 Demographic data

Population estimates for each division were obtained from the Fiji Bureau of Statistics from the 2007 and 2017 Population and Housing Census [27]. Linear interpolation was used to estimate the population size between these two time periods for each division.

2.3.4 Meteorological data

The analysis was performed at both the weekly and monthly time scale, therefore daily climatic data was aggregated to both time scales. Daily precipitation, minimum daily temperature and maximum daily temperature were obtained from the Fiji meteorological services. Exploratory analysis was performed to select one meteorological station in each division, based on data completeness for the study period. These were Laucala Bay (Central division; latitude: -18.13, longitude: 178.45), Nadi Airport (Western division; latitude: -17.75, longitude: 177.43) and Labasa Airfield (Northern division; latitude: -16.47, longitude: 179.33; Fig. 2.1). We also explored using averages over all meteorological stations in a division and found that there was little impact on the results obtained, therefore for simplicity we selected one station per division. Weekly and monthly Optimum Interpolation SST version 2.1 (OISSTV2.1) anomalies in region 3.4 (Niño 3.4 index) and region 4 (Niño 4 index) were obtained from the NOAA [31].

To capture extreme precipitation, five precipitation indicators were chosen based on descriptive indices defined by the World Meteorological Organisation Expert Team on Climate Change

Detection and Indices [32]. These five indicators are described in Table 2.1. Different durations of the time period (j) were tested, (two, four, six and eight weeks for the weekly surveillance data, and one, two and three months for the monthly surveillance data).

Long-term periods of abnormal wetness can also be captured using the Standardised Precipitation Index (SPI) and the Standardised Precipitation Evapotranspiration Index (SPEI) [33, 34]. Positive values of SPI and SPEI correspond to wet periods, whilst negative values correspond to dry periods. SPI and SPEI were calculated using the SPEI package in R [35]. SPI was calculated for each division using daily precipitation from 1990 to 2018 from three meteorological stations in Fiji (Laucala Bay, Nadi Airport and Labasa Airfield). To calculate SPEI, first minimum and maximum daily temperature, as well as latitude coordinates of the meteorological stations, were used to calculate monthly reference evapotranspiration (ETO) according to Hargreaves equation. Then the climatic water balance ($d_{i,j}$), which provides a measure of the water surplus or deficit for a specific month '*i*' in the year '*j*', was calculated as precipitation minus reference evapotranspiration:

$$d_{i,j} = P_{i,j} - ETO_{i,j} \tag{2.1}$$

SPI and SPEI were calculated for different time scales, one, three and six months.

To account for the time between infection to symptom onset, as well as the delayed effects of climate indicators on disease, different time lags for temperature, precipitation indicators, SPI and SPEI were tested, from 1-12 weeks (weekly surveillance data) and 1-3 months (monthly surveillance data). Changes in SST anomalies can take longer to impact the local climate; therefore, longer time lags were used to assess the effect of Niño 3.4 and Niño 4 indices on leptospirosis transmission, from 1-20 weeks (and 1-4 months).

2.3.5 Meteorological events

In Fiji, between 2007 and 2017 (the study period) there were six tropical cyclones and five major flooding events (with an additional five flooding events triggered by the tropical cyclones) recorded by the Emergency Events Database [EM-DAT [36]; Supplementary Table 1]. Data on disasters were obtained from the EM-DAT database, which includes events if either there have been 10 or more deaths; more than 100 people affected, injured or homeless; or a declaration by the country of a state of emergency and/or an appeal for international assistance. The primary disaster may trigger another event (i.e., a tropical cyclone may trigger a flooding event), and this is recorded in Supplementary Table 1. The timing of the tropical cyclones and flooding events is displayed in Supplementary Fig. 1, along with weekly precipitation data.

2.3.6 Statistical analysis

First, we formulated a hierarchical mixed-effects model using counts of leptospirosis cases per week over 12 years (January 2006 to December 2017) in Fiji. Counts of leptospirosis cases, yst,

Table 2.1: Definition of precipitation indicators defined and adapted from the Expert Team on Climate Change Detection and Indices [32]

Precipitation indicator	Definition
Total precipitation (TP)	Total precipitation (TP) on wet days (≥ 1mm). Let P_{wj} be the daily precipitation amount on a wet day w (P ≥ 1 mm) in period j. Then, Total precipitation$_j$ =sum(P$_{wj}$)
Heavy precipitation days (P10)	Count of days where daily precipitation amount ≥ 10 mm. Let P_{ij} be the daily precipitation amount on day i in period j. Count the number of days where P$_{ij}$ ≥ 10 mm.
Very heavy precipitation days (P20)	Count of days where daily precipitation amount (P) ≥ 20 mm. Let P_{ij} be the daily precipitation amount on day i in period j. Count the number of days where P$_{ij}$ ≥ 20 mm.
Number of wet days (WD)	Count of days where daily precipitation amount (P) ≥ 1 mm Let P_{ij} be the daily precipitation amount on day i in period j. Count the number of days where P$_{ij}$ ≥ 1 mm.
Mean consecutive wet days (CWD)	Mean number of CWD (consecutive wet days) (≥ 1mm) in period j. Let P_{ij} be the daily precipitation amount on day i in period j. Count the largest number of consecutive days where P$_{ij}$ ≥ 1 mm. Then, Mean consecutive wet days$_j$ = $mean$(CWD$_j$)

(where s is division and t is time), were assumed to follow a negative binomial distribution to account for the overdispersion within the data, with mean μ and overdispersion parameter κ,

$$y_{st}|\mu_{st} \sim NegBin(\mu_{st}, \kappa) \tag{2.2}$$

which we modelled using the linear predictor,

$$log(\mu_{st}) = log(P_{st}) + \alpha + \sum \beta_i x_{ist} + \delta_{sa(t)} + \gamma_{w(t)} \tag{2.3}$$

where α is the model intercept and $log(P_{st})$ is the population size per 100,000 per year per division, which we inputted as an offset. $\sum \beta_i x_{ist}$ is a vector of covariate climatic coefficients. To account for the seasonality of leptospirosis cases, a weekly random effect, $\gamma_{w(t)}$, where $w(t) = 1, ..., 52$. This was modelled using a first-order random walk, which allows leptospirosis incidence rates in one week to depend on the previous week. Independent random effects for each year ($\delta_{sa(t)}$), 2006–2017 replicated by division were included to allow for additional sources of variation due to unobserved confounding factors such as variations in healthcare access, case reporting and changes in diagnostic capacity over time and between divisions.

Model parameters were estimated using Integrated Nested Laplace Approximation (INLA). Model selection was performed using the widely applicable information criterion (WAIC), which balances model fit with model complexity, and therefore aims to balance the risks of overfitting and

underfitting. Models with a lower WAIC indicate a more parsimonious model [37]. The cross-validated logarithmic score (CV log score) was also used to assess model fit. This is based on the conditional predictive ordinate (CPO) leave-one-out cross-validation score, where smaller values indicate greater predictive power of the model [38]. An R^2_{LR} statistic was also calculated based on a likelihood ratio test between the candidate model and the baseline model (seasonal and interannual random effects). R^2_{LR} is useful as a measure of goodness-of-fit and provides an intuitive measure of the ability of the model to account for the variation in the dependent variable.

A baseline model was first developed, which included weekly and yearly random effects. Exploratory analysis and selection criteria were used to select the most appropriate time lags for the climate covariates, and a subset of covariates were chosen for further analysis. We then explored combining the different precipitation indicators with different temperature and ENSO measures. The final model was selected using the model selection criteria described above and comparing models of increasing complexity (with regard to input variables and model structure) to the baseline model. We were also interested in the differences between the divisions; therefore, the final model was fitted separately for each division.

To check for correlation and collinearity between variables, we calculated Pearson's rank correlation index using the "corrplot" package in R [39]. A Pearson's correlation r > 0.6 was considered to be high correlation. We also calculate the variance inflation factor (VIF) using the "car" package in R [40]. A VIF > 5 was considered to be indicative of high variance inflation.

Given the potential for heterogeneity in weekly data, we performed a sensitivity analysis to test how the model results changed at different spatial and temporal scales. We repeated the model formulation and selection, using counts of leptospirosis cases per month. Instead of using a weekly random effect, a monthly random effect was used, again using first order random walk. Independent random effects for each year ($\delta_{sa(t)}$), 2006–2017 replicated by division were included as before. Finally, we repeated the analysis for the whole country, instead of by division. As before we repeated the model formulation and selection, using counts of leptospirosis cases per month. Again, a monthly random effect was used, using first order random walk. This time, independent random effects for each year ($\delta_{a(t)}$), 2006–2017 were included, not replicated by division.

2.3.7 Ethics statement

Ethical approval for this study was granted by the London School of Hygiene and Tropical Medicine (reference number 16171) and by the Fiji National Health Research and Ethics Review Committee (reference number 2019.72.NW).

2.4 Results

2.4.1 Leptospirosis incidence in Fiji

Between 2006 and 2017, a total of 3,485 ELISA-positive cases of leptospirosis were reported in Fiji (979 in the Central division, 1,481 cases in the Western division, 1,019 cases in the Northern division and six in the Eastern division; Fig. 2.1). Since only six cases were reported in the Eastern division over the study period, the Eastern division was excluded from the analysis. Over this time period, the Northern division reported the highest case rates (759.9 cases per 100,000) followed by the Western division (452.0 cases per 100,000) and the Central division (272.8 per 100,000). The majority of leptospirosis cases were reported between February and May.

2.4.2 Weekly leptospirosis model

Using the weekly cases data a final model was selected (Model 6, Table 2.2), comprising of weekly random effects and yearly random effects replicated by division (to account for seasonality and unmeasured inter-annual variability by division), minimum temperature lagged by one week (Tmin.1), Niño 3.4 lagged by four weeks (Niño34.4) and total precipitation from the previous six weeks lagged by one week (TotPrcp6.1). Table 2.2 shows the model goodness of fit results for a series of models with increasing complexity. When minimum temperature was included alone in the model it did not improve model fit (Model 3), however, when included in combination with Niño 3.4 index and total precipitation it did improve model fit (Model 6). We identified total precipitation from the previous six weeks (with a one-week lag) as the best precipitation indicator to capture leptospirosis cases in Fiji (Supplementary Table 2.2). However, there was only a small improvement compared with other indicators such as the number of very heavy rainfall days (P20). Increased levels of precipitation (TotPrcp6.1) was associated with increased leptospirosis risk (0.24 [95% CrI 0.15 – 0.33]; Fig. 2.2). In addition, we found negative Niño 3.4 (Niño34.4) to be associated with increased leptospirosis incidence rates (-0.2 [95% CrI -0.29 – -0.11]; Fig. 2.2). Finally, we identified minimum temperature (Tmin.1) to be slightly associated with increases in leptospirosis incidence rates (0.15 [95% CrI 0.01 – 0.30]; Fig. 2.2).

The time series of observed cases and model fit is shown in Fig. 2.3. The final model is better able to capture the outbreak peaks (e.g. in 2012 and 2013 in the Western division, in 2016 in the Central, Northern and Western division, and in 2017 in the Western and Northern division) compared with the baseline model (Model 1; which includes only random effects). This is highlighted in Supplementary Fig. 2, which shows the relative difference between the baseline and final model. In 58.1% (362 out of 623) of weeks the full model performed better than the random effects model (256 out of 623; 41.1%). However, the model does not appear to capture the peaks in the Central division as well as in the Northern and Western division. The posterior marginal contribution of the seasonal random effects decreased with the inclusion of the hydrometeorological variables (Supplementary Fig. 3), demonstrating that climate is accounting

for some of the seasonal variation that is observed. However, overall, the posterior marginal contribution of the inter-annual random effects did not appear to shrink towards zero with the inclusion of hydrometeorological variables, indicating that there are other non-climatic factors influencing interannual variability in leptospirosis incidence (Supplementary Fig. 4). Using the parameter estimates associated with the climate variables from the best performing model, we extracted the variation in leptospirosis incidence accounted for by the combined impact of total precipitation, minimum temperature, and the Niño 3.4 index (Supplementary Fig. 5). This plot suggests that before 2012, the climatic conditions may have been suitable for a leptospirosis outbreak, particularly in the Western and Northern division in 2008 and 2009, but this is not reflected in the case data. It also shows that in the Central division the role of climate appears to be more consistent compared with the other two divisions.

Table 2.2: Model goodness of fit results for models of ELISA-positive leptospirosis cases per week reported in Fiji from 2007 to 2017. The widely applicable information criterion (WAIC), the cross-validated (CV) mean logarithmic score and the likelihood ratio RLR2 statistic are shown for models of increasing complexity.

	Model	WAIC	CV log score	R^2_{LR} (%) RE
	$\alpha + \delta_{sa(t)} + \gamma_{w(t)}$			
1	Baseline model (seasonal and interannual random effects)	5328	1.426	0
	$\alpha + \delta_{sa(t)} + \gamma_{w(t)} + \beta_1 x_{st}$			
2	Baseline + Tmin.1	5325	1.425	0.1
	$\alpha + \delta_{sa(t)} + \gamma_{w(t)} + \beta_2 x_{st}$			
3	Baseline + Niño34.4	5302	1.419	1.8
	$\alpha + \delta_{sa(t)} + \gamma_{w(t)} + \beta_3 x_{st}$			
4	Baseline + TotPrcp6.1	5298	1.418	1.4
	$\alpha + \delta_{sa(t)} + \gamma_{w(t)} + \beta_2 x_{st} + \beta_3 x_{st}$			
5	Baseline + Niño34.4 + TotPrcp6.1	5279	1.413	2.8
	$\alpha + \delta_{sa(t)} + \gamma_{w(t)} + \beta_1 x_{st} + \beta_2 x_{st} + \beta_3 x_{st}$			
6	Baseline + Tmin.1 + Niño34.4 + TotPrcp6.1)	5276	1.412	2.9

Tmin.1: Minimum temperature (lagged by one week); Niño34.4: Niño 3.4 (lagged by four weeks); TotPrcp6.1: Total precipitation from the previous six weeks (lagged by one week).

2.4.3 Weekly leptospirosis model by division

To understand differences in parameter estimates between the divisions, we explored three separate models for each division. We found that minimum temperature was still weakly positively associated with leptospirosis cases, but not significant in each division. In addition, we found that negative Niño 3.4 anomalies were still associated with increased cases in all divisions (although not significant in the Northern division). Total precipitation was found to be more strongly associated with leptospirosis cases in the Western division, compared with the Northern and Central divisions, and not statistically significant in the Central division. The R^2_{LR} for each division model indicates that the climate covariates better account for leptospirosis variation in the Western division compared with the Northern and Central divisions. In the

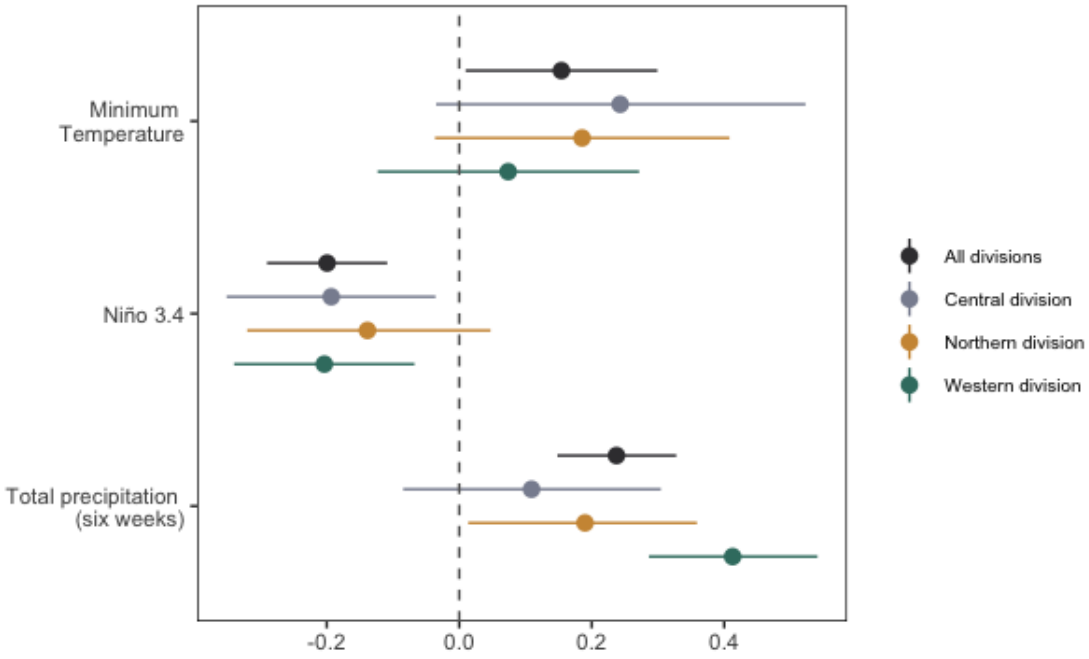

Figure 2.2: Parameter estimates for explanatory variables for models of ELISA-positive leptospirosis cases per week reported in Fiji from 2007 to 2017 for all divisions (black) and separately by division. Posterior mean and 95% credible intervals are shown for minimum temperature (lagged by one week), total precipitation from the previous six weeks (lagged by one week), and Niño 3.4 (lagged by four weeks).

Western division the R^2_{LR} explained an additional 6.7% of the variation compared with the baseline model, whilst for the Central and Northern division the R^2_{LR} was 1.6% and -1.2%, respectively (Supplementary Table 3). The negative values indicate that for the Northern division, the baseline model explained more of the variation than the full model.

2.4.4 Monthly leptospirosis model

As a sensitivity analysis we explored how the model estimates differed by changing temporal scale. We aggregated cases to the monthly scale and performed model selection and evaluation for climate covariates. At the monthly scale, we found that the best performing model included total precipitation from the previous two months (no lag), and Niño 3.4 index (two-month lag; Supplementary Table 4; Supplementary Fig. 6). These are similar to the climate covariates identified at the weekly scale. However, minimum temperature was no longer found to increase model fit, and there was no positive association between minimum temperature and leptospirosis cases at the monthly scale. The time series for observed and modelled cases is shown in Supplementary Fig. 7. Once again, the final model is better able to capture the outbreak peaks compared to the baseline model (random effects only). However, it does not appear to capture the variability as well in the Central division. The monthly model is bet-

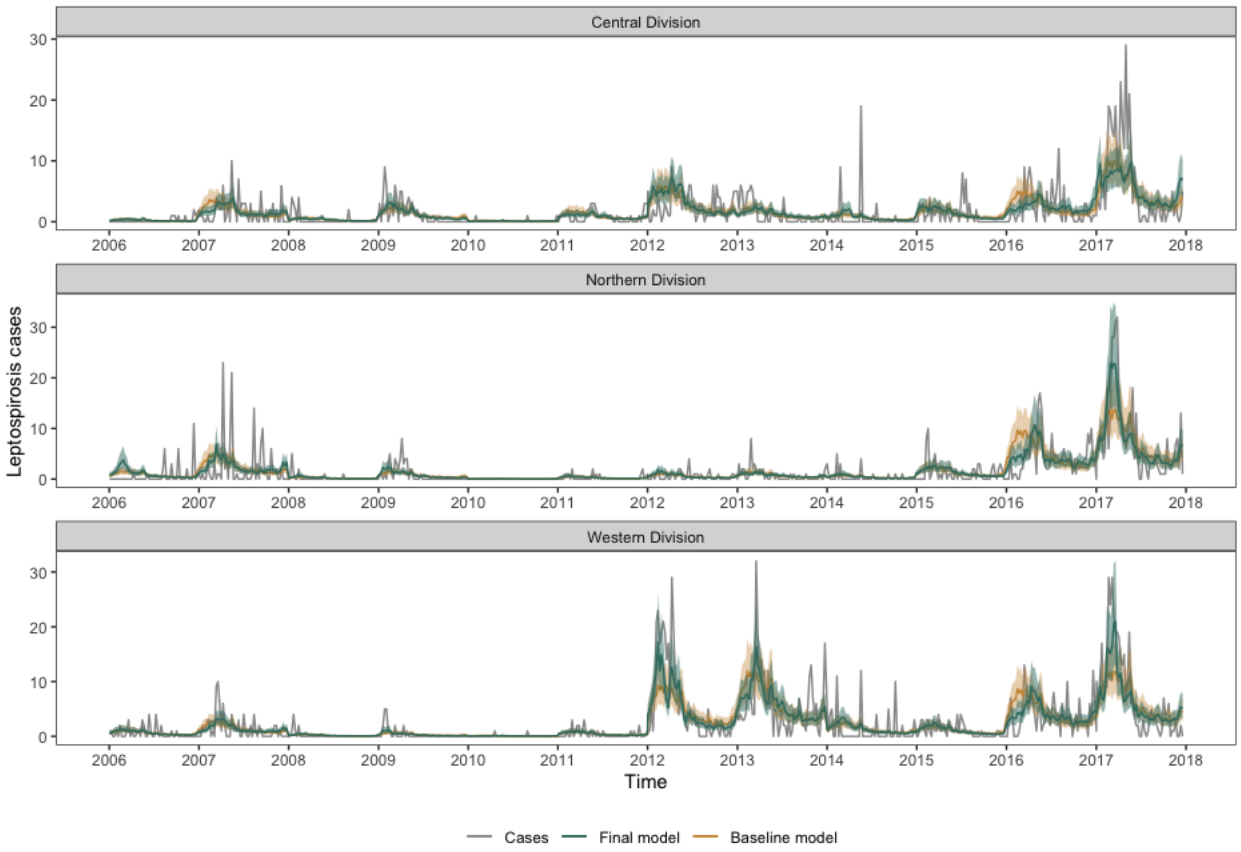

Figure 2.3: Model posterior estimates for models of ELISA-positive leptospirosis cases per week reported in Fiji from 2007 to 2017 by division. Observed ELISA-positive cases (grey line), posterior model mean (green line) and 95% credible intervals (green shading) are shown for the best performing model which included total precipitation, minimum temperature and Niño 3.4. The random effect only model is shown as an orange dashed line.)

ter able to capture the variability in the data compared with the weekly data (R^2_{LR} for the final weekly model was 2.9%, compared with 7.4% for the monthly model; supplementary Table 3), which may be due to the increased heterogeneity in the data at the weekly scale. Again, looking at the model goodness of fit results, the difference in R^2_{LR} for each division model shows that climate information in the Western division better explains the variability compared with the Northern and Central division. In the Western division the R^2_{LR} explained an additional 19.8% of the variation compared with the baseline model, whilst for the Central and Northern division this was 5.8% and -3.0% respectively (Supplementary Table 3). Finally, we also explored how the modelling results changed if we moved from a division level to the whole country. We identified that the same climate covariates at the country level as the division level and saw very little difference in the parameter estimates (Supplementary Fig. 6).

2.5 Discussion

Climate is known to influence the timing and size of leptospirosis outbreaks. However, the role of specific climate factors has not been well quantified in Fiji. In the present study, we explored the role of different hydrometeorological indicators, including precipitation, temperature and ENSO, on leptospirosis risk. The results from this study further our understanding of the effect of hydrometeorological variables on leptospirosis outbreaks in Fiji, which may allow for a more targeted public health approach in the future.

In this study we found total precipitation in the preceding six weeks, lagged by one week, was the best precipitation indicator for this setting, and was positively associated with leptospirosis cases. This supports previous studies that showed precipitation was an important driver of leptospirosis outbreaks, in Fiji and elsewhere [4, 18, 19, 24]. We identified six weeks as the best time period, suggesting that cumulative precipitation is important - rather than a few days of sudden heavy rain. In addition to total precipitation, we also found that the number of very heavy rainfall days (number of days in a period where rainfall exceeded 20mm), also over six weeks, was strongly associated with leptospirosis cases, indicating the importance of exploring different hydrometeorological indicators in different settings. Minimum temperature, lagged by one week, was also found to be positively associated with leptospirosis risk. Several studies have previously identified that temperature may have a role in leptospirosis outbreaks [41–44], although this appears to be context specific, as other studies have not found this association in different settings [21, 45, 46]. The short lag time observed in the present study suggests that temperature may play a role by changing human behaviour and how humans interact with the environment (i.e., in warmer conditions there is more recreational water activity and changes in agricultural activity). In addition, we found that the Niño 3.4 index was negatively associated with leptospirosis outbreaks. This suggests that La Niña phases are associated with increased leptospirosis risk in Fiji, and a similar result was observed in New Caledonia [21]. In Fiji, La Niña is associated with increased rainfall and flooding events. However, given ENSO events occur on average every four years, a longer time series is required to be able to fully understand the relationship between ENSO and leptospirosis risk.

We found that the role of climate appears to vary by division, with the model better able to capture cases in the Western division compared with the Northern and Central divisions. Flooding events and tropical cyclones appear to be correlated with increased rainfall in the Western and Northern divisions, however, in the Central division rainfall appeared to be more consistent and less correlated with these events. This suggests that the role of climate on leptospirosis risk may differ by division, or that tropical cyclones and flooding events are not well captured with the precipitation data in the Central division. In the present study, we only had case information by division. By aggregating by division we assume that risk is homogenous across this region, however, these are large areas which encompass many different environmental and socio-demographic settings. There are likely large differences in the transmission pathways, risk factors and environment between the divisions, therefore, climate may be acting differently in each division, and within each division. For example, risk factors are known to differ in

urban, peri-urban, and rural settings, and this was not known for cases [17, 25, 47]. Additionally, natural environmental factors, such as the proximity of rivers and floodplains, influence the likelihood of experiencing a leptospirosis outbreak in a community. Inadequate sanitation and waste disposal are also risk factors for leptospirosis, and these are linked to poverty. Poverty, particularly in urban areas in Fiji, is known to be associated with a high seroprevalence of leptospirosis [48]. In addition to environmental and socio-economic differences between divisions, the importance of different animal hosts, and therefore transmission pathways and risk factors, has been shown to vary geographically and by ethnic group [25, 47]. For example, in urban settings, exposure to livestock was associated with a high risk of infection, which is hypothesised to be a result of closer contact between animals and humans. Furthermore, as many as 19 different serovars and 11 different animal hosts have been identified in Fiji [12, 49]. Certain serovars are more commonly associated with certain animal hosts, and serovars also have different pathogenicity associated with them, and disease severity may also vary as a result. Finally, it is known that control practices, for example, rodent control, have taken place in Fiji, although the timing and exact location are not known, and so these are not accounted for in the model. Therefore, due to the complex process driving the transmission of leptospirosis in Fiji, it is likely that the importance and influence of the climatic factors vary depending on geographic and environmental settings. To untangle these differences, enhanced spatial resolution of surveillance data, along with detailed case and serovar information, would be required. Despite this, we were still able to identify significant climatic drivers of leptospirosis variation in Fiji.

As is common for studies of leptospirosis using routine data streams, the results from our analysis are limited by the surveillance data available. In this study, we used surveillance data for leptospirosis over 12 years and only included ELISA-positive cases. This requires individuals to be unwell, report to healthcare, and for samples to be sent for diagnostic testing. It is known that the majority of leptospirosis infections result in mild or asymptomatic infection. In addition, to conserve testing capability, once an outbreak has been declared, it is recommended that diagnosis is done based on case definitions and clinical judgement [30]. Therefore, the cases and the outbreaks reported by the ELISA-positive data are likely to be a small fraction of the true cases occurring in Fiji [50]. Furthermore, changes in case detection, case reporting and diagnostic capabilities have occurred over time. The number of cases has been increasing in recent years, with several large outbreaks occurring. This may be due to real increases in the number of cases, or due to enhanced surveillance and testing capabilities over time, or enhanced clinical suspicion following the release of new leptospirosis guidelines in 2016. Furthermore, case detection and reporting are likely to vary by division, due to differences in healthcare access, health-seeking behaviours, access to laboratory diagnosis, and clinical and public health capacity. This may have contributed to the differences observed between divisions on the importance of the different climate factors.

We found that the inclusion of climate covariates within the model better captured the outbreak peaks than the random effects only model (e.g., in 2012 and 2013 in the Western division, in 2016 in the Central, Northern and Western division, and in 2017 in the Western and

Northern division). We also found that the full model performed better overall than the random effects only model. This suggests that climate information explains some of the seasonal and inter-annual variation in leptospirosis cases and demonstrates the potential use of climate information within an early warning system for leptospirosis. However, looking at the overall yearly random effects, the interannual variation changed very little with the inclusion of climate covariates. This suggests other non-climatic or unknown factors were important in driving interannual variation in cases. To help understand both seasonal and interannual drivers of leptospirosis transmission, improved surveillance and spatially explicit case data is needed, along with spatially resolved climatic, environmental, and socio-economic variables. While climate may be a significant environmental driver of transmission, the model's current capacity for prediction is limited. This poses a challenge for the development of any climate-based early warning system for leptospirosis in Fiji and highlights the need for enhanced surveillance. The development of a climate-based early warning system would allow for enhanced knowledge of the timing and the severity of outbreaks which would enable public health responses to mitigate outbreaks.

The results from the present study can be interpreted together with the results from previous studies which have explored socio-demographic and environmental risk factors, to form a more complete view of leptospirosis risk in Fiji. In 2013, a seroprevalence study was conducted in Fiji which identified individual demographic risk factors for leptospirosis [17]. This data was further analysed to understand how these risk factors varied geographically [25, 48]. Seroprevalence studies have the advantage that they can capture the prevalence of previous infections, including asymptomatic and mildly symptomatic cases. However, they are a snapshot at one point in time, and are unable to explore how these risk factors vary over time or at different times of the year. Despite the limitations associated with surveillance data, it is longitudinal data which allows for the effect of climate on leptospirosis risk to be explored over time, as was done in the present study. Together, these studies can be thought of as moving towards a precision public health approach, providing more specific insights into differences in incidence between "populations", "place" and "time", and a more complete picture of leptospirosis risk in Fiji. Precision public health can be defined as using the best available data to target interventions more efficiently and effectively [51]. This is particularly important in resource-limited settings such as Fiji, as being able to accurately target interventions can provide a cost-effective strategy. In this study, we show how quantifying the effect of climate on weekly surveillance data, combined with the knowledge of those individuals who are most at risk [17], and those "hotspot" locations where prevalence is particularly high [48], can be used to target interventions to those most vulnerable and at risk. These measures could include targeted health promotion and awareness (i.e., encouraging the use of personal protective equipment and covering cuts and abrasions), raising awareness and clinical suspicion, hospital preparedness and ensuring diagnostic capabilities.

Weekly case data is more sensitive to collection processes and reporting delays, and we observed a lot of heterogeneity in the reported weekly cases. Therefore, as a sensitivity analysis, we aggregated the weekly case data into monthly case data and explored how the temporal scale

affected our results. We found very similar results, suggesting that there was good agreement between the models. However, minimum temperature was no longer found to be associated with leptospirosis cases at the monthly scale. In the weekly model, we identified that minimum temperature was associated with a one-week lag, suggesting that the effect of temperature occurred on a short time scale, and therefore, it may no longer be observed at a monthly time scale. This suggests that using weekly case data may allow the detection of climatic drivers within short timeframes. However, the choice of temporal scale depends on the research question and the data available. Using weekly case data is more computationally intensive, and many climate covariates are not readily available at the weekly scale. Using a monthly time scale may reduce the heterogeneity in the data as it will be less sensitive to small fluctuations in sample collection and reporting delays. This may allow long-term trends to be more easily identified, and a monthly time scale may be better suited for the development of an early warning system, particularly for neglected zoonotic diseases where surveillance is limited. A summary of the advantages and disadvantages is shown in Table 2.3.

In summary, we were able to quantify the association between different climate variables and leptospirosis incidence in Fiji. This study furthers our understanding of how climate affects leptospirosis outbreaks and combined with previous studies exploring the geographical distribution and sociodemographic risk factors, allows us to move towards a precision public health framework. This contributes to our understanding of the climatic risk factors and may allow for more targeted public health interventions in the future. This study also highlights that enhanced surveillance in the future may allow for further studies which untangle the spatial effects of climate on leptospirosis risk, and this is a necessary first step to allow for the development of an early warning system in the future. This will be increasingly important given that climate change in Fiji is predicted to lead to increased rainfall and extreme weather events, and leptospirosis will likely continue to pose a significant burden in this region.

Table 2.3: Summary of the advantages and disadvantages of fitting a climate-driven statistical model to weekly and monthly surveillance data.

	Advantages	Disadvantages
Weekly case data	• Finer temporal resolution, which allows for the effects of climate on disease to be detected at finer time scales, which may be more reflective of disease transmission processes.	• Often not available. • Climatic indicators are often available at monthly scales. • More computationally intensive. • More heterogeneity and uncertainty in the data ("noise"). For diseases and settings where surveillance is very thorough and complete, weekly case data is preferable. However, for diseases such as leptospirosis, where there are varying reporting delays, changes in reporting over time and space, trends may be more apparent at monthly time scales. • Shorter time scales are not always useful, one week does not enable enough time to react and anticipate outbreaks.
Monthly case data	• More readily available. • Aggregated data may allow for trends to be more apparent and stronger and therefore may be easier to identify long-term trends. • More computationally efficient – particularly important if you have high spatial resolution • May be more useful for early warning systems, as the associations may be more robust.	• May hide real patterns and trends. • Short term effects of climate on infection may not be apparent in the data.

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3

Estimating the duration of antibody positivity and likely time of *Leptospira* infection using data from a cross-sectional serological study in Fiji

The timing and the magnitude of infectious disease outbreaks can be determined by numerous factors, including climate (which was discussed in the previous chapter), and the level of population immunity to a pathogen, which is the focus here. Population immunity changes over time as new susceptibles enter the population (either through births or through human movement), and as protective immunity wanes. Reinfection is known to occur with *Leptospira* [1, 2], but the duration of protective immunity is not well understood. This has epidemiological and clinical implications since it can provide insights into the frequency of reinfections and the level of under-reporting of a disease, as well as allow for improved interpretation of serosurveys for leptospirosis. Serological studies of healthy populations have been used to study population dynamics. However, they can be difficult to interpret and compare to surveillance data in cases where antibodies wane. In fully immunising infections seroprevalence studies provide a population estimate of any past exposure to infection. For diseases which are not fully immunising, more historic infections become undetectable due to antibody levels waning over time, and this leads to an underestimation of population exposure. Instead, serocatalytic models can be used, as they estimate the force of infection (FOI), which is the rate at which susceptible individuals acquire infection and seroconvert, whilst accounting for antibody waning. Therefore, the aim of this study was to estimate the FOI and antibody persistence (as a proxy

for antibody-mediated immunity) from a large population-proportionate seroprevalence survey of *Leptospira* infection conducted in 2013 in Fiji [3]. Furthermore, I explored whether it was possible to reconstruct the most likely timing of *Leptospira* infection. This provided new insights into population-level serology data, and may be particularly relevant in resource-limited settings where financial constraints can limit longitudinal studies.

This paper was published in PLOS Neglected Tropical Diseases in June 2022 [4]. The Supplementary material of the paper is included as Appendix C.

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Primary Supervisor	Adam Kucharski		

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PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Estimating the duration of antibody positivity and likely time of *Leptospira* infection using data from a cross-sectional serological study in Fiji

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Abstract

Background

Leptospirosis is a zoonotic disease prevalent throughout the world, but with particularly high burden in Oceania (including the Pacific Island Countries and Territories). Leptospirosis is endemic in Fiji, with outbreaks often occurring following heavy rainfall and flooding. As a result of non-specific clinical manifestation and diagnostic challenges, cases are often misdiagnosed or under-ascertained. Furthermore, little is known about the duration of persistence of antibodies to leptospirosis, which has important clinical and epidemiological implications.

Methodology and principal findings

Using the results from a serosurvey conducted in Fiji in 2013, we fitted serocatalytic models to estimate the duration of antibody positivity and the force of infection (FOI, the rate at which susceptible individuals acquire infection or seroconversion), whilst accounting for seroreversion. Additionally, we estimated the most likely timing of infection.

Using the reverse catalytic model, we estimated the duration of antibody persistence to be 8.33 years (4.76–12.50; assuming constant FOI) and 7.25 years (3.36–11.36; assuming time-varying FOI), which is longer than previous estimates. Using population age-structured seroprevalence data alone, we were not able to distinguish between these two models. However, by bringing in additional longitudinal data on antibody kinetics we were able to estimate the most likely time of infection, lending support to the time-varying FOI model. We found that most individuals who were antibody-positive in the 2013 serosurvey were likely to have been infected within the previous two years, and this finding is consistent with surveillance data showing high numbers of cases reported in 2012 and 2013.

breaching participant confidentiality. The communities in Fiji are very small, and individual-level data such as age, sex, and village of residence could potentially be used to identify specific persons. Instead aggregated data by five year age groups and can be found here: https://github.com/erees/leptoSerology. The full data can be requested via The University of Queensland's Human Research Ethics Committee for researchers who meet the criteria for access to confidential data. Email: humanethics@research.uq.edu.au Phone: + 61 (7) 3365 3924.

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Conclusions

This is the first study to use serocatalytic models to estimate the FOI and seroreversion rate for *Leptospira* infection. As well as providing an estimate for the duration of antibody positivity, we also present a novel method to estimate the most likely time of infection from seroprevalence data. These approaches can allow for richer, longitudinal information to be inferred from cross-sectional studies, and could be applied to other endemic diseases where antibody waning occurs.

Author summary

Leptospirosis is a bacterial zoonotic disease that occurs in almost all regions of the world, with a particularly high burden of disease in Oceania. It is widely considered to be a Neglected Zoonotic Disease, and it is often mis-diagnosed and under-ascertained. Very little information exists about the persistence of antibodies to leptospirosis, which is important for understanding how long individuals may have partial protection against reinfection. In this study, we show how data collected from a large population survey of leptospirosis antibodies can be used to estimate the duration of antibody persistence. Knowledge of the duration of antibody persistence enables an estimation of the duration of immunity to re-infection, which is most likely antibody-mediated. We also estimate the rate at which susceptible individuals acquire infection (force of infection), whilst accounting for antibody waning. This provides more accurate estimates of population-wide disease burden. Finally, we show how the results from a cross-sectional population survey can be used to estimate when infections may have occurred. This is particularly useful in areas with limited surveillance. This approach could be applied to other neglected diseases for which data are limited and where antibody waning occurs.

Introduction

Leptospirosis, a zoonotic bacterial disease, is found throughout the world, but is particularly prevalent in tropical and subtropical regions [1–3]. It is widely considered to be a Neglected Zoonotic Disease [4], with an estimated 1.03 million leptospirosis cases and 58,000 deaths reported worldwide each year [1], and the disease disproportionately affects resource-limited populations [5–8]. In humans, *Leptospira* infection produces a wide range of clinical symptoms, ranging from nonspecific febrile illness to jaundice, meningitis, and liver and renal failure [6,7,9]. Recent laboratory advances isolating novel species of the genus *Leptospira* from the environment using Next-Generation Sequencing has expanded the number of named species to 68, which includes both pathogenic and non-pathogenic species, and these have been proposed to be organised into two clades, and four subclades [10–12]. Leptospira can also be serologically classified into serogroups and serovars, and serotyping based on the heterogeneity of the surface lipopolysaccharide (LPS) has led to the identification of 25 serogroups and over 300 serovars [11,13–16]. Certain serovars are more commonly associated with particular hosts, for example *Leptospira interrogans* serovar Hardjo is frequently associated with cattle, and *Leptospira interrogans* serovar Canicola with dogs [16,17]. However, these associations are not absolute, and there is considerable heterogeneity in the dominant serovars in both animals and humans each country, even in remote islands [3].

Accurate diagnosis of leptospirosis remains a challenge, particularly in low and middle-income countries. Firstly, it requires clinicians to suspect leptospirosis, and since symptoms can resemble other more prevalent acute febrile illnesses, such as dengue fever, it is often misdiagnosed or underdiagnosed. Secondly, the laboratory tests are not always available, and there are several limitations associated with each test [18–20]. The gold-standard test for diagnosing leptospirosis infection is the microscopic agglutination test (MAT), which has a high specificity and can distinguish between serogroups. However, this test has complex technical requirements. The enzyme-linked immunosorbent assay (ELISA) test is most commonly used in this context as it is easier to perform and is more sensitive than the MAT test during the acute phase of the illness, but it is not serogroup or serovar-specific. A summary table of the advantages and disadvantages of both tests is shown in S1 Table. Since both of these tests detect specific antibodies, it is important to consider the timing of testing in relation to onset of illness, as there needs to be sufficient time for the immune response to occur, and IgG or IgM antibodies to be detectable (from five to seven days post-infection) [19].

Immunity against *Leptospira* infection appears to be mediated by humoral responses [13,21], with the antibodies produced mainly targeting the surface-exposed leptospiral LPS. Anti-LPS antibodies appear to provide immunity to homologous serovars [22,23]. In addition, IgG and IgM antibody titres remain serologically detectable three to six years following infection [24,25]. The duration of protective immunity conferred following *Leptospira* infection is uncertain, and there is evidence that reinfection does occur [17,23,26,27]. Most commonly, reinfection occurs with a different *Leptospira* serogroup, and appears to result in a milder clinical disease. This suggests some degree of cross-reactive protective immunity [17,23]. However, severe disease following reinfection with the same serovar has been observed [27]. Current understanding of leptospirosis immunity is incomplete and there are gaps in the knowledge regarding leptospiral antibody dynamics, including the duration of antibody persistence, the relationship between antibody titre and reinfection, and the peak antibody levels that occur following infection.

A systematic review found that Oceania suffers the largest per capita leptospirosis morbidity (150.68 cases per 100,000 per year), mortality (9.61 deaths per 100,000 per year) [1], and disability-adjusted life years [28]. This may be an under-estimate of the true burden of disease, as access to testing is limited in the Pacific Islands, and cases are likely to be under-diagnosed [8,29]. This was evidenced by a large population-representative serological survey conducted in Fiji in 2013, which found that 19.2% of individuals sampled had evidence of a past infection [29], yet the total number of cases reported for the five years prior to the survey was around 1,200 [30] [with Fiji population size reported to be 884,887 in 2017 Census [31]]. Leptospirosis is endemic in Fiji and has been identified as one of the four priority climate-sensitive diseases of major public health concern [32]. In addition to endemic transmission, outbreaks of leptospirosis frequently occur, usually following flooding events [33].

Serological studies of healthy individuals have been used to study the population dynamics of leptospirosis [29]. However, these studies can be problematic to interpret because antibody levels wane, and therefore it is difficult to directly compare case data to seroprevalence. Serocatalytic models can be used to overcome these limitations, as they estimate the annual force of infection (FOI, the rate at which susceptible individuals acquire infection or seroconversion) whilst accounting for antibody waning (seroreversion), thus providing a better estimate of disease burden [34]. These models have been used previously for many other diseases, including infections such as measles and rubella which induce life-long immunity, as well as infections like malaria where immunity wanes [34–36]. The aim of this study is to use seroprevalence data from Fiji to estimate the FOI and the duration of antibody persistence in Fiji. Furthermore, this paper aims to demonstrate how serological data can be used to estimate the most

likely time of infection, providing additional information to enhance the analysis and interpretation of seroprevalence studies.

Methods

Ethics statement

Ethical approval for this study was granted by the London School of Hygiene and Tropical Medicine (reference number 16171) and by the Fiji National Health Research and Ethics Review Committee (reference number 2019.72.NW). Informed written or thumb-printed consent was obtained from adult participants, and informed written or thumb-printed parental/guardian consent and informed assent was obtained for child participants for the 2013 Fiji seroprevalence survey data [29]. Secondary analysis of an anonymised subset of this data was used in the present study.

Study setting

Fiji, a nation in the South Pacific Ocean, comprises of 323 islands and is classified by the United Nations as a small island developing state [37]. The two biggest islands are Viti Levu, where most of the population resides, and Vanua Levu, and together they make up 87% of the total land area in Fiji. The population size was 837,217 in 2007 [31], and it is estimated that 90% of the population in Fiji are coastal dwellers [38]. The largest administrative units are Divisions (Central, Western, Northern and Eastern) followed by Provinces (14 in total).

Data

2012–2013 suspected clinical leptospirosis cases in Fiji. We used a serum bank of 199 individuals with clinical suspected leptospirosis and positive IgM-ELISA, collected from April 2012 to November 2013 tested positive using an IgM-ELISA following an outbreak in Fiji [29,33]. MATs were conducted on serum from these patients, and 66 had detectable antibodies using MAT. The MAT tests were conducted on samples collected approximately two weeks following infection, although exact time lag between the onset of illness and testing were not known.

2013 Fiji seroprevalence survey. A total of 2,152 participants were included in the human serosurvey conducted in Fiji from September to December 2013 [29]. The population-representative survey included healthy community members across the Central Administrative Division (on the eastern side of Viti Levu), the Western Division (on the western side of Viti Levu), and the Northern Division (the islands of Vanua Levu and Taveuni). The age of participants ranged from 1 to 90 years (mean 33.6 years, standard deviation 19.8 years) and 45.8% were males. The presence of anti-*Leptospira* antibodies in sera collected from participants was determined using the MAT with a panel of six serovars, *Leptospira interrogans* serovars Pohnpei (serogroup Australis), Australis (serogroup Australis), Canicola (serogroup Canicola), Copenhageni (serogroup Icterohaemorrhagiae), Hardjo (serogroup Sejroe), and *Leptospira borgpetersenii* serovar Ballum (serogroup Ballum). An initial panel of 21 pathogenic serovars was used on a random selection of ~10% of the total samples. In addition, this 21 serovar panel was used on 199 *Leptospira* ELISA-positive samples collected from patients with suspected clinical leptospirosis in Fiji in 2012 and 2013. The serogroups most commonly detected in the clinical and serosurvey samples were then chosen and included in the final panel of six serovars. Further details on selection of the serovars for the MAT panel have been previously described by Lau *et al.* [29]. Samples were tested at titre dilutions from 1:50 to 1:3200, and MAT titres of $\geq$1:50 were defined as seropositive. A higher antibody titre dilution is usually

considered indicative of a more recent infection (i.e. MAT ≥1:400), whilst a lower antibody titre of a past infection. MATs were conducted at the WHO Collaborating Centre for Reference and Research on Leptospirosis in Brisbane, Australia.

Of the 2,152 individuals included within the study, 417 were seropositive to at least one serovar (19.4%). The age distribution of individuals included in the study by five-year age groups is shown in S1 Fig. A total of 351 individuals were seropositive to serovar Pohnpei (84.2%), 56 to serovar Copenhageni (13.4%), 49 to serovar Canicola (11.8%), 43 to serovar Australis (10.3%), 18 to serovar Ballum (4.3%) and three to serovar Hardjo (0.7%). Of these, 89 individuals were seropositive for more than one serovar. The ages of 12 individuals were missing, and they were excluded from the analysis. The age distribution of seropositive individuals by ten-year age group by serovar is shown in S2 Fig. The distribution of MAT titres by serovar is shown in S3 Fig.

Lupidi point-source outbreak. A point source outbreak of leptospirosis occurred in Italy in 1984 that involved 18 individuals who drank water from a common source that was contaminated with infected animal urine [25]. They were followed up over a five-year period, with MAT tests conducted at five different time points.

Serocatalytic models. Serocatalytic models can be used to reconstruct the annual force of infection (FOI, defined as the per capita rate at which susceptible individuals are infected each year) from cross-sectional serological surveys [34]. If an infection provides long-term immunity (e.g. measles), then we would expect seroprevalence to accumulate with time, and therefore increase with age. These dynamics can be captured using a catalytic model which assumes that susceptible individuals are infected at a given rate per year (i.e. FOI), and once infected, individuals recover and remain immune. An extension of this is the reverse catalytic model, which allows for antibody decline over time, and for previously infected individuals to become susceptible again. These simple models assume a constant FOI, however, variation in FOI with age and/or over time may lead to more complicated dynamics. Examples of different seroprevalence profiles that may be observed are shown in Fig 1.

The catalytic model follows individuals from birth and assumes that there is a life-long constant FOI (λ), which is independent of age (a) and calendar year. The rate of change in the proportion of individuals who are infected *z(a)* with age is as follows:

$$z(a) = 1 - e^{-\lambda a}$$

where λ is the FOI and *a* is age.

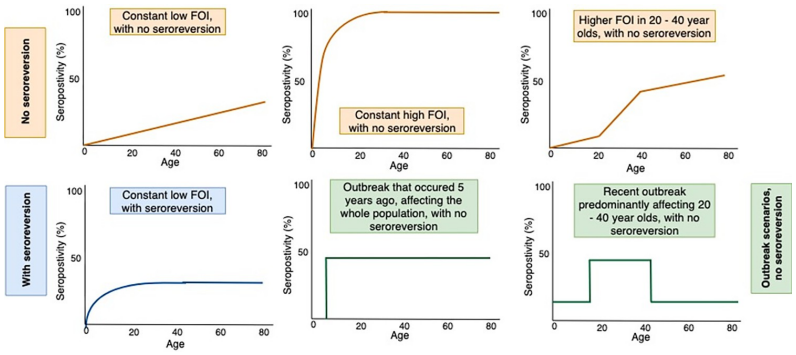

Fig 1. Schematic representations of different possible seroprevalence profiles by age that could be observed, depending on underlying epidemic and immunological dynamics.

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The reverse catalytic model assumes that antibody prevalence declines over time, at a rate ω. The expression for the proportion of individuals aged *a* who are seropositive, *z(a)*, in the reverse catalytic model is as follows:

$$z(a) = \frac{\lambda}{\lambda + \omega}\left(1 - e^{-a(\lambda+\omega)}\right)$$

where λ is the FOI, ω is seropositivity waning rate and *a* is age. Both models assume the mortality rates for susceptible and infected individuals are the same. 1/ω is the duration of antibody persistence (years). Annual attack rates were calculated after estimating the FOI using the following expression,

$$Attack\ rate = 1 - e^{-\lambda}$$

To reflect uncertainty in knowledge of the transmission dynamics of leptospirosis in Fiji uninformative priors were chosen for the FOI and rate of waning over time. Specifically, a uniform distribution between 0 and 0.5 was chosen for the FOI (corresponding to a yearly attack rate between 0 and 39%) and a uniform distribution between 0 and 10 for the rate of waning (S2 Table).

We then fitted the reverse catalytic model by sex, administrative division and serovar. In all models, waning was held constant and FOI was allowed to vary. For the serovar-specific analyses, 89 individuals were seropositive for more than one serovar. If the titre was higher for one serovar, this serovar was used for the analyses. For 18 individuals, the titres were the same for more than one serovar, and these were labelled as "mixed". Only a small number of individuals were considered seropositive for serovar Hardjo (n = 3) and serovar Australis (n = 1), and so were excluded from the analysis. For the analysis by sex and administrative division, the same priors were used as above, a uniform distribution between 0 and 0.5 for FOI, and a uniform distribution between 0 and 10 for the rate of waning. For the analysis by serovar, the FOI was allowed to vary by serovar, whilst waning was held constant across serovars. A narrower uniform distribution between 0 and 0.1 was used for the FOI instead, whilst the rate of waning was the same (uniform between 0 and 10; S2 Table).

Waning was held constant across serovars as when the FOI is lower, FOI and waning can be more challenging to estimate. This is because there are fewer infection events over time and hence greater uncertainty. To highlight this, we did a simulation recovery study where we recovered the FOI and waning estimates from two settings, a high FOI and low FOI setting. Using the reverse catalytic model we generated two models, a high FOI model (FOI, 0.05 and waning 0.1) and low FOI model (FOI 0.005 and waning 0.1). We then sampled 50 times from each 5-year age group using a binomial distribution to generate seropositive and seronegative individuals (S4 Fig). We then re-fitted a reverse catalytic model to both datasets to estimate the FOI and waning in both settings. In the high FOI setting we were able to get similar estimates for both FOI and waning, with the input parameter estimates included within the 95% credible intervals. However, in the low FOI setting, although the true parameter values were included within the 95% credible intervals, there was much greater uncertainty in the parameter estimates (S3 Table and S5 Fig).

Bayesian inference was used to fit the serocatalytic models to empirical data, using Markov chain Monte Carlo (MCMC) with the Gibbs sampling algorithm to estimate model parameters. The models were implemented in RJags (version 4–10) [39]. The Gelman-Rubin statistic was used to evaluate MCMC convergence, and a threshold of <1.1 was chosen. The effective sample size (ESS), which is the estimated number of independent samples accounting for autocorrelations generated by the MCMC run, was checked, and an ESS >200 was used. Model

selection was based on the lowest value of the widely applicable information criterion (WAIC), which balances the goodness of fit of the model with model complexity, and therefore aims to balance the risks of overfitting and underfitting [40,41]. WAIC was estimated using the R package Loo (version 2.4.1) [42]. All analysis and calculations were performed using R version 4.1.1. All R code is available on Github (https://github.com/erees/leptoSerology).

Time-varying FOI

The models described above assumed that the FOI was constant over time. We also considered exceptions to this assumption by exploring models which allow outbreaks to occur, where the FOI was instead given as a sum of Gaussian distributions, as described in the Rsero package [43]. The timing of the outbreak and the infection probability were estimated. A model with only one outbreak was compared with models which combined a constant FOI with an outbreak. A uniform distribution between 0 and 10 was chosen for the FOI and a uniform distribution between 0 and 10 for the rate of waning. Two different priors were tested for the timing of the outbreaks based on the earlier calculated duration of antibody persistence (S2 Table).

Analysis of time-varying FOI was performed using the Rsero package [43]. Parameter estimation was performed using MCMC using the No-U-Turn sampler (NUTS) sampling algorithm. Convergence was assessed by ensuring Gelman-Rubin statistic <1.1 and effective sample size >200. WAIC was estimated using the R package Loo (version 2.4.1) [42].

Reconstructing timing of historic infections

Using the MAT antibody titres from the 2013 Fiji seroprevalence survey, we estimated the timing of infection of participants. Due to uncertainty associated with individual titre estimates–and hence timings–the dynamics of infection was aggregated and reported as the population level expectation. Firstly, we estimated the rate at which individual responses wane by one antibody dilution titre. This was done using data from the point source outbreak in Italy reported by Lupidi *et al.* [25]. Since leptospirosis is not endemic in Italy, this presented an opportunity to look at antibody decay, in a setting where reinfection is unlikely. Using these data, decline in antibody titres for each individual was assumed to follow exponential decay, so that the log antibody titre decays linearly with time. A linear mixed effects model was used, with a random effect for the intercept as described below:

$$\text{titre} \sim \text{time} + (1|\text{id}) + \varepsilon$$

We implemented this model in R using the lme4 package [44]. Three serovars were identified by the MAT in the Lupidi *et al.* [25] point source outbreak, however, it was not clear which was the infecting serovar (likely due to cross-reactivity of the MAT). Therefore, all three serovars were analysed individually, and the results pooled.

To reconstruct the timing of infection from the 2013 seroprevalence survey we combined the 2012 Fiji clinically suspected cases with the estimated rate at which individual responses wane by one antibody dilution titre. First, using the 2012 Fiji clinically suspected cases (n = 199), we estimated the geometric mean antibody titre from the MAT-positive cases (n = 66). We then used the MAT antibody distribution of the 2012 Fiji clinically suspected cases, combined with the antibody decay estimates from Lupidi *et al.* [25], to analyse the 2013 seroprevalence data. For each titre level from the 2013 seroprevalence survey, the possible initial titre levels were estimated, based on the proportions from the 2012 Fiji clinically suspected case distribution results. Using the rate of decline of antibody titres, the initial titre levels were transformed into an estimated time since infection, reconstructing the potential timing of infection at the population level. An example for one titre is shown in Fig 2. As individuals

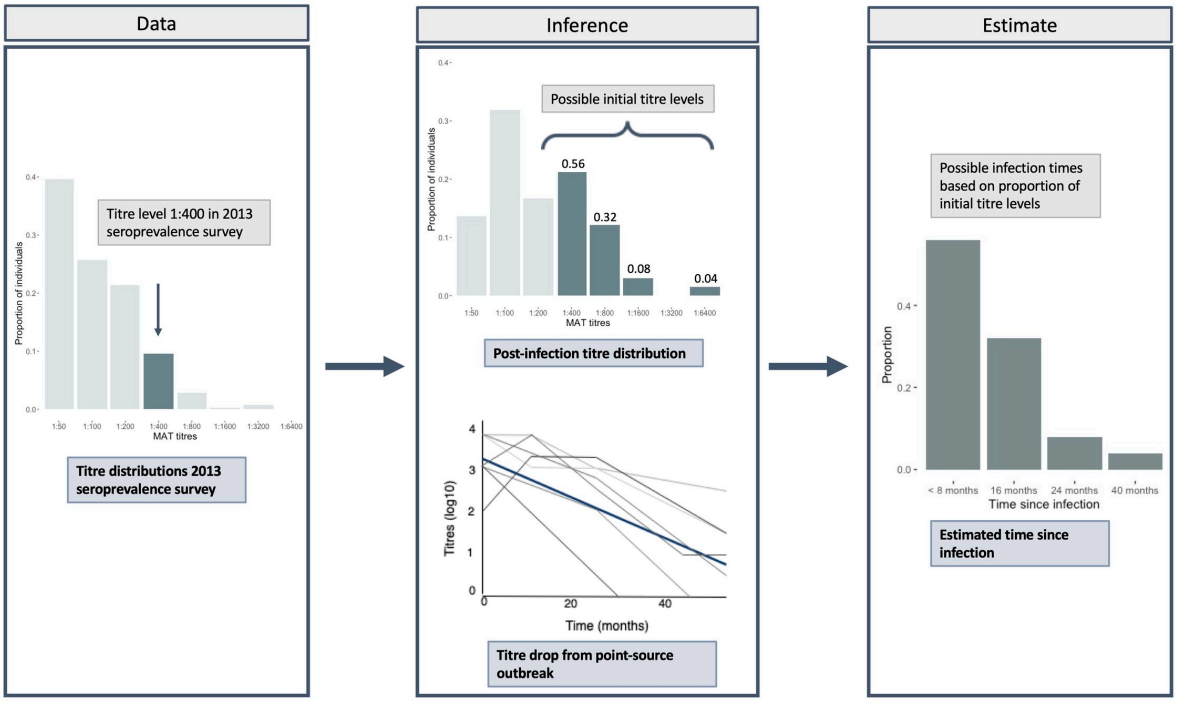

Fig 2. Schematic representation of the methods used for estimating the historic time of infection from the seroprevalence survey data. Firstly, we have the titre distributions from the 2013 seroprevalence survey (Data panel). Then we have the titre distribution of recent infections (Inference panel, upper plot) and the estimated antibody titre decay rate (Inference panel, lower plot). These are both used to estimate the possible time of infection based on the initial titre level (Estimate panel). As an example, individuals who had a titre level of 1:400 in the 2013 seroprevalence survey (Data panel) could have a titre level of 1:400 or higher (upper panel "Inference") ~ two weeks post-infection. If the initial titre level was higher than 1:400, the antibody titre must have waned to reach 1:400. The proportion of initial titre levels was obtained from 2012 clinically suspected cases, and in this case, 56% were likely to have had an infecting titre of 1:400 while 44% were likely to have had a higher infecting titre. Then, transforming this using the antibody decay rate from a point source outbreak in Italy (lower panel "Inference"), we can say that 56% are likely to have been infected <8 months ago (Estimate panel). This was repeated for each dilution level.

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could be seropositive for more than one serovar, two separate analyses were conducted, one where infections with different serovars were assumed to be independent events (n = 520), and one where only the highest titre was used (n = 417).

Since samples were obtained approximately two weeks post-infection from recently infected individuals, we hypothesised that antibody titres may not have peaked. We compared the geometric mean antibody titres to the peak antibody titres reported in Lupidi *et al.* [25] and found a 1–3 fold difference in geometric mean antibody titres. Therefore, we conducted a sensitivity analysis where the distribution of recently infected individuals was shifted, corresponding to a higher overall geometric mean, and estimated a new distribution for time of infection.

Results

Serocatalytic models

When catalytic and reverse catalytic models were fitted to the 2013 Fiji seroprevalence data, we found that the reverse catalytic model, which allows for seroreversion, fitted the data better

Table 1. Parameter estimates for the force of infection (FOI) and waning rate from the catalytic and reverse catalytic model (median [95% CrI]).

Model	FOI (95% CrI)	Waning rate (95% CrI)	WAIC
Catalytic Model	0.007 (0.006–0.007)	-	2215
Reverse catalytic model	0.032 (0.022–0.053)	0.12 (0.08–0.21)	2091

FOI, force of infection; WAIC, widely applicable information criterion; CrI, credible interval.

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(Table 1; Fig 3), with a lower estimated widely applicable information criterion (WAIC difference = 124). The WAIC is an information criterion used for model selection, that aims to balance model complexity with fit to the data. The reverse catalytic model estimated the duration of antibody persistence to be 8.33 years (95% CrI: 4.76–12.50 years), and the force of infection, FOI, to be 0.032 (95% CrI: 0.022–0.053) (Table 1), which corresponds to an annual attack rate 3.15% (95% CrI: 2.18% - 5.16%).

FOI and waning by serovar, sex and administrative division

The reverse catalytic model was also extended to explore whether sex, administrative division and serovar affected the estimated rate of seroreversion (Table 2). Overall, the estimates of seroreversion for all three models were consistent with the previous estimate of the reverse catalytic model using aggregated data. The differences in FOI estimated between the groups in the model correspond to the observed variation in seroprevalence measured in the serosurvey. When analysed by sex, a higher FOI was observed in males compared with females, and this is in accordance with the results from the serosurvey, where it was found that the seroprevalence in males was higher than females. When analysed by administrative division, the Western Division was found to have the highest FOI compared with the Central and Western Divisions, although the credible interval was large. Finally, the results by serovar were also in accordance

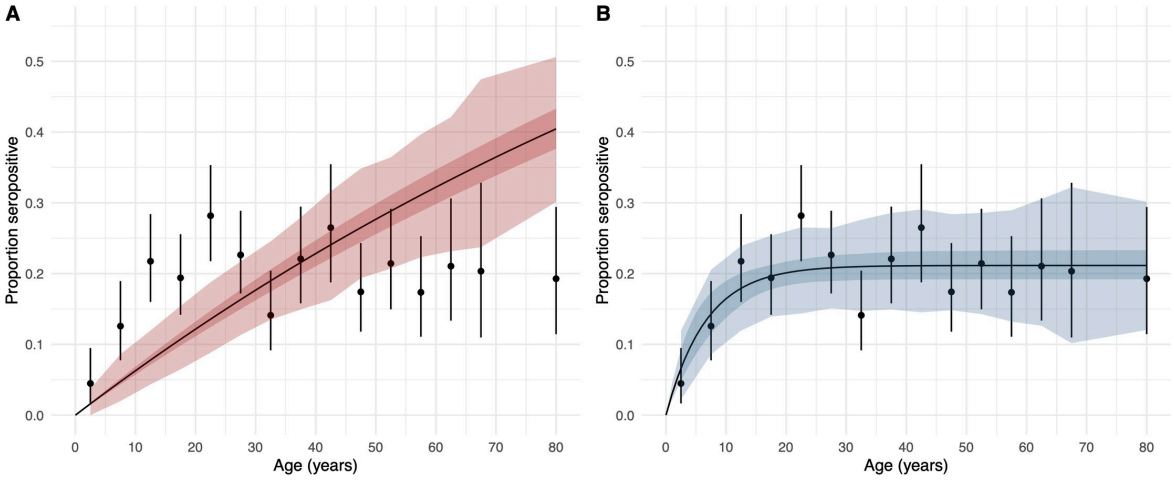

Fig 3. Proportion of seropositive individuals by age (black points represent the mean and the error bars represent the binomial 95% confidence intervals), from national serosurvey conducted in Fiji in 2013 (n = 2,152). Results from the catalytic model is shown in red (A) and reverse catalytic model is shown in blue (B), including model 95% credible intervals (darker shading) and the sampling uncertainty (binomial, lighter shading).

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Table 2. Parameter estimates for the FOI and waning for the reverse catalytic model by sex, by administrative division and by serovar (median [95% CrI]).

Model	FOI (95% CrI)	Waning (95% CrI)
Reverse catalytic model by sex	Female: 0.025 (0.017–0.040) Male: 0.042 (0.029–0.067)	0.120 (0.078–0.200)
Reverse catalytic model by administrative Division	Central: 0.033 (0.022–0.058) North: 0.035 (0.022–0.065) West: 0.038 (0.025–0.068)	0.135 (0.085–0.250)
FOI allowed to vary by serovar, waning held constant	Ballum: 0.0009 (0.0004–0.003) Canicola: 0.0028 (0.0015–0.0070) Copenhageni: 0.0021 (0.0011–0.0053) Pohnpei: 0.0340 (0.0208–0.0830)	0.175 (0.101–0.449)

FOI, force of infection; CrI, credible interval.

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with the serosurvey (S6 Fig). Serovar Pohnpei was found to have the highest FOI, which was also the most commonly identified serovar in the serosurvey.

Time-varying FOI

Our baseline catalytic and reverse catalytic models assumed a constant FOI. Therefore, we also assessed whether varying the FOI over time impacted the estimate for seroreversion (Table 3). Firstly, a constant FOI was assumed, but with the addition of one recent outbreak (allowed to occur two years prior to the seroprevalence survey). This approach was then extended, allowing for the outbreak to have occurred anytime in the five years preceding the seroprevalence survey. These models had similar estimates of seroreversion [7.25 years (3.36–11.36), for the constant FOI with one outbreak in the last five years], which were comparable with the estimate from the simple reverse catalytic model. There was little difference in WAIC between the two models which included a constant FOI and an outbreak, indicating both models performed equivalently well. Furthermore, the estimates of WAIC were similar to the reverse catalytic model (Table 3). The timing of the outbreak, when allowed to occur in the preceding five years, estimated the outbreak to be in April 2013 (95% CrI: September 2009—December 2013; S7 Fig), albeit with wide credible intervals and there was a lot of uncertainty regarding the height of the peak. Finally, a subsequent model assessed the effects of having no constant FOI and one outbreak (outbreak only scenario) occurring in the 10 years preceding the survey. This model estimated a higher rate of seroreversion, and a higher WAIC (WAIC difference: 13, compared with constant FOI with an outbreak in the previous five years), indicating that the model did not have as much support.

Reconstructing historic time of infection

Our above modelling analysis used population level seroprevalence data to estimate the most likely timing of the outbreak. The model estimated a recent outbreak, however the credible

Table 3. Time-varying FOI models. Parameter estimates for the constant FOI, outbreak timing and waning for the reverse catalytic model with a constant FOI and one outbreak in the last two years, the reverse catalytic model with a constant FOI and one outbreak in the last five years, and the reverse catalytic model with no constant FOI and one outbreak in the last ten years (outbreak only model).

Model	Constant FOI estimate (95% CrI)	Outbreak timing (95% CrI)	Waning (95% CrI)	WAIC
Constant FOI with 1 outbreak (2 years)	0.036 (0.024–0.060)	2013–05 (2012–08–2013–12)	0.139 (0.089–0.241)	2089
Constant FOI with 1 outbreak (5 years)	0.036 (0.022–0.061)	2013–04 (2009–09–2013–12)	0.138 (0.088–0.298)	2090
No constant FOI & 1 Outbreak (10 years)	-	2009–02 (2008-05- 2010–03)	0.492 (0.095–0.779)	2103

FOI, force of infection; WAIC, widely applicable information criterion; CrI, credible interval.

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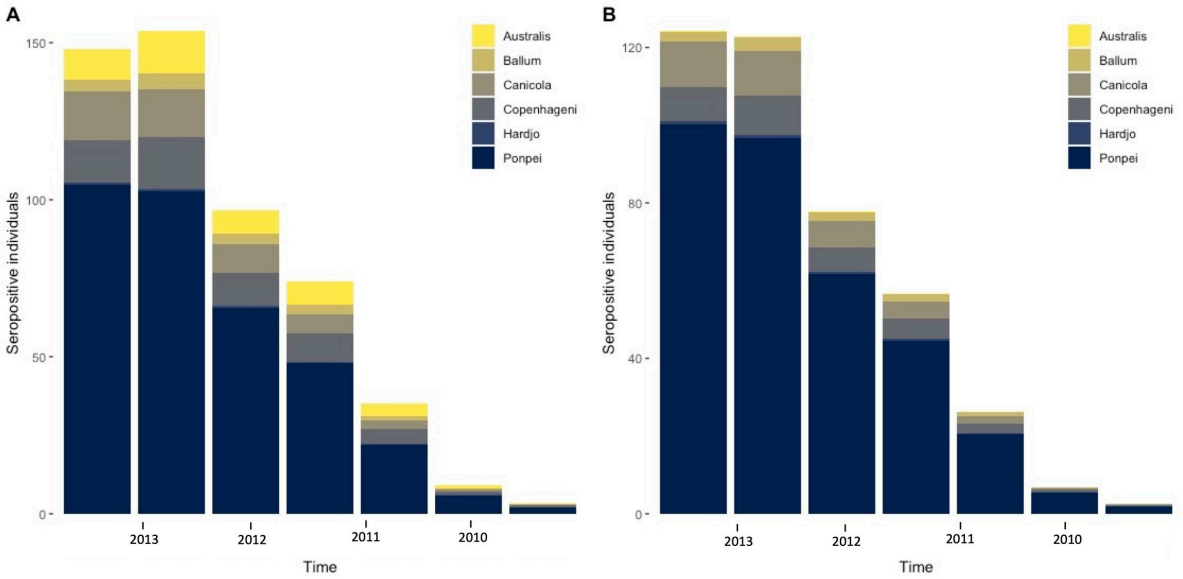

Fig 4. Estimating the most likely time of infection from leptospirosis seroprevalence data from Fiji. (A) assumes that individuals can be seropositive for more than one serovar at different times (n = 520), whilst (B) using results of the serovar associated with the highest titre (n = 417).

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intervals surrounding the estimated timing were large. Therefore, we also conducted a complementary analysis to estimate the timing of infection at the individual level, using the MAT titres by serovar instead of aggregated binary seropositivity. First, using a mixed-effects linear model and data from the point-source outbreak from Lupidi *et al.* [25], the rate that antibody titres drop by one dilution level was estimated to be 7.92 (6.30–11.08) months. The time taken to reach undetectable levels was estimated as 6.57 years following infection (S4 Table). These results were pooled across all three serovars reported by Lupidi *et al.* [25] since there was no clear infecting serovar identified in the study. The antibody decay rate, along with the titre distribution of recently infected individuals sampled in 2012 and 2013, were then used to estimate when individuals included in the seroprevalence survey might have become infected (schematic representation shown in Fig 2). The results indicate that a recent outbreak most likely caused the majority of infections, with estimated time of infection predominantly in 2012 and 2013 (Fig 4). This was true under both assumptions of infection; firstly, where infections were assumed to be independent events, and an individual can be seropositive for more than one serovar (Fig 4A); and secondly where only the highest antibody titre was used, and we assumed individuals could not be infected with more than one serovar (Fig 4B). These results correspond with what is known from surveillance data reported by the Fiji Ministry of Health and Medical Services, which show large outbreaks in 2012 and 2013, with 563 and 453 cases reported respectively [30,33]. In comparison, an annual mean of 72 cases were reported between 2008 and 2011 (although data were known to be less accurate for 2010, where only five cases were reported). A breakdown by serovar is shown in S8 Fig.

The samples from individuals with clinically suspected leptospirosis from 2012 were collected approximately two weeks following infection. There may not have been sufficient time for antibody levels to peak, therefore the geometric mean antibody titres were compared to the

peak antibody titres from Lupidi *et al*.. The mean antibody titre in Lupidi *et al*. was found to be 1–3 dilutions higher than in the clinically suspected individuals from Fiji, so a sensitivity analysis was conducted. The 2012 titre profiles were shifted so that the mean geometric titre corresponded to those observed in Lupidi *et al*. [25]. This placed the peak of the infection further in the past, but still within the last three years (S9 Fig).

Discussion

Serocatalytic models can be used to estimate time-dependent values such as the rate of infection and duration of seropositivity from cross-sectional seroprevalence studies [34]. They are particularly useful tools in serological studies on diseases where seroreversion occurs, as we can make comparisons between seroprevalence and surveillance data, whilst accounting for waning of antibodies, and this has important public health implications. For example, in a setting where there is a high force of infection, FOI, and rapid seroreversion, it could be wrongly concluded from an overall low seroprevalence estimate that little transmission is occurring. In our analysis, the estimated annual attack rate for *Leptospira* infection in Fiji (3.15%, 2.18% - 5.16%) using the reverse catalytic model would suggest that there may be as many as 28,000 (19,000–46,000) infections in Fiji per year, using the 2017 population census. Annually reported cases in Fiji have typically varied from a couple of hundred cases to over a thousand, but our findings quantify the potential extent of unascertained community infection. Reasons for this under-ascertainment could be due to clinical misclassification (e.g. misdiagnosis as dengue fever), limited access to laboratory diagnosis, individuals with mild symptoms not seeking health care, or asymptomatic infections [45]. While the data supports evidence that there is under-reporting, it is worth noting that the serosurvey was conducted during a period of high incidence, and the FOI may have been estimated to be lower in other years.

Using the reverse catalytic model we also estimated the persistence of detectable anti-*Leptospira* antibodies to be 8.33 years (4.76–12.50 years). Similar estimates were obtained when analysed by sex, administrative division and serovar. Furthermore, since large seasonal outbreaks of leptospirosis are known to occur in Fiji, we explored how a time-varying FOI influenced our estimates of the duration of seropositivity and found that our estimates remained similar [7.25 years (3.36–11.36), for the constant FOI with one outbreak in the last five years]. There was little difference between the WAIC estimates of the reverse catalytic model and the time-varying FOI model, indicating that both models performed equivalently using the seropositivity data. Therefore, using the seroprevalence study alone, we were not able to identify which scenario had the most support. The duration of antibody persistence estimated in this study is longer than that found by previous studies, which estimated it to be between 3–6 years [24,25]. However, the follow up duration in previous studies was between 5 and 6 years, and some individuals remained seropositive at the conclusion of the study in both Lupidi *et al*. [25] (follow up duration of five years) and in Cumberland *et al*. [24] (follow up time of six years). This indicates a longer period of follow-up may be required to accurately measure the duration of antibody persistence. We estimated (using a linear mixed effects model) that in Lupidi *et al*. the time taken to reach undetectable levels was 6.57 years, which extended beyond the follow-up period, and this is in accordance with our estimate of the duration of antibody persistence from the Fiji serosurvey, suggesting that antibody decay rates are comparable across settings. However, care needs to be taken when comparing the duration of immunity in different contexts. Fiji is an endemic setting where repeated infections are more likely. These may boost antibody responses, resulting in longer persistence of measurable antibodies [6,46]. In a different, non-endemic setting, antibody persistence may be estimated to be shorter. Therefore,

additional longitudinal datasets from settings with high prevalence would be useful to validate our results.

In our study, we focus on antibody responses that provide a correlate of *Leptospira* infection. However, understanding the dynamics of infection more fully would require more detailed analysis of the relationship between seropositivity, development of symptomatic disease and protective immunity. One of the most accurate ways to assess the duration of immunity is to conduct longitudinal reinfection studies. Reinfection generally occurs with a different infecting serovar and appears more likely to result in asymptomatic infection or mild clinical disease, suggesting protective specific-immunity but also cross-reactive protection following initial infection. However, severe disease following a second infection [17,27], and repeat infections with the same serovar have also been observed [26,27]. The exact timing of prior infection was often not known in these studies and many only had short follow-up periods, highlighting the need for prospective studies in well characterised populations with sufficient follow up periods. These studies would address many unanswered questions, including the nature and duration of immunity to *Leptospira* in terms of whether it is serovar or serogroup specific, whether it results in milder clinical disease, and finally, whether it is correlated with antibody titre levels. These questions could have implications for the successful development and deployment of a vaccine in humans.

In the absence of more detailed prospective studies, antibodies may act as a correlate for protective immunity, however, care needs to be taken in interpretation. Despite low and possibly un-detectable levels of antibodies, immunity may persist. Memory B-cells can reside outside serum and are therefore difficult to detect from blood samples, but can rapidly produce antibodies following an infection. Furthermore, immunity is not driven solely by antibody-mediated processes, as cell-mediated immunity may also play a role [13,14]. Therefore, antibody titres may under-estimate immunity against pathogens. Leptospires are extracellular pathogens, and as such humoral-mediated immunity is thought to play a central role [13,21]. Previous studies have shown that protective immunity can be transferred via the serum [47,48], demonstrating the role of antibodies, and suggesting that immunity to leptospirosis is driven primarily via the humoral immune response. Therefore, the duration of antibody persistence is likely to be a good correlate for immunity.

Since antibodies can act as a marker of exposure to infection, we explored two complementary approaches to estimate the timing of infection at the population level. In the first, we used the population seroprevalence data, and allowed for a time-varying FOI, which inferred that there was endemic transmission occurring, and a large outbreak in 2013. However, there was a lot of uncertainty regarding the timing and the size of the peak, with large credible intervals, when only the binary seroprevalence data was used. In the second approach, we used the MAT antibody titres by serovar, MAT antibody titres from clinically suspected leptospirosis cases and longitudinal information on antibody decay rates from Lupidi *et al.* [25] to estimate the most likely timing of infection, fully utilising the available seroprevalence data. From this, we found that most individuals included in the 2013 seroprevalence study were likely to have had a recent infection within the last two years. These results appear to correspond with what is known from surveillance data collected by the Fiji Ministry of Health, which show high numbers of cases in 2012 and 2013 [30,33]. We demonstrate that by incorporating additional sources of data, including longitudinal information on antibody kinetics, we were able to identify the timing of infection. Identifying a time window when infection may have occurred could be useful when analysing results from serosurveys, as this would allow for data to be chosen based on temporal proximity to the likely infection period. This may increase the accuracy of analyses and reduce confounding that may occur through the combination of disparate datasets. We did not observe any patterns of infection by serovar, suggesting that there may be

simultaneous circulation of multiple serovars in Fiji, rather than multiple outbreaks with different serovars. A previous study describing the human serosurvey in Fiji found that there were differences in serovar distribution by age and location, suggesting that there are different risk factors of disease transmission between sub-groups [29]. For example, livestock could be more important drivers in rural areas, with rodents being more important in urban areas. However, in this setting there was one dominant serovar (serovar Pohnpei), limiting the ability to identify serovar-specific risk factors. Since *Leptospira* exposure does not induce lifelong immunity (i.e antibodies wane following *Leptospira* infection), it was not possible to estimate infection beyond the time it takes for seropositivity to wane. Therefore, such data cannot provide insights further back in time than the duration of antibody waning.

The results from our analysis are to some extent limited by the quality of the data available. We used MAT titres from recently infected individuals from Fiji, however, the exact timing of infection was not known, and it is possible that individuals may not have reached their peak antibody titre levels yet [18]. In addition, standardisation of the MAT test is challenging, and the results may not be fully comparable across settings [46]. Finally, very little data exist on antibody profiles following infection with leptospirosis, and the available evidence demonstrates high levels of inter-individual heterogeneity. This is highlighted by Lupidi *et al.* [25], who reported a point source outbreak in Italy, where leptospirosis is not endemic. Each individual followed up over time in their study showed distinct antibody profiles. Despite these limitations in data quality and uncertainties in antibody dynamics, our methods were able to identify a time window in which transmission was most likely to have occurred, and which corresponds to known outbreaks in Fiji. This provides a novel way of using seroprevalence data to gain longitudinal information and insight into more recent transmission dynamics. A better understanding of antibody waning, and antibody profiles following infection, particularly given the level of inter-individual heterogeneity, would allow for this method to be further developed for leptospirosis and also other diseases.

By using serocatalytic models, we showed that it is possible to obtain insights into the underlying dynamics of leptospirosis transmission from cross-sectional data as well as providing an estimate for the duration of seropositivity. We also provide a novel method for extrapolating seroprevalence data to estimate when individuals may have become infected, showing how evidence synthesis can allow for richer, longitudinal information to be inferred from cross-sectional studies.

Supporting information

S1 Table. Summary, advantages and disadvantages of MAT and ELISA test used for the diagnosis of leptospirosis.
(PDF)

S2 Table. Description of the different models fitted and priors used.
(PDF)

S3 Table. Simulation recovery study. Estimating the FOI and waning from a high FOI and low FOI setting.
(PDF)

S4 Table. Results from the mixed-effects linear model from the point source outbreak in Italy (Lupidi *et al.*). Antibody drop time was defined as the time taken in months for antibodies to drop one antibody titre level (e.g. from 1:100 to 1:50).
(PDF)

S1 Fig. Number of individuals included within the 2013 leptospirosis serosurvey by five-year age groups.
(TIFF)

S2 Fig. Number of individuals seropositive by serovar by ten-year age groups (n = 399). Individuals that had the same titre for two serovars, and therefore infecting titre could not be assumed, were excluded (n = 18).
(TIFF)

S3 Fig. Distribution of MAT titres by serovar for seropositive individuals. 89 individuals had titres for more than one serovar, and so are included more than once in this plot (n = 520).
(TIFF)

S4 Fig. Simulation recovery study. Sample estimates (mean and 95% binomial confidence interval) and model fit (solid line) for the high FOI (shown in orange) and low FOI (shown in blue) scenario. Under the high FOI scenario, the parameter estimates obtained were similar to the true parameter values. Under the low FOI scenario, the model was able to reproduce the data, but there was much greater uncertainty in the true underlying parameters.
(TIFF)

S5 Fig. Simulation recovery study. Posterior distributions for waning and force of infection (FOI) for the high FOI scenario (orange) and low FOI scenario (blue). Under the high FOI scenario, the parameter estimates obtained were similar to the true parameter values. Under the low FOI scenario, although the true parameter values were included within the 95% credible intervals, there was much greater uncertainty in the estimates.
(TIFF)

S6 Fig. Proportion of seropositive individuals by age (black points represent the mean and the error bars represent the binomial 95% confidence intervals), from national serosurvey conducted in Fiji in 2013 (n = 2,152) by serovar Pohnpei (A), Canciola (B), Copenhageni (C) and Ballum (D). The reverse catalytic model is shown for each serovar including model 95% credible intervals (red shading).
(TIFF)

S7 Fig. Time-varying FOI from the constant FOI model with one outbreak (occurring in the preceding five years).
(TIFF)

S8 Fig. Estimating the most likely time of infection from leptospirosis seroprevalence data from Fiji by serovar. (A) assumes that individuals can be seropositive for more than one serovar at different times (n = 520), whilst (B) using results of the serovar associated with the highest titre (n = 417).
(TIFF)

S9 Fig. Sensitivity analysis for estimating the most likely time of infection from the seroprevalence data, using different initial titre distributions based on the geometric mean reported in Lupidi *et al*. The initial titre distributions were shifted to correspond to a geometric mean (a) one dilution titre higher, (b) two dilutions titres higher and (c) three dilution titres higher.
(TIFF)

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Writing – original draft: Eleanor M. Rees.

Writing – review & editing: Eleanor M. Rees, Colleen L. Lau, Mike Kama, Simon Reid, Rachel Lowe, Adam J. Kucharski.

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4

Estimating the duration of seropositivity of human seasonal coronaviruses using seroprevalence studies

SARS-CoV-2 emerged in December 2019, and had a devastating impact, resulting in 500 million cases and 6.2 million reported deaths globally as of June 2022 [1]. Due to the inevitable right censoring of data during an emerging infectious disease pandemic, at the end of 2020 and the beginning of 2021 there were many unanswered questions regarding the likely duration of protective immunity and the risk of reinfection. In September 2020 Huang *et al.* [2] presented a comprehensive systematic review of seasonal human coronaviruses (HCoVs), including data which they extracted from a number of different seroprevalence studies. The authors fitted a catalytic model to do this data by strain, however, they did not allow for waning immunity within their model. Given that reinfection by the same strain is known to occur within seasonal HCoVs [2], and the observed age profile of the seropositivity, this offered an opportunity to extend the methodology developed for leptospirosis in Chapter 3 and adapt it to seasonal HCoVs to help understand an unravelling public health emergency. I aimed to estimate the duration of antibody persistence using a reverse catalytic model (accounting for waning immunity). Furthermore, I explored how the infection rate varied by age and combined age-stratified seroprevalence data within an age-varying FOI reverse catalytic model to investigate how waning immunity and age-variation infection risk could shape population level seroprevalence.

This paper was published in Wellcome Open Research in June 2021 [3], with a final version accepted in December 2021. The Supplementary material of the paper is included as Appendix

D.

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Primary Supervisor	Adam Kucharski		

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RESEARCH ARTICLE

REVISED Estimating the duration of seropositivity of human seasonal coronaviruses using seroprevalence studies [version 3; peer review: 3 approved]

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Abstract

Background: The duration of immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still uncertain, but it is of key clinical and epidemiological importance. Seasonal human coronaviruses (HCoV) have been circulating for longer and, therefore, may offer insights into the long-term dynamics of reinfection for such viruses.
Methods: Combining historical seroprevalence data from five studies covering the four circulating HCoVs with an age-structured reverse catalytic model, we estimated the likely duration of seropositivity following seroconversion.
Results: We estimated that antibody persistence lasted between 0.9 (95% Credible interval: 0.6 - 1.6) and 3.8 (95% CrI: 2.0 - 7.4) years. Furthermore, we found the force of infection in older children and adults (those over 8.5 [95% CrI: 7.5 - 9.9] years) to be higher compared with young children in the majority of studies.
Conclusions: These estimates of endemic HCoV dynamics could provide an indication of the future long-term infection and reinfection patterns of SARS-CoV-2.

Keywords

Seasonal coronavirus, Seroprevalence, Catalytic model, waning immunity

Open Peer Review

Approval Status ✓ ✓ ✓

	1	2	3
version 3 (revision) 21 Dec 2021			✓ view
version 2 (revision) 22 Nov 2021	✓ view	✓ view	✓ view
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Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Rees EM: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Visualization, Writing – Original Draft Preparation; **Waterlow NR**: Formal Analysis, Methodology, Writing – Review & Editing; **Lowe R**: Formal Analysis, Methodology, Supervision, Visualization, Writing – Review & Editing; **Kucharski AJ**: Conceptualization, Formal Analysis, Methodology, Supervision, Visualization, Writing – Review & Editing

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REVISED **Amendments from Version 2**

This article has been updated in response to reviewer comments. We have added standard error estimates to WAIC and LOO.

Any further responses from the reviewers can be found at the end of the article

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel beta coronavirus, was first detected in December 2019 and has since spread globally causing high morbidity and mortality. There is evidence of some short-term sterilising immunity (protection against reinfection and symptoms) following infection with SARS-CoV-2[1], but also some reports of reinfection[2]. However, there is currently limited evidence on the duration of immunity conferred by SARS-CoV-2 infection. Given the limited duration of SARS-CoV-2 circulation to date, the dynamics of antibody responses of seasonal human coronaviruses (HCoV) could provide insights into the possible long-term potential for reinfections[3]. The duration of immunity following infection is of both clinical and epidemiological importance, as it provides information as to how long previously infected individuals may no longer be at risk of infection and disease, as well as influencing the long-term dynamics of epidemics[4] and enabling the interpretation of population-wide serological data[5].

There are four circulating HCoVs: HCoV-NL63 and HCoV-229E (alpha coronaviruses), HCoV-OC43 and HCoV-HKU1 (beta coronaviruses). HCoV-OC43 and HCoV-229E were first identified in the 1960s, but HCoV-NL63 and HCov-HKU1 were not identified until 2004 and 2005 respectively[6,7]. Like SARS-CoV-2, these typically cause respiratory tract infections. A small number of human challenge studies have looked at the duration of immunity to these viruses. Callow *et al.*[8] found that six out of nine participants were reinfected when challenged with HCoV-229E again one year later, as measured by a rise in IgG antibodies and viral shedding. However, the period of viral shedding was shorter following the second inoculation, and none of the participants developed symptoms. Reed[9] found that reinfection did not occur when participants were re-inoculated with a homologous strain approximately one year following infection, but participants had partial immunity against reinfection with a heterologous strain. Taken together these results suggest that immunity against infection with a homologous strain could last at least one year[8,9].

There are also a small number of cohort and community-based surveillance studies which have looked at reinfection of seasonal HCoV. One study looked at HCoV reinfection in a small cohort of ten individuals over 35 years and found the median reinfection times to be 30 months, but with reinfection often occurring at 12 months[10]. A larger study looking at data from Flu Watch, a community cohort study which measures the incidence and transmission of respiratory viruses, found that between 2006 and 2011, eight subjects were reinfected with a seasonal HCoV (of 216 with confirmed first infection), and the time between reinfection ranged from 7 to 56 weeks. None of these reinfections were with the same strain, providing some evidence of lasting immunity[11]. However, a community surveillance study of 483 participants conducted in Kenya in 2010 over six months found evidence of high numbers of repeat infections of HCoV-NL63 (20.9%), HCoV-OC43 (5.7%), and HCoV-229E (4.0%). The majority of these reinfections showed reduced virus replication in the second infection, and a lower proportion of individuals had symptoms following the second infection[12]. Furthermore, another study conducted in New York City which included 191 participants found that reinfections with the same strain can occur within one year[13]. Care should be taken with the interpretation of these studies since we do not know the background exposure rates, and this will influence the estimates of duration of immunity.

If infections are fully immunising – as is the case for pathogens like measles and varicella zoster – then seroprevalence would be expected to accumulate over time[14], and hence with age, with little waning of responses. The dynamics can therefore be captured with catalytic models of seroconversion[15], which enables estimation of the force of infection (FOI, the rate at which susceptible individuals acquire infection and seroconvert). In contrast, when individuals serorevert, i.e. their immunity wanes by the progressive loss of protective antibodies against a disease over time, 'reverse catalytic models' can jointly estimate FOI and waning of immunity[16]. Variation in FOI with age may further complicate the dynamics, particularly if a high infection rate in children is followed by a lower rate in adults as well as waning of seroprevalence. To understand how seroconversion, waning and age-variation in infection risk could shape population-level seroprevalence, we combine age-stratified data with age-structured reverse catalytic models, and estimate the likely duration of seropositivity following seroconversion for the four seasonal coronaviruses.

Methods

Human seroprevalence from four different human coronavirus strains (229E, HKU1, NL63, and OC43) were identified in a recent systematic review[7]. Studies which did not include estimates for individuals under 10 years old[17] were excluded, as well as studies with which only reported two age groups[18]. A total of six different studies were included, covering the four seasonal HCoVs, with some studies reporting on multiple strains[19–24]. Two studies were reported separately for two different strains, but the overall study population was the same[21,22]. A summary of these studies is presented in Table 1. The different assays used in each study for the different strains is shown, and where the antibody detected was specified this is included in the table. To account for maternal immunity individuals aged ≤1 year were excluded. The full dataset used for this analysis can be found as underlying data[25].

To explore the duration of antibody persistence for different seasonal coronaviruses, where detectable antibodies is defined as seropositivity, we developed age-structured reverse catalytic models. The basic reverse catalytic model follows individuals from birth and assumes that there is a constant FOI (λ),

Table 1. Characteristics of studies used to fit the model.

Strain	Author (year published)	Pubmed ID	Sample size	Country/ region	Years sampled	Assay	Antigen	Assay cut-off
HCoV-HKU1	Chan (2009)	19342289	709	Hong Kong	Not specified	ELISA (IgG)	S protein	Mean + 3SD (OD>0.495)
	Zhou (2013)[a]	24040960	789	China	1999 – 2011	IFA (IgG)	S protein	>1:20
HCoV-OC43	Zhou (2013)[a]	24040960	789	China	1999 – 2011	IFA (IgG)	S protein	>1:20
	Monto (1974)[c]	4816305	910	USA	1965 – 1969	CF or HI	Whole virus	<1:8 to >1:8 or 4-fold rise
	Sarateanu (1980)	6248465	3,016	Germany	1974 – 1976	HI	Whole virus	>1:8
HCoV-NL63	Shao (2007)[b]	17889596	243	USA	2003 – 2004	ELISA (IgG)	N protein	OD>0.2 at dilution of 1:80 or greater
	Zhou (2013)[a]	24040960	789	China	1999 – 2011	IFA (IgG)	S protein	>1:20
HCoV-229E	Shao (2007)[b]	17889596	243	USA	2003 – 2004	ELISA (IgG)	N protein	OD>0.2 at dilution of 1:80 or greater
	Zhou (2013)[a]	24040960	789	China	1999 – 2011	IFA (IgG)	S protein	>1:20
	Cavallaro (1970)[c]	5504709	307	USA	1966	Neutralization	Whole virus	>1:4

Human coronavirus (HCoV), Enzyme-linked immunosorbent assays (ELISA), immunofluorescence assays (IFA), complement fixation (CF), hemagglutination inhibition assays (HI), Immunoglobulin G (IgG), standard deviation (SD), optical density (OD). Studies which occurred in the same setting are denoted by the superscripts, a, b and c.

which is independent of age (a) and calendar year, and that immunity (as measured by serological status) wanes over time, at a rate ω. This model also assumes that the mortality rate for susceptible and infectious individuals is the same. The expression for the proportion of individuals age a who are seropositive, $z(a)$, in the reverse catalytic model is as follows:

$$z(a) = \frac{\lambda}{\lambda + \omega}(1 - e^{-a(\lambda+\omega)})$$

where λ is the FOI, ω is seropositivity waning rate and a is age. The duration of antibody persistence was estimated as follows:

$$Duration\ of\ antibody\ persistence = 1/\omega$$

We then extended the reverse catalytic model to allow for a different FOI by age. The expressions for seroprevalence in the reverse catalytic model with age-varying FOI are as follows:

$$z(a) = \frac{\lambda_1}{\lambda_1 + \omega}(1 - e^{-a(\lambda_1+\omega)}) \qquad when\ a < a_0$$

$$z(a) = (\frac{\lambda_1}{\lambda_1 + \omega}(1 - e^{-a_0(\lambda_1+\omega)}) - \frac{\lambda_2}{\lambda_2 + \omega})(e^{-(\lambda_2+\omega)(a-a_0)}) + \frac{\lambda_2}{\lambda_2 + \omega} \qquad when\ a \geq a_0$$

$$\lambda_2 = \lambda_1\ \alpha$$

Where z(a) is those who are seropositive at age a, λ_1 is the FOI in young age groups, λ_2 is FOI in the old age group, ω is waning, a is age, a_0 is the age cut-off used to define the young and old group, and the relative change in FOI, α, is the change in FOI in the older age group. In our analysis, we allowed λ_1 to vary by study and strain, to account for local differences in population-level transmission dynamics, while the average rate of waning within a given individual was assumed to be universal and was jointly estimated across all studies and strains. This means that one overall estimate of waning was obtained. Some of the studies occurred in the same setting, and so the underlying contact patterns were presumed to be the same (in total we identified five settings). Therefore, the relative change in FOI (α) and the age at cut-off (a_0) were jointly estimated across settings. This model assumes no cross-protection between strains. Annual attack rates were calculated after estimating the FOI using the following expression,

$$Attack\ rate = 1 - e^{-\lambda}.$$

To reflect uncertainty in current knowledge about the transmission dynamics of HCoVs, weakly informative distributions were chosen as priors for ω, the rate of waning over time. Specifically uniform priors from 0 to 5 years. For the FOI, there is little information on the attack rate of HCoVs. However, there have been several systematic reviews and meta-analyses looking at influenza in unvaccinated individuals which have reported the attack rates to range between 15.2% – 22.5% in children and 3.5% – 10.7% in adults[26–28]. Modelling studies using serological influenza data predicted estimates from 20 – 60%[29,30]. Based on the epidemiology of these viruses in children[31], we expect the attack rate for HCoV may be lower. Therefore, we selected a Gamma distribution, with a mean of 0.3 (shape = 1.2 and scale = 0.25) and this corresponds to an attack rate of 26% and covers a range of plausible values.

For the age at cut-off (a_0), uniform priors from 0 to 20 years were chosen as we were interested in the difference in FOI in children and young adults. For the relative change in FOI (α) we did not have any prior information. Therefore, we selected a prior with median 1, which presumes no difference between FOI in young compared with FOI in old and allowed for a range of plausible values using a gamma distribution (shape = 5, scale = 0.2).

Several sensitivity analyses were conducted to assess the robustness of these results. First, the choice of priors for the FOI was explored, and a less informed prior was tested (FOI ~ Normal (mean 0.3, standard deviation 0.5)). Second, waning was estimated by strain, instead of being jointly fitted across all studies. The relative change in FOI (α) and age at cut-off (a_0) were then held across all studies (instead of allowing them to vary by setting) to explore the impact on the estimate for waning. The impact of excluding the youngest age groups (≤1 year) was also explored, and a model was run which included individuals ≤1 year. The impact of the assay used in the study on the estimate of waning was also explored, where FOI was allowed to vary by study, alpha and the age at cut-off varied by setting and waning varied by assay (ELISA, IFA, HI and neutralisation). Finally, the primary model (age-varying FOI model) was fitted using only half the data (seroprevalence studies from two strains), to explore whether the results from one study was heavily influencing the results. For this model, waning, the relative change in FOI (α) and age at cut-off (a_0) were held across all studies. A description of these models is presented in Table 2.

Bayesian inference was used to fit the sero-catalytic models to the seroprevalence data, using Markov chain Monte Carlo (MCMC) with the Gibbs sampling algorithm to estimate model parameters. To do so, we used the following binomial likelihood representing seropositivity by age (a), study (i) and strain (j)

$$y_{ija} \sim Binomial\,(P_{ija}, N_{ija}),$$

Table 2. Description of models explored.

Model	Priors	Number of parameters
Main model: Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) - More informed priors	FOI ~ gamma(shape = 1.2, scale = 0.25) Waning ~ uniform(0,5) Alpha ~ gamma(shape = 5, scale = 0.2) Cut-off ~ uniform(0,20)	21
Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) - less informed priors	FOI ~ normal(0.3,0.5) Waning ~ uniform(0,5) Alpha ~ gamma(shape = 5, scale = 0.2) Cut-off ~ uniform(0,20)	21
Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings, waning varying by strain)	FOI ~ gamma(shape = 1.2, scale = 0.25) Waning ~ uniform(0,5) Alpha ~ gamma(shape = 5, scale = 0.2) Cut-off ~ uniform(0,20)	24
Reverse catalytic model with age-varying FOI (alpha and cut-off held across settings)	FOI ~ gamma(shape = 1.2, scale = 0.25) Waning ~ uniform(0,5) Alpha ~ gamma(shape = 5, scale = 0.2) Cut-off ~ uniform(0,20)	13
Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) including data <1 year	FOI ~ gamma(shape = 1.2, scale = 0.25) Waning ~ uniform(0,5) Alpha ~ gamma(shape = 5, scale = 0.2) Cut-off ~ uniform(0,20)	21
Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings, waning varying by assay)	FOI ~ gamma(shape = 1.2, scale = 0.25) Waning ~ uniform(0,5) Alpha ~ gamma(shape = 5, scale = 0.2) Cut-off ~ uniform(0,20)	24
Reverse catalytic model	FOI ~ gamma(shape = 1.2, scale = 0.25) Waning ~ uniform(0,5)	11

Force of infection (FOI), relative change in FOI (Alpha,α), age at which the FOI changes (Cut-off).

where N_{ija} is total number of individuals by age group, strain and study, and P_{ija} is the proportion of individuals who are seropositive. The inference was implemented in RJags (version 4–10)[32]. The Gelman-Rubin statistic was used to evaluate MCMC convergence, and a threshold of <1.1 was chosen. The effective sample size (ESS), which is the estimated number of independent samples accounting for autocorrelations generated by the MCMC run, was checked, and an ESS >200 was used. All analysis and calculations were performed using R version 3.6.1. Model selection was based on the lowest value of the widely applicable information criterion (WAIC) and the leave-one-out cross validation (LOO) using Pareto-smoothed importance sampling[33,34]. WAIC and LOO were estimated using the R package Loo (version 2.4.1)[34]. All code is available here at GitHub[25].

Results

Using a reverse catalytic model, which allowed the FOI to change in individuals by age, we estimated the duration of antibody persistence for the four seasonal HCoVs. Despite having only four parameters by study, our model could capture the overall trends in most studies (Figure 1). Waning was jointly fitted across all studies and strains to obtain one overall estimate, and the duration of antibody persistence was estimated to be 3.75 (95% credible interval [CrI]: 1.96 – 7.38) years (Table 3). The FOI across all studies and strains in the young age group ranged from 0.02 (95% CrI: 0.01 – 0.05) to 1.06 (95% CrI: 0.57 – 1.68). The cut-off (age at which the FOI changes) ranged between 2.35 (95% CrI: 0.31 – 17.51) to 16.58 (95% CrI: 7.71 – 19.81) years. The relative change in FOI (Alpha) which measures the relative value of FOI in the young age group compared with the older age group ranged from 0.72 (95% CrI: 0.3 – 1.17) to 2.48 (95% CrI: 1.96 – 2.99). For three of the study settings, the FOI in the older age group was higher (Figure 2). A sensitivity analysis was conducted using less informative priors for the FOI parameters, where a normal distribution was used (extended data Figure 1, Table 1[35]). This model estimated a shorter duration of antibody persistence [0.93 (95% CrI: 0.60 – 1.64) years]. The FOI across all studies and strains were higher, ranging from 0.09

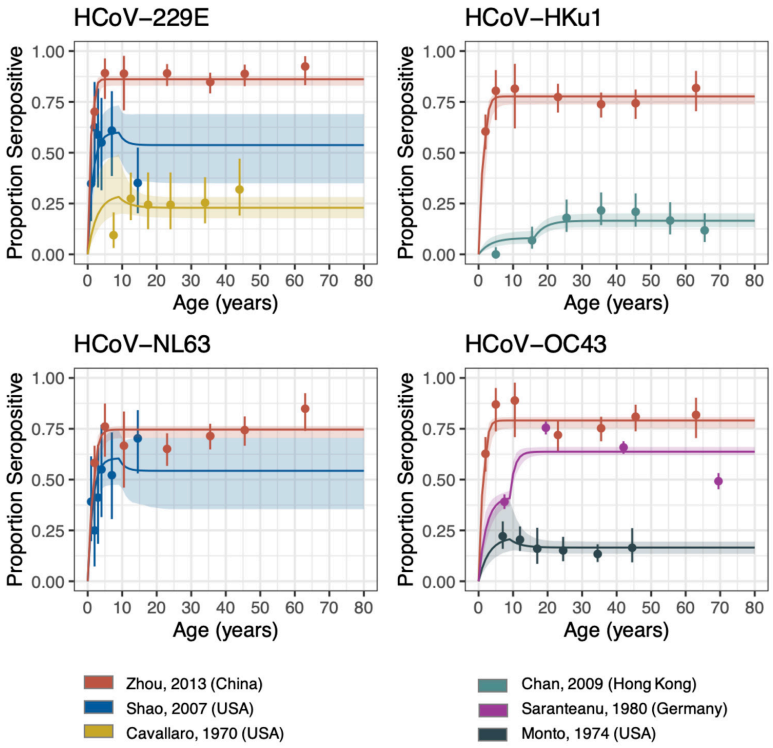

Figure 1. Reverse catalytic model with age-varying FOI. The points are the observed proportion of seropositive individuals from each study (with confidence intervals), i.e. the data that was fit to. The lines are the seroprevalence curves, sampled from the fitted model, where the shaded region represents the 95% credible interval of the predictive posterior distribution. FOI was allowed to vary by study, whilst the relative change in FOI (Alpha) and cut-off were allowed to vary by setting. Waning was jointly fit across all studies and strains.

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Table 3. Parameter estimates from the age-varying FOI reverse catalytic model (median [95% CrI]). FOI was allowed to vary across study, while waning was simultaneously estimated across all studies. The relative change in FOI (Alpha) and the cut-off were allowed to vary across study settings.

Strain	First Author	FOI (youngest age group)	Relative change in FOI (Alpha)	Age at which the FOI changes (cut-off)	Waning
HCoV-229E	Shao	0.40 (0.26 – 0.64)	0.78 (0.35 – 1.68)	9.5 (0.59 – 19.47)	0.27 (0.14 - 0.51)
	Zhou	1.06 (0.57 – 1.68)	1.57 (0.8 – 2.65)	2.35 (0.31 – 17.51)	
	Cavallaro	0.11 (0.06 – 0.3)	0.72 (0.3 - 1.17)	9.14 (0.57 - 19.28)	
HCoV-HKU1	Chan	0.02 (0.01 - 0.05)	2.27 (1.44 – 3.45)	16.58 (7.71 – 19.81)	
	Zhou	0.59 (0.32 – 0.89)	1.57 (0.8 – 2.65)	2.35 (0.31 – 17.51)	
HCoV-OC43	Zhou	0.64 (0.35 – 0.96)	1.57 (0.8 – 2.65)	2.35 (0.31 – 17.51)	
	Monto	0.07 (0.04 – 0.19)	0.72 (0.3 – 1.17)	9.14 (0.57 – 19.28)	
	Sarateanu	0.19 (0.11 – 0.35)	2.48 (1.96 – 2.99)	9.93 (7.34 – 14.84)	
HCoV-NL63	Zhou	0.50 (0.27 – 0.74)	1.57 (0.8 – 2.65)	2.35 (0.31 – 17.51)	
	Shao	0.41 (0.26 – 0.67)	0.78 (0.35 – 1.68)	9.5 (0.59 – 19.47)	

Human coronavirus (HCoV), force of infection (FOI).

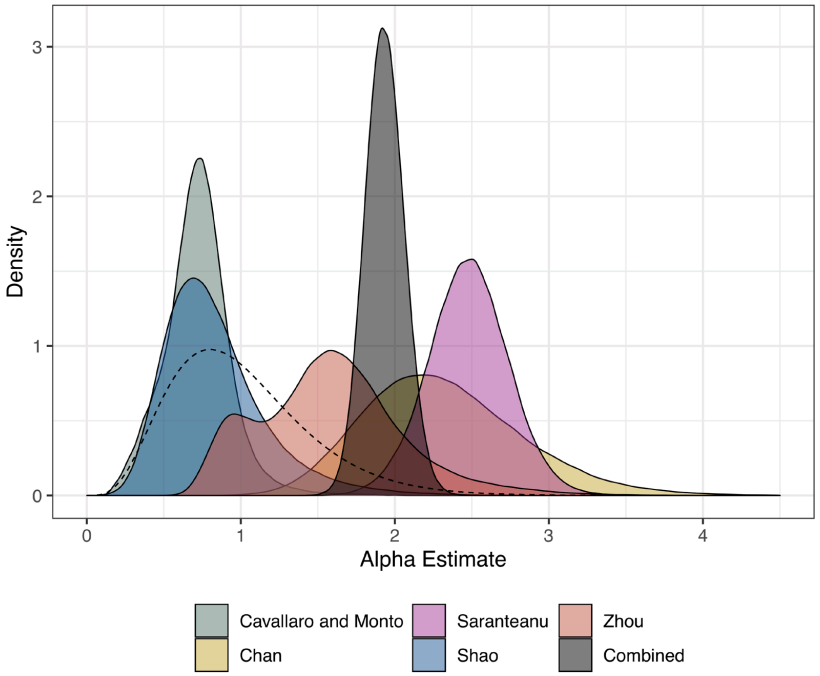

Figure 2. Posterior estimates for the relative change in FOI (alpha) from the age-varying reverse catalytic model for each study setting. The alpha estimate from the model where alpha and cut-off were simultaneously estimated across studies is shown in grey as "combined". The prior is shown as a dashed line.

(95% CrI: 0.04 - 0.16) to 3.22 (95% CrI: 1.95 - 4.85), with six studies reporting FOI estimates > one, which is equivalent to an attack rate of >63%. The relative change in FOI and cut-off were similar for both models. This model had a lower WAIC (536.4 compared with 545.9) and LOO (546.0 compared with 557.8), which suggests that this model may have an improved fit compared with the model with more informed priors, however, large standard errors (SE) were reported for both WAIC and LOO. Furthermore, the high FOI estimates indicate that this model may be less plausible (Table 4). As an additional sensitivity we allowed the waning estimate to vary by strain (extended data Table 2[35]). This model estimated the duration of antibody persistence to be similar for all strains, ranging from 2.26 (1.06 – 5.07) years for HCoV-OC43 to 4.09 (1.91 – 9.60) years for HCoV-229E.

When the relative change in FOI and cut-off parameters were simultaneously estimated by setting (extended data Figure 2, Table 3[35]) the duration of antibody persistence was estimated to be shorter, 2.20 (95% CrI: 1.57 - 3.08) years, although the confidence intervals overlap with the main model. The FOI ranged from 0.04 (95% CrI: 0.03 - 0.06) to 0.88 (95% CrI: 0.67 - 1.19). The overall model WAIC (622.1 compared with 545.9) and LOO (632.5 compared with 557.8) were higher, indicating that this model did not have as much support, although the SEs reported were large for WAIC and LOO (Table 4).

We also tested a basic reverse catalytic model, where the FOI was not allowed to vary by age, and this model estimated a longer duration of antibody persistence (7.69 [95% CrI: 6.25 - 9.09] years; extended data Table 4, Figure 3[35]). The WAIC (717.2) and LOO (718.5) values for the basic reverse catalytic model were higher compared with the other models, indicating that this basic model did not have strong support among the models considered (Table 4).

To explore the effect of excluding the youngest ages (≤1 year), a sensitivity analysis was done where these individuals were included within the analysis. The duration of antibody persistence was found to be slightly shorter (2.04 [95% CrI: 0.1.28 -1.4.76] years) and the FOI was found to be higher for all studies, ranging from 0.04 (95% CrI: 0.02 - 0.07) to 2.92 (95% CrI: 2.08 - 4.01); extended data Table 5, Figure 4[35]). The estimates for the relative change in FOI were found to be very similar to the model which excluded this age group.

As an additional sensitivity analysis, we refit the models using data for only two strains at a time, and estimated the FOI, waning and the relative change in FOI (extended data Table 6[35]). We found that although the results varied, the overall trends were the same, indicating that the model did not rely heavily on one dataset. The duration of antibody persistence varied from 1.80 years (95% CrI: 1.17 - 2.67) to 5.26 years (95% CrI: 2.53 - 13.56).

Finally, we explored the impact of the different assays used in the studies on the waning estimates. We allowed the waning estimate to vary by assay (extended data Table 7, Figure 5[35]), whilst allowing FOI to vary by study, and alpha and cut-off to vary by setting. This model estimated the duration of antibody persistence to be similar for ELISA (2.63 [95% CrI: 0.94-9.09] years), HI (1.08 [95% CrI: 0.44-3.33] years) and neutralisation (1.28 [95% CrI: 0.25-50.0] years) assays, but longer for IFA (7.69 [95% CrI: 3.03-14.29] years). The credible intervals were wide, likely due to the small number of studies by assay.

To demonstrate the relationship between FOI and seropositivity at age 30, we created simulated scenarios under different seroconversion models. Using the parameters for the relative change in FOI and waning estimated from the age-varying reverse catalytic model (where the relative change in FOI and the age at cut-off were simultaneously estimated across settings), we simulated the proportion of individuals aged 30 years that would be seropositive using a range of FOI estimates to show how the proportion changes using the different models. The catalytic model, which does not allow for seroreversion, results in the highest estimates of seropositivity at age 30 with increasing FOI. The age-varying FOI model results in higher estimates of seropositivity at age 30 compared with the reverse catalytic model. This is due to the FOI which was estimated to be almost twice as high in the older age

Table 4. Comparison of duration of antibody persistence estimates from the different models explored.

Model	Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) - More informed priors	Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) - less informed priors	Reverse catalytic model with age-varying FOI (alpha and cut-off held across settings)	Reverse catalytic model
Duration of antibody persistence (years)	3.75 (95% CrI: 1.96 – 7.38)	0.93 (95% CrI: 0.60 – 1.64)	2.20 (95% CrI: 1.57 – 3.08)	7.69 (95% CrI: 6.25 – 9.09)
WAIC	545.9 (SE: 100.2)	536.4 (SE: 99.6)	622.1 (SE: 103.3)	717.2 (SE: 156.8)
LOO	557.8 (SE: 102.3)	546.0 (SE: 100.6)	632.5 (SE: 105.6)	718.5 (SE: 151.8)

Force of infection (FOI), relative change in FOI (Alpha), age at which the FOI changes (Cut-off), widely applicable information criterion (WAIC), leave-one-out cross validation (LOO), Standard Error (SE).

group (with age at cut-off 8.49 [7.52 – 9.94] years) in the age-varying FOI model (Figure 3A). We further explored the relationship between FOI, attack rates and the estimated number of infections by age. We used the pooled estimate across all studies of FOI to estimate the proportion exposed at a given age to provide an indication of how many infections we might expect to see by age under our modelling assumptions (Figure 3B). We estimate that by two years, over 50% of the population will have at least one infection, and by age ten over 75% will have had more than four infections.

Discussion

To date, there has been limited evidence about the duration of immunity to SARS-CoV-2. Given the inevitable right censoring of data during an emerging infectious disease pandemic, understanding the duration of protection following infection with HCoV could help provide insights which will be relevant to SARS-CoV-2. Using an age-varying reverse catalytic model, we estimated the overall duration of immunity, as measured by seropositivity, to be between 0.9 (95% CrI: 0.6 - 1.6) years and 3.8 (95% CrI: 2.0 - 7.4) years for HCoV's. When waning was estimated by strain, we found comparable estimates of the duration of seropositivity, indicating that the assumption that waning is similar across strains holds true. Previous studies have produced varied estimates for the duration of immunity for HCoVs. One study estimated the median duration of immunity to be 2.5 years[10], and Reed found immunity lasts at least one year[9]. However, several studies have reported reinfection occurring in less than one year[8,11–13]. Aldridge *et al.*[11] found that reinfection with HCoV did not occur with the same strain, but Kiyuka *et al.*[12] found reinfection frequently occurred with the same strain within a six month period. The reverse catalytic model assumes that waning occurs at a constant rate, however, individuals may become reinfected within a shorter time period than average, and conversely some will take longer. Some evidence also exists for the duration of immunity to SARS-CoV-2. A recent survey of health care workers in Oxford, UK, found that protection against reinfection with SARS-CoV-2 lasts at least six months[36], whilst another study of health care workers from across the UK conducted by Public Health England found that immunity lasts for at least five months[2]. This seems to align with what is known about reinfection in seasonal HCoVs. However, these studies only followed up individuals for six months and five months respectively, and longer follow-up times are needed. Future studies could also work to untangle the relationship between seroreversion as a result of waning homotypic antibody responses and antigenic evolution leading to a mismatch between prior immunity and circulating viruses[37].

More informed priors for the FOI based on attack rates for influenza, resulted in higher estimates for the duration of seropositivity. When we used less informed priors for the FOI, a lower estimate of duration of seropositivity was obtained. However, this model produced higher estimates of FOI, with six studies reported FOI estimates in the young age group greater than one (attack rate >63%). There is limited information on the attack rate of seasonal HCoV, however there have been numerous studies looking at influenza. Previous systematic reviews have estimated the attack rate of influenza to be between 3.5% and 22.5%[26–28], whilst modelling studies have estimated this to be higher, 20 – 60%[29,30]. Based on reporting rates of seasonal HCoV we would expect the attack rate to be lower than influenza. Therefore, this suggests that

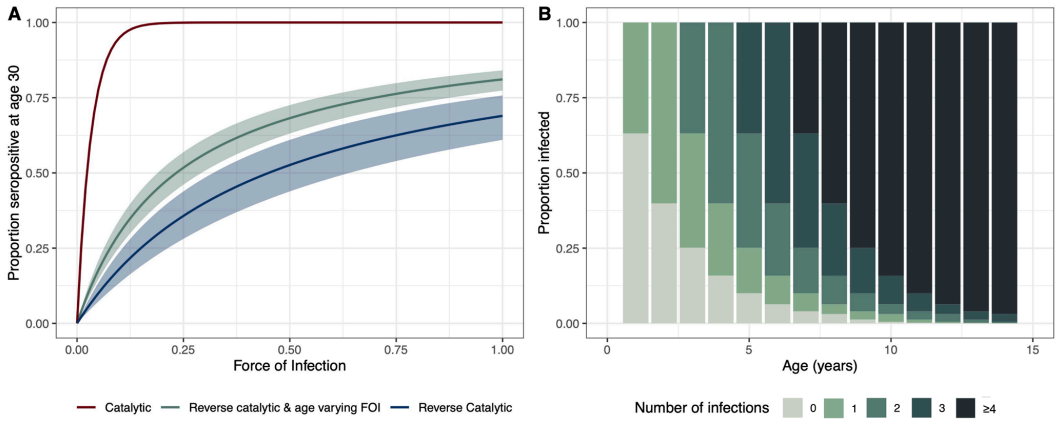

Figure 3. (**A**) Proportion of individuals age 30 who are seropositive for different estimates of force of infection (FOI). The catalytic model is shown in red, the reverse catalytic model in green, and the reverse catalytic model with age-varying FOI is shown in blue. Model estimates were used for the parameter values (relative change in FOI (alpha),1.93 [1.69 – 2.19]; waning, 0.45 [0.32 – 0.64]; cut-off, 8.49 [7.52 – 9.94]). (**B**) Estimated proportion of individuals experiencing infections by age estimated from the age-varying reverse catalytic model (more informed priors) using the pooled median estimate across studies for FOI (0.46), and median estimates for waning (0.45), alpha (1.93) and cut-off (8.49).

the results from the model with less informative priors are less plausible. Maternally derived immunity may also have a role, protecting young infants from infection[38]. We tested this with a model which included individuals ≤1 year. This resulted in a shorter estimate of the duration of antibody persistence, and a higher FOI, suggesting that maternal immunity may be important.

A wide range of different assays were used in the studies we considered in our analysis, including enzyme-linked immunosorbent assays (ELISA), immunofluorescence assays (IFA), western blots, and complement fixation (CF), hemagglutination inhibition assays (HAI) and neutralisation assays. Neutralisation assays are considered to be the gold standard as they measure the ability of the sera to inhibit viral processes[7,39]. Only Cavallaro and Monto[22] used a neutralisation assay. Other assays, such as ELISA and IFA, do not assess the functionality of the antigen, but instead detect the presence of antibodies in a sample. Zhou *et al.*[19] used IFA to detect levels of IgG antibodies. When we allowed the waning estimate to vary by assay, we found a similar estimates of antibody persistence for ELISA, HI and neutralisation assays, ranging from 1.1 years to 2.6 years, and these are comparable to the estimates from the main model. However, for IFA, we observed a longer estimate of 7.7 years (CrI: 3.0-14.3). Due to the small number of studies, the credible intervals were large, particularly for the IFA and neutralisation assay, which only had one study setting for each assay. This highlights the need for more studies, and better standardisation of assays. A recent study provided evidence that IgG antibodies in SARS-CoV-2 are correlated with neutralising antibodies, and may therefore act as a correlate of sterilising immunity[40], whilst another study suggested that neutralizing antibodies may be correlated with protection against reinfection[1]. Therefore, although antibody prevalence does not equate to immunity for seasonal HCoVs, prevalence of IgG antibody may be a good correlate of immunity. However, all of these assays only assess humoural immunity, and it is thought that cellular immunity also has a role SARS-CoV-2, and so it is likely to be also important in seasonal HCoVs[41–43].

The seroprevalence surveys included in this study were conducted in different countries and settings (USA, China, Germany and Hong Kong), as well as in different time-periods (ranging from 1965–2011). It is likely that there are differences in social structure and contact patterns between these settings. Furthermore, individual level data was not available for these studies, and instead aggregated data was used. Finer resolution, particularly for the younger age groups, would have helped to provide more certainty with these estimates. In addition, we did not take into consideration cross-protection between seasonal coronavirus strains. There is some evidence of cross protective immunity between seasonal coronavirus strains, and in settings where there is co-circulating HCoV strains, this may lead to a higher prevalence. There is also evidence that there is cross-reactivity between different coronaviruses, which may lead to false positive results. A recent systematic review found that there was some cross-reactivity that occurred within alpha (HCoV-229E and HCoV-NL63) and beta (HCoV-OC43 and HCoV-HKU1) coronaviruses, but minimal reactivity between alpha and beta coronaviruses[7]. However, it is not clear whether cross-reactivity equates to cross-protection. False positives due to cross-reactivity would lead to an over-estimation of seroprevalence in a setting. This would lead to a higher plateau in older ages, and therefore generally lead to an over-estimation of both the FOI and the duration of antibody persistence. We also did not account for seasonality within this model, which may have under-estimated our FOI. Ferrari *et al.*[44] found that ignoring seasonality may overemphasize the role of adults in the transmission, however, this was observed in measles in Niger, with outbreak peaks ranging over severalorders of magnitude, and long periods between epidemics. Theepidemic profile is different for seasonal coronaviruses, and therefore, this is unlikely to apply in this context. Whitaker & Farrington[45] found that accounting for seasonality resultingfrom past epidemics only had a marginal effect on the estimates, and that regular epidemic dynamics do not strongly bias the catalytic model. The time of year data collection occurred may influence seropositivity estimates, particularly given that the duration of antibody persistence is estimated to range between 0.9 (95% CrI: 0.6 - 1.6) years and 3.8 (95% CrI: 2.0 - 7.4) years. Data collection during high transmission periods would lead to an overestimate of both the FOI and the duration of antibody persistence. All the studies (except for Chan *et al.*[23] who did not report this information), included within this analysis collected data over at least a six-month period. For this reason, the timing of data collection is unlikely to have biased our results. We also assume an overall FOI by age, and we do not account for differences in population susceptibility, for example health care workers or immunocompromised individuals. Despite these limitations, the duration of immunity estimated in this study is in line with literature estimates, suggesting the age-varying reverse catalytic model was able to capture overall dynamics.

Numerous studies have looked at the age pattern of HCoV patients presenting to hospital and healthcare settings, and predominantly found that the burden of disease is higher in younger children and the elderly[46–48]. However, it is likely that these age groups may have more severe symptoms and are therefore more likely to be reported. In contrast, seroprevalence data makes it possible to examine the whole population for evidence of past exposure, and hence can provide a clearer understanding of the underlying transmission dynamics of disease, rather than just the resulting burden.

In this study, when the relative change in FOI and the age of cut-off were simultaneously estimated across studies, we found that the FOI was estimated to be twice as high in the older age group (in this case, those over 8.49 [CrI: 7.52 - 9.94] years), compared with the younger age group. A similar pattern was observed for three of five settings when the relative change in FOI and the cut-off age were allowed to vary by setting. This suggests that older children and adults may be important for the transmission of seasonal HCoVs in some settings. A previous study looking at social mixing patterns in Europe[49] found that children are expected to have the highest incidence during the initial stages of an epidemic as a result of

their social mixing patterns, and this is what is found for some diseases, such as seasonal influenza, where there is evidence young children drive transmission[50,51]. However, a more recent study looking at a large scale dataset of movement and contact patterns in the United Kingdom data found contact intensity was highest in the 18–30 year age group when looking at all types of contacts (conversational, which was defined as face-to-face conversation of three or more words, and physical), although for physical alone, those aged 5–9 years had the highest contact[52]. Therefore, any association between contact intensity and transmission will depend on the contacts considered, particularly if a pathogen is more commonly spread via conversational contacts or via prolonged physical contacts. One possible explanation for the higher FOI we estimate in older age groups is that conversational contacts – which are typically higher in volume but lower in duration and intensity – could be more important for the transmission of seasonal HCoVs.

The results from this study are in accordance with what studies have observed in children during the coronavirus disease 2019 (COVID-19) pandemic, with low numbers of cases reported in young age groups, and several large seroprevalence studies have reported lower seroprevalence in children compared with adults[53,54]. As well as differences in contact structure, this could be explained in part by reduced susceptibility to acquisition of infection; a meta-analysis of contact tracing studies found that children had 56% (31% – 71%) lower odds of becoming an infected contact compared with adults[55].

The duration of immunity to SARS-CoV-2 is still largely unknown and is of significance for the interpretation of population wide serological data, the understanding of the long-term dynamics of the epidemic, as well as of clinical importance. Given the long-term circulation of seasonal HCoVs, data on these related coronaviruses could provide indications of the possible future dynamics of SARS-CoV-2. With infection likely to become endemic in parts of the world, the duration of antibody-mediated immune responses will be particularly important in shaping transmission patterns in years to come. Using seroprevalence data, in this study we estimated the duration of seropositivity to seasonal HCoVs following seroconversion to be between 0.9 (95% CrI: 0.6 - 1.6) years and 3.8 (95% CrI: 2.0 - 7.4) years. We allowed the FOI to vary by age group and found it to be lower in young children (≤8.5 years) compared with older children and adults, which is corroborated with what has been observed in the COVID-19 pandemic. This suggests individuals in settings with endemic HCoVs accumulate multiple infections over the course of their lifetime, punctuated by periods of waning seropositivity against circulating viruses.

Data availability statement

Underlying data

Zenodo: erees/seasonalHCoV: First release. https://doi.org/10.5281/zenodo.5707764[25]

This project contains the following underlying data:

- Data extracted from Huang *et al.*[7] ("41467_2020_18450_MOESM7_ESM-1.csv")

GNU General Public License v3.0.

Extended data

Zenodo: Extended data: Estimating the duration of seropositivity of human seasonal coronaviruses using seroprevalence studies. https://doi.org/10.5281/zenodo.5784018[35].

This project contains the following extended data

- SupplementaryMaterial.pdf
  - Sensitivity analysis: Less informed priors for FOI (supplementary Table 1 and Figure 1)
  - Sensitivity analysis: Waning estimated by strain (supplementary Table 2)
  - Sensitivity analysis: Alpha and cut-off jointly simultaneously by study (supplementary Table 3 and Figure 2)
  - Reverse catalytic model (supplementary Figure 3 and Table 4)
  - Sensitivity analysis: Including the youngest age groups (<1 year) (supplementary Table 5 and Figure 4)
  - Sensitivity analysis: Refitting the model using data from only two strains (supplementary Table 6)
  - Sensitivity analysis: Waning estimated by assay (supplementary Table 7 and Figure 5)

Software availability

Source code available from: https://github.com/erees/seasonalHCoV

Archived source code at time of publication: https://doi.org/10.5281/zenodo.5707764[25]

License: GNU General Public License v3.0.

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5

Transmission modelling of environmentally persistent zoonotic diseases: a systematic review

Following on from Chapter 2 where I explore the role of climate on leptospirosis incidence, and Chapter 3 where I explored antibody dynamics following *Leptospira* infection, this chapter was motivated by a desire to explore how these could be brought together more holistically within a single modelling framework. Mechanistic transmission models are a natural tool for this as they allow for the inclusion of explicit assumptions regarding the biological mechanisms driving transmission, compared with statistical models which aim to quantify (rather than explain) associations between explanatory and response variables. Very few studies consider the full transmission pathway of leptospirosis within a transmission model, therefore, I identified other zoonotic diseases with environmentally persistent pathogens which share similarities in their transmission dynamics. The aim of this study was to systematically review and critically appraise transmission models of environmentally persistent zoonotic diseases in order to identify key themes and best practices, as well as areas for improvement in the future. This may allow for shared knowledge across these diseases, and be of particular benefit to diseases such as leptospirosis which have a limited knowledge base.

The results from this study were published as a systematic review in The Lancet Planetary Health in July 2021 [1]. The Supplementary material of the paper is included as Appendix E.

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Thesis Title	Understanding complex drivers of infectious disease transmission dynamics		
Primary Supervisor	Adam Kucharski		

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Transmission modelling of environmentally persistent zoonotic diseases: a systematic review

Eleanor M Rees, Amanda Minter, W John Edmunds, Colleen L Lau, Adam J Kucharski, Rachel Lowe

Transmission of many infectious diseases depends on interactions between humans, animals, and the environment. Incorporating these complex processes in transmission dynamic models can help inform policy and disease control interventions. We identified 20 diseases involving environmentally persistent pathogens (ie, pathogens that survive for more than 48 h in the environment and can cause subsequent human infections), of which indirect transmission can occur from animals to humans via the environment. Using a systematic approach, we critically appraised dynamic transmission models for environmentally persistent zoonotic diseases to quantify traits of models across diseases. 210 transmission modelling studies were identified and most studies considered diseases of domestic animals or high-income settings, or both. We found that less than half of studies validated their models to real-world data, and environmental data on pathogen persistence was rarely incorporated. Model structures varied, with few studies considering the animal–human–environment interface of transmission in the context of a One Health framework. This Review highlights the need for more data-driven modelling of these diseases and a holistic One Health approach to model these pathogens to inform disease prevention and control strategies.

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Introduction

WHO defines zoonotic diseases as diseases that can transmit naturally between vertebrate animals and humans.[1] Such zoonoses can be transmitted either directly from animals to humans, or indirectly via food or the environment. Diseases that can be transmitted indirectly via the environment, such as leptospirosis and hantavirus disease, are particularly challenging to control as the natural environment also acts as a reservoir. For this reason, it is important to consider this additional dimension of the transmission process within a One Health framework, which accounts for interconnectedness between the health of humans, animals and their environment.[2–4] These diseases at the animal–human–environment interface are the focus of this Review.

Understanding disease transmission processes at the animal–human–environment interface is an increasingly important issue, especially because climate change, loss of biodiversity, land use, and land-cover change alter and often increase pathogen transfer to, and from, the environment. The multihost and environmental persistence of such pathogens can lead to complex disease dynamics.[5] For example, many different factors drive the transmission of leptospirosis; there are numerous exposure routes (ie, occupational, recreational, and socioeconomic circumstances) and many animals are known to be involved, including both rodents and domestic animals.[6] Understanding the underlying disease dynamics can enable insight into how anthropogenic change will affect transmission. Furthermore, because of these complex transmission dynamics, these diseases can be difficult to control, with several possible interventions. Many of these diseases will not be controlled using just one intervention, but instead with multimodal control programmes, targeting vaccination, health education and disease awareness, and improved sanitation and environmental hygiene. Dynamic models can be used to explore the underlying transmission dynamics, answer questions as to the effect of environmental change on transmission and provide insight into the most effective interventions. Furthermore, formulating models within a One Health framework provides an integrated approach for understanding these transmission processes.[3,4]

Dynamic disease transmission models can be used to improve understanding of the disease transmission process, predict the risk of disease outbreaks, and inform the development of effective control policies. In a basic dynamic transmission model, a population is divided into epidemiological classifications (eg, susceptible, infected, and recovered) and populations can be tracked over time.[7,8] Unlike non-communicable diseases, the risk of infectious disease transmission depends not only on individual risk factors, but also on the infectious state of others in the population. Because of this epidemiology, it is important to understand how the infectious state of the population changes over time. Compartmental models

Key messages

- We identified a group of environmentally persistent zoonotic diseases, which share similarities in their transmission dynamics and appraised the methodological approaches used to develop transmission dynamic models
- We highlight the need for more data-driven modelling for this class of diseases, particularly neglected tropical diseases and diseases with a wildlife host
- The full transmission process was often not considered, and models were rarely formulated using a One Health framework, including interactions between humans, animals, and the environment
- We identified gaps in our knowledge about the environmental pathogen burden, despite it being a major source of transmission to humans for many of these diseases
- Moving forward, it will become increasingly important to consider the effect of environmental change and global heating, particularly because of the environmental pathogen burden many of these diseases are climate sensitive and expected to increase their range in the future

	Pathogen species	Pathogen class	Animal reservoirs or hosts	Primary animal reservoir or host	Climate sensitive	Human–human transmission	Primary transmission route	Environmental transmission pathway	Duration environmental persistence	Considered to be an NTD*
Anthrax[18–21]	*Bacillus anthracis*	Bacteria	Domestic and wild animals, including cattle, sheep, goats, antelope, and deer	Domestic and wild animals	Changing range as a result of climate change	No	Direct transmission with infected animal, or environmental transmission	Inhalation	Up to 48 years	No
Brucellosis[22–24]	*Brucella abortus, B melitensus, B suis, B neotomae, B ovis, and B canis*	Bacteria	Domestic and wild animals, including cattle, swine, goats, dogs, and bison	Domestic animals	Yes	Rare	Multiple routes; primary route unknown	Inhalation	21 days–8 months	No
Campylobacteriosis[25–27]	*Campylobacter jejuni* and *C fetus*	Bacteria	Domestic and wild animals (eg, cattle, poultry, and rodents)	Domestic animals	Yes	Rare	Foodborne	Ingestion via contaminated water	2–14 days	No
Cryptosporidiosis[28–30]	*Cryptosporidum parvum* (most common zoonotic species, but many others exist)[31]	Protozoan	Mammals	Domestic and wild animals	Yes	Yes	Multiple routes; primary route unknown	Ingestion of contaminated water and food	Several months	Yes (by PLoS)†
Echinococcosis[31,32]	*Echinococcus granulosus and E multilocularis*	Helminth (cestode)	Dogs, sheep, and foxes	Domestic and wild animals	Yes	No	Direct transmission from an infected animal, or environmental transmission	Ingestion food, water or soil	Up to 1 year	Yes (by WHO and PLoS)
E coli[33,34]	*Escherichia coli*	Bacteria	Predominantly cattle, but also other mammals and birds	Domestic animals	Yes	Rare	Foodborne	Ingestion via contaminated water or food	1 day–1 year	Yes (by PLoS)
Erysipeloid[35–37]	*Erysipelothrix rhusiopathiae*	Bacteria	Predominantly pigs, but also turkeys, chickens, ducks, emus, and sheep	Domestic animals	Some evidence‡	No	Direct transmission from an infected animal	Environmental transmission from contaminated animal waste and soil	2–35 days	No
Fascioliasis[38–41]	*Fasciola hepatica* and *Fasciola gigantica*	Helminth (trematode)	Domestic and wild ruminants, including cattle, sheep, buffaloes, donkeys, and pigs	Domestic and wild animals	Yes	No	Environmental transmission	Environmental transmission via ingestion of contaminated aquatic plants or water	Several months	Yes (by WHO and PLoS)
Giardiasis[42–44]	*Giardia duodenalis*	Protozoan	Cats and dogs	Domestic animals	Yes	Yes	Multiple routes; primary route unknown	Ingestion contaminated water and food	Several months	Yes (by PLoS)
Glanders[45–47]	*Burkholderia mallei*	Bacteria	Primarily horses, but also donkeys, mules, goats, dogs, and cats	Domestic animals	No	Rare	Direct transmission from an infected animal, or inhalation of the bacteria from the environment	Inhalation of the bacteria from the environment	2–6 weeks	No
Hantavirus[48–52]	*Puumala* spp, *Seoul* spp, *and Sin Nombre* spp	Virus	Rodents	Wild animals	Yes	Rare	Environmental transmission	Inhalation	Up to 18 days	Yes (by PLoS)
Leptospirosis[6,12,53]	*Leptospira* spp	Bacteria	Domestic and wild animals including rodents, cattle, sheep, and dogs.	Domestic and wild animals	Yes	No	Multiple routes; primary route unknown	Ingestion or via cuts and abrasions in the skin from contaminated water or soil	1–12 months	Yes (by PLoS)

(Table 1 contines on next page)

	Pathogen species	Pathogen class	Animal reservoirs or hosts	Primary animal reservoir or host	Climate sensitive	Human–human transmission	Primary transmission route	Environmental transmission pathway	Duration environmental persistence	Considered to be an NTD*
(Continued from previous page)										
Melioidosis[54,55]	*Burkholderia pseudomallei*	Bacteria	Domestic and wild animals, including sheep, goats, swine, cattle, and rodents	Domestic and wild animals	Yes	No	Multiple routes; primary route unknown	Contact, inhalation, or ingestion	Up to 7 days	Yes (by PLoS)
Nipah virus[56,57]	*Nipah virus*	Virus	Pigs, dogs, goats, cats, horses, and sheep; the virus is thought to be maintained in nature by bats	Domestic and wild animals	Some evidence‡	Yes	Direct transmission from an infected animal	Environmental transmission as a result of ingesting food contaminated with bat saliva and urine	Several days	Yes (by PLoS)
Q fever[58-60]	*Coxiella burnetii*	Bacteria	Predominantly cattle, sheep, and goats	Domestic animals	Some evidence‡	Rare	Multiple routes; primary route unknown	Inhalation	Up to 3 years	Yes (by PLoS)
Salmonellosis[61-63]	*Salmonella enterica* Dublin, *S enterica* Enteritidis, *S enterica* Typhimurium, *S enterica* choleraesuis	Bacteria	Domestic and wild animals, including poultry, pigs, cattle, and cats	Domestic animals	Yes	Yes	Foodborne	Ingestion of contaminated water or food	7 weeks	Yes (by PLoS)
Toxoplasmosis[64-66]	*Toxoplasma gondii*	Protozoan	Domestic animals and wild animals (eg, cats, pigs, sheep, and goats)	Domestic and wild animals	Climate change might increase cases	Yes	Foodborne	Ingestion of contaminated soil, water, or food	Up to 24 months	Yes (by PLoS)†
Toxocariasis[67,68]	*Toxocara canis and T cati*	Helminth (nematode)	Cats and dogs	Domestic animals	No	No	Multiple routes; primary route unknown	Ingestion contaminated soil	Several months	Yes (by PLoS)
Tularaemia[69,70]	*Francisella tularensis*	Bacteria	Rabbits, rodents, squirrels, and other small mammals	Wild animals	Climate change might increase cases	No	Multiple routes; primary route unknown	Inhalation or ingestion of contaminated water and soil	Several weeks	No
Yersinosis[71,72]	*Yersinia enterocolitica* and *Y pseudotuberculosis*	Bacteria	Predominantly rodents, but also sheep and pigs	Wild animals	No	Rare	Foodborne and contaminated water	Ingestion of contaminated water or food	7–36 days	No

NTD=neglected tropical disease. PLoS=Public Library of Science. *Based on the WHO list of NTDs[73] and PLoS list of major Neglected Tropical Diseases.[74] †Classed as on the cusp; which is defined by PLoS as diseases that could be classed as NTD's depending on the availability of disease estimates for that condition, and whether they occur in resource-poor settings.[74] ‡Some available studies suggesting the disease might be climate-sensitive, but the link has not yet been clearly established.

Table 1: **Summary of diseases included within the systematic review**

can include more than one population, or in the case of zoonotic diseases, models can include both humans and animal reservoirs.[9] Additionally, individual-based models can be formulated to track individuals, rather than populations, over time. We can further distinguish between models, describing them as deterministic, in which the same results are always obtained from a given set of parameters, and stochastic, in which chance has a role in governing events.[7,8,10,11]

In their simplest form, models can be used theoretically to understand observed patterns and behaviours in different systems, for example, they can be used to find theoretical thresholds for disease elimination or the existence of an endemic equilibrium. Modelling also allows exploration of different scenarios, such as the comparative effectiveness of different control measures, a comparison that can be ethically or logistically unfeasible during a real-world outbreak.[7,8,10,11] Advances of computational capabilities and advances in statistical software has enabled the development of more complex models, and for real-world data to be used to validate or calibrate models, allowing these models to predict disease outbreaks and directly inform policy and interventions.[7,9] Because of these advancements, methods of analysis and fitting models to data have improved, becoming more refined and better able to incorporate real-life complexity.[8] In this Review we define model validation as the comparison of model simulations with observed data, even qualitatively, whereas model calibration takes this definition further

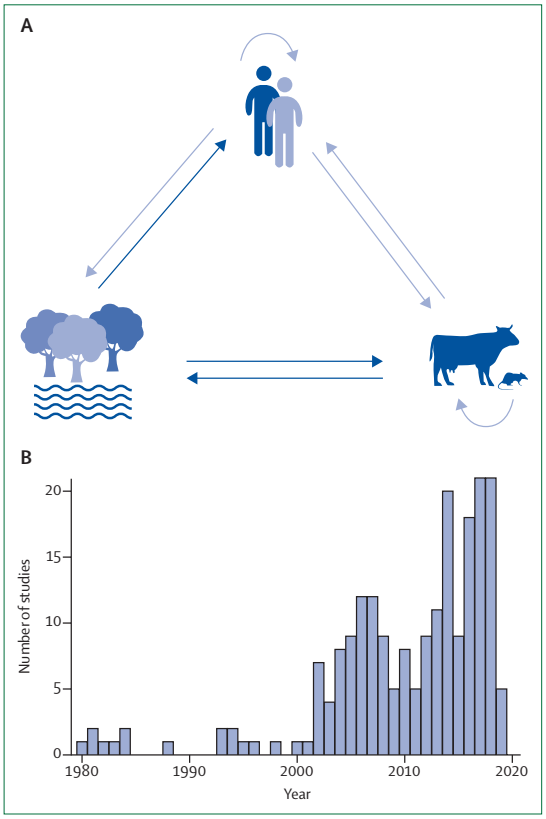

Figure 1: **Transmission pathways and studies included in the systematic review**

(A) Transmission pathways of the diseases included within this study; solid arrows show shared transmission routes across all diseases, dashed arrows show transmission routes that only occur in some diseases. (B) Number of studies (n=208) identified in the systematic review from 1980 to 2019, studies which present models on more than one disease are only included once.

See Online for appendix

and fits models to observed data to estimate key unknown biological parameters (eg, by using methods such as Markov chain Monte Carlo to estimate parameters).[7] Studies will have different aims and purposes, and the model should only be as complex as needed to fulfil the intended objective.

In this Review, we critically appraise studies that have attempted to model infectious diseases at the animal–human–environment interface to quantify traits of models across diseases and identify studies that have adequately accounted for these three One Health components. Previous reviews of modelling studies have focussed on vector-borne diseases or zoonotic diseases generally[9,12,13] and, to the best of our knowledge, this is the first review that focusses specifically on environmentally persistent pathogens. Of particular interest is the way by which models are validated or calibrated, and the data that have been used to do so. First, we identified diseases in which indirect transmission can occur from animals, more specifically land mammals, to humans via the environment. This human–environment transmission could be the only transmission route, or there might be multiple transmission routes to humans, of which environmental transmission is just one. Second, we reviewed modelling studies using a systematic approach. For each paper, we extracted information on the type of model, the data used, and the quality of model validation and calibration attempts. Finally, using this information, we evaluated the current state of transmission modelling studies and identified key themes and best practices, which could be incorporated in future disease transmission analyses and shared between different diseases.

Methods

Disease selection

Two criteria were used to select diseases for inclusion in the study: the disease must be zoonotic (transmissible from animals to humans, specifically affecting land mammals), and the pathogen must persist in the environment for at least 48 h and then remain able to cause subsequent human infections.

Vector-borne diseases and fungi were excluded. Lists of zoonotic diseases were obtained from Public Health England,[14] the European Centre for Disease Control,[15] and WHO.[1] Following these criteria, 20 diseases that had free-living pathogens were identified. We considered free living to mean the pathogen could survive in the environment for more than 48 h outside of a host. We focussed on land mammals as we were particularly interested in animals that live alongside humans in the same environment, and as a result of our criteria very few diseases were excluded (appendix pp 1–3). For example, rabies was excluded because transmission to humans occurs via direct contact with an infected animal or human, and there is no evidence of environmental transmission to humans. Ebola was excluded as, although there is some evidence of environmental persistence, transmission to humans occurs via an infected animal, or human–human transmission, and not via the environment. Although Lassa fever and Bolivian haemorrhagic fever anecdotally have the ability to survive in the environment, no evidence was found of this, and so these diseases were also excluded from this Review.[16,17] A summary of each disease is presented in table 1 and a generalised schematic representation of the transmission pathways for the diseases is shown in figure 1A.

There are many different serovars of *Salmonella enterica* subspecies *enterica*, not all of which are zoonotic. Therefore, four common zoonotic serovars were selected for the study, *S enterica* serotype Dublin, *S enterica* serotype Enteritidis, *S enterica* serotype Typhimurium, and *S* serotype Choleraesuis. Melioidosis is not always considered a zoonotic disease because transmission to humans occurs primarily via the contaminated environment;[75] animals can be the source of the environmental contamination, but not necessarily so.

However, because environmental transmission to humans is of key interest for this Review, this disease matched our inclusion criteria and was included.

Inclusion and exclusion criteria

To qualify for inclusion, studies had to model one of the 20 diseases described (table 1) and include a dynamic population model (ie, models that track populations over time), both compartmental and individual-based models were included.

The following studies were excluded from the review: PhD theses, grey literature (including conference abstracts), statistical models (including time-series analysis, regression, and ARIMA [Auto Regressive Integrated Moving Average] models), within-host models, models using cellular automata, and review articles (unless new models were presented).

Search strategy

In June, 2019, we searched Embase, MEDLINE, and Web of Science for articles published between January, 1970, and June, 2019. Only articles in English were included. We used disease specific and model-specific search terms (appendix pp 4–5). An example search strategy used in the database Embase for leptospirosis is shown (appendix p 6). We aimed to identify all published articles that included population dynamic models of the 20 diseases. To ensure all relevant papers were captured, EMR examined the title, abstract and keywords of known modelling studies to identify relevant search terms, and these were discussed and finalised with other coauthors (AM, AKJ, and RL). Each disease was included as a search term and as a keyword.

We combined and stored the results from database searches using Mendeley reference manager, and duplicates were removed manually. We screened the titles and abstracts of all papers to remove irrelevant studies (eg, experimental animal models). Subsequently, abstracts and full texts of potentially relevant papers were independently reviewed by two reviewers (EMR and AM), and any conflicts were resolved through discussion. Any additional studies identified from the reference lists of these studies were also included (appendix p 7).

Data extraction

To compare studies, we extracted information (including model structure, model type, and model features) from each study (table 2). For studies including models for more than one relevant pathogen, we extracted information separately for each disease.

	Description
Components	
Animals	Animals included in the model
Environment	Environmental pathogens included in the model
Humans	Humans included in the model
Structure of the model	
Deterministic or stochastic	Model structure of the model was deterministic or stochastic
Compartmental or IBM	Model structure of the model was ODE-based or an IBM
Model Features	
Data-driven parameters	Parameters informed by empirical data
Model validation	Model outputs compared with data in any way, even qualitatively
Model calibration	Model fitted to data to estimate parameters
Prediction	Model used to generate predictions about future cases (limited to studies that compared their model with data)
Control measures	Were any control measures included within the model, examples include vaccination and culling
Climate factors	If applicable, were any climate factors (eg, temperature and rainfall) included within the model
Data sources	
Data used	What data was used for model validation (if applicable), including information on type of data, time period, and whether data was for animals, humans, the environment, or a combination of these three factors
Country	Country the study was done in (if applicable)

IBM=individual-based model. ODE=ordinary differential equation.

Table 2: **Summary of information recorded from all studies**

Results

Overall, 20 different diseases were identified that matched the disease inclusions criteria (table 1). After removal of duplicates, a total of 13420 studies were identified using the search terms, and these were screened by title and abstract. A further full-text screen was done for 504 studies, and in total 208 studies were found as meeting all inclusion criteria (table 3; appendix pp 9–33). For papers that included multiple models of relevant diseases, data extraction was done for each disease individually, resulting in 210 models being included in this Review. As expected, the number of published studies has increased over time (figure 1B), with an average of 0·7 studies published per year between 1990 and 2000, rising to 6·8 studies per year from 2000 to 2009 and 13·5 studies per year from 2010 to 2019. Although the overall number of studies has increased over time, the proportion of studies that have included model validation has not changed (figure 2b). The number of studies that had model validation varies considerably by disease and is more common in diseases where domestic animals are the predominant host (figure 2B). When interrogated by study region, model validation is more common for diseases studied in Europe and Asia (figure 2C).

There were no modelling studies identified for Glanders, Nipah virus, erysipeloid, yersinosis, and toxocariasis. Overall, more studies (n=96) were identified for diseases for which domestic animals are the predominant host species (eg, brucellosis, echinococcosis, and *Escherichia coli*) rather than wild animals (n=27; figure 2A). Five diseases were found to have fewer than five studies identified: Q fever, tularaemia, melioidosis, giardiasis, and fascioliasis. 165 (79%) of 210 studies were deterministic, compartmental based models (table 3), with only 55 (26%) of 210 studies using stochastic

	Anthrax (n=19)	Brucellosis (n=37)	Campylo-bacteriosis (n=8)	Crypto-sporidiosis (n=6)	*E coli* (n=24)	Echino-coccosis (n=23)	Fascio-liasis (n=5)	Giardiasis (n=2)	Hantavirus (n=25)	Lepto-spirosis (n=23)	Melioi-dosis (n=1)	Q fever (n=4)	Salmonella (n=20)	Toxoplas-mosis (n=11)	Tularaemia (n=2)	Total (n=210)
Components																
Animals	17 (89%)	37 (100%)	6 (75%)	1 (17%)	20 (83%)	23 (100%)	5 (100%)	1 (50%)	24 (96%)	23 (100%)	0	4 (100%)	19 (95%)	9 (82%)	2 (100%)	191 (91%)
Environment	15 (79%)	14 (38%)	1 (13%)	5 (83%)	18 (75%)	12 (52%)	5 (100%)	2 (100%)	9 (36%)	4 (17%)	0	4 (100%)	13 (65%)	6 (55%)	1 (50%)	109 (52%)
Humans	6 (32%)	8 (22%)	4 (50%)	5 (83%)	4 (17%)	4 (17%)	0	2 (100%)	5 (20%)	18 (78%)	1 (100%)	0	1 (5%)	5 (45%)	1 (50%)	64 (30%)
Model type																
Deterministic	18 (95%)	29 (78%)	7 (88%)	5 (83%)	8 (33%)	19 (83%)	3 (60%)	2 (100%)	19 (76%)	22 (96%)	1 (100%)	0	11 (55%)	9 (82%)	2 (100%)	155 (74%)
Stochastic	1 (5%)	6 (16%)	1 (13%)	1 (17%)	14 (58%)	4 (17%)	2 (40%)	0	3 (12%)	1 (4%)	0	3 (75%)	8 (40%)	1 (9%)	0	45 (21%)
Deterministic and stochastic	0	2 (5%)	0	0	2 (8%)	0	0	0	2 (8%)	0	0	1 (25%)	1 (5%)	1 (9%)	0	9 (4%)
Model structure																
Compartmental	18 (95%)	33 (89%)	8 (100%)	5 (83%)	18 (75%)	19 (83%)	3 (60%)	2 (100%)	23 (92%)	23 (100%)	1 (100%)	1 (25%)	20 (100%)	10 (91%)	2 (100%)	186 (89%)
IBM	1 (5%)	3 (8%)	0	1 (17%)	5 (21%)	4 (17%)	2 (40%)	0	2 (8%)	0	0	3 (75%)	0	1 (9%)	0	22 (10%)
Compartmental and IBM	0	1 (3%)	0	0	1 (4%)	0	0	0	0	0	0	0	0	0	0	2 (1%)
Model features																
Data driven parameters	15 (79%)	28 (76%)	8 (100%)	6 (100%)	24 (100%)	19 (83%)	5 (100%)	2 (100%)	19 (76%)	15 (65%)	1 (100%)	4 (100%)	19 (95%)	8 (73%)	2 (100%)	175 (83%)
Model validation	6 (32%)	15 (41%)	6 (75%)	5 (83%)	19 (79%)	8 (35%)	3 (60%)	2 (100%)	7 (28%)	5 (22%)	1 (100%)	3 (75%)	12 (60%)	0	1 (50%)	93 (44%)
Model calibration	5 (26%)	14 (38%)	5 (63%)	5 (83%)	14 (58%)	6 (26%)	0	1 (50%)	4 (16%)	2 (9%)	1 (100%)	2 (50%)	6 (30%)	0	0	65 (31%)
Prediction	2 (11%)	4 (11%)	2 (25%)	2 (33%)	0	2 (9%)	3 (60%)	0	1 (4%)	0	0	0	1 (5%)	0	0	17 (8%)
Control measures	8 (42%)	29 (78%)	2 (25%)	3 (50%)	11 (46%)	10 (43%)	4 (80%)	1 (50%)	4 (16%)	7 (30%)	0	3 (75%)	5 (25%)	6 (55%)	1 (50%)	94 (45%)
Climatic factors	..	4 (11%)	2 (25%)	2 (33%)	3 (13%)	2 (9%)	2 (40%)	0	4 (16%)	2 (9%)	0	0	1 (5%)	..	..	22 (10%)
Data																
Animals (domestic)	0	7 (19%)	3 (38%)	0	13 (54%)	2 (9%)	1 (20%)	0	0	1 (4%)	0	3 (75%)	11 (55%)	0	0	41 (20%)
Animals (wild)	5 (26%)	2 (5%)	0	0	0	4 (17%)	0	1 (50%)	5 (20%)	3 (13%)	0	0	0	0	1 (50%)	21 (10%)
Environment	0	0	0	0	3 (13%)	0	2 (40%)	0	0	0	0	0	0	0	0	5 (2%)
Humans	1 (5%)	7 (19%)	3 (38%)	5 (83%)	3 (13%)	2 (9%)	0	2 (100%)	2 (8%)	1 (4%)	1 (100%)	0	1 (5%)	0	0	28 (13%)

No studies were identified for toxocariasis, Nipah virus, erysipeloid, glanders, or yersinosis. IBM=individual-based model.

Table 3: **Summary of data extraction by disease**

models, and 24 (11%) studies using stochastic or individual-based models, or both.

93 (44%) of the 210 included studies validated their models against real-world data, 65 (30%) calibrated their models to data, and 17 (8%) used the model to predict future disease transmission (figure 2A; table 3).

Of the 93 studies validated against real-world data, 62 (67%) used animal data, with 28 (30%) studies using human case data (figure 2D). Of the 62 studies with animal data, 41 (66%) concerned domestic animals. Five (5%) of the 93 validated studies included data on the environmental pathogen prevalence (table 3). Data on the environmental prevalence was only considered for fascioliasis and *E Coli*; including field studies that investigated cow pat sampling (*E Coli*) and faecal egg counts from dairy cows (fascioliasis).

While similarities exist, many of the selected diseases have unique transmission pathways. For example, campylobacter and *E coli* infections are usually a result of foodborne transmission,[25,76] whereas leptospirosis transmission can occur either by contaminated water or soil, or through direct contact with the urine of an infected animal.[77] Therefore, differing modelling structures have been chosen to model these diseases, with varying degrees of complexity (table 3; figure 3A; appendix p 8). For most diseases, animals were included within the models (191 [901%] of 210 studies). The environmental reservoir, was included within the model less often (109 [52%] of 210 studies), and humans less frequently still (64 [31%] of 210 studies). Looking specifically at the inclusion of the environmental reservoir, we found five diseases (brucellosis, leptospirosis, campylobacteriosis, Hanta virus, and tularaemia) by which less than half of published models did not include the environmental component (figure 3B). Regarding the proportion of studies that validated and calibrated their models to data by the number of components included (ie, animal, human and, environmental components), there was little difference in model validation by number of components, but a slightly higher proportion of model calibration in modelling studies that included all three components (figure 3C). In total, 17 (8%) of the studies included all three modelling components; of these studies, nine (4%) validated their models to data, and six (3%) calibrated their models to data.

Of the diseases that are climate sensitive, very few models considered the climatic factors within their models (22 [12%] of 178 studies; figure 3D).

Approximately half of studies included control measures within their models (94 [44%] of 210 studies). Control measures investigated included vaccination strategies, disposal of infectious carcasses and contaminated material, livestock movement restrictions, and environmental controls such as water treatment.

Discussion

This Review provides biological and epidemiological insights into modelling approaches used to study

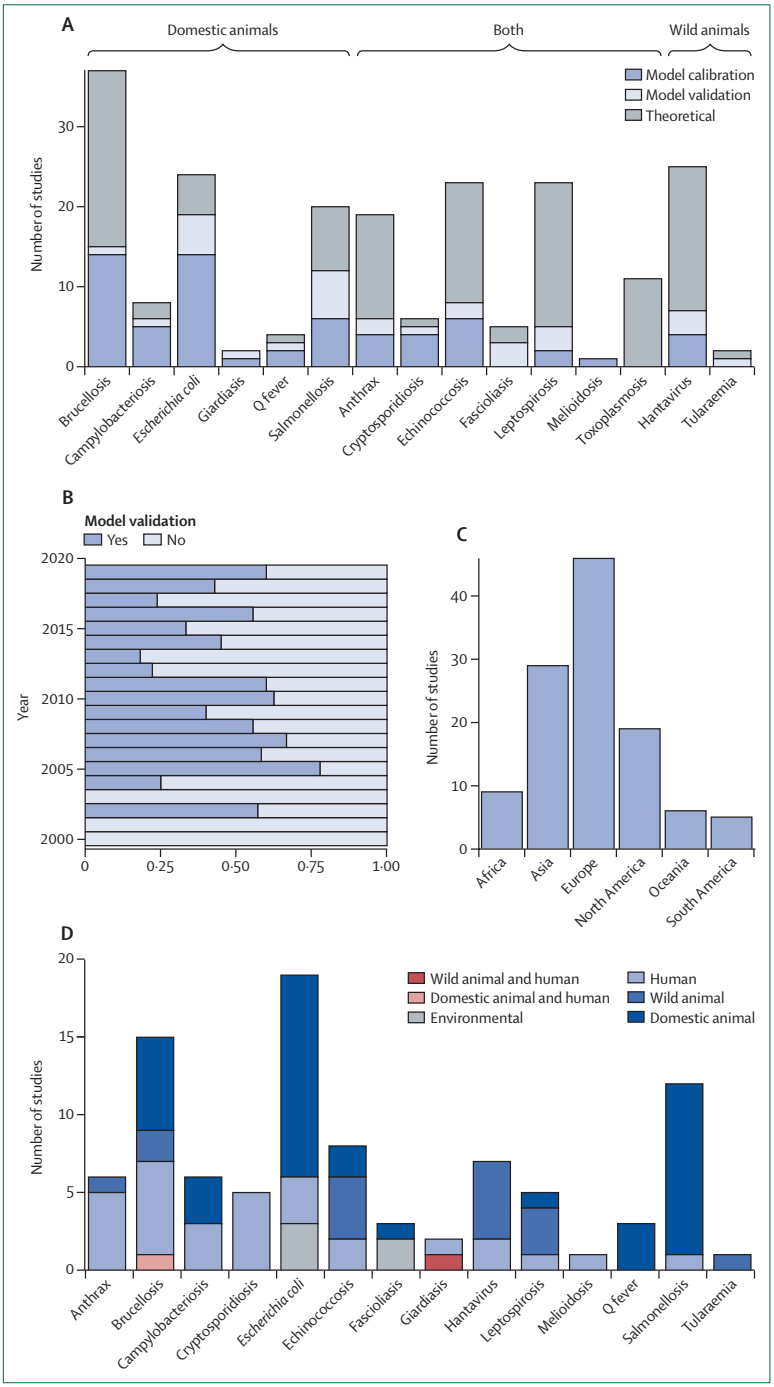

Figure 2: **Summary of model validation and calibration for all included studies**
(A) Number of studies by disease (n=210). Theoretical studies had neither model validation nor calibration; all studies that include model calibration also include model validation. (B) Proportion of studies that include model validation for all diseases, between 2000 and 2019 (n=195). (C) The number of studies by case study region (n=114). (D) Types of data used for model validation by disease (n=93).

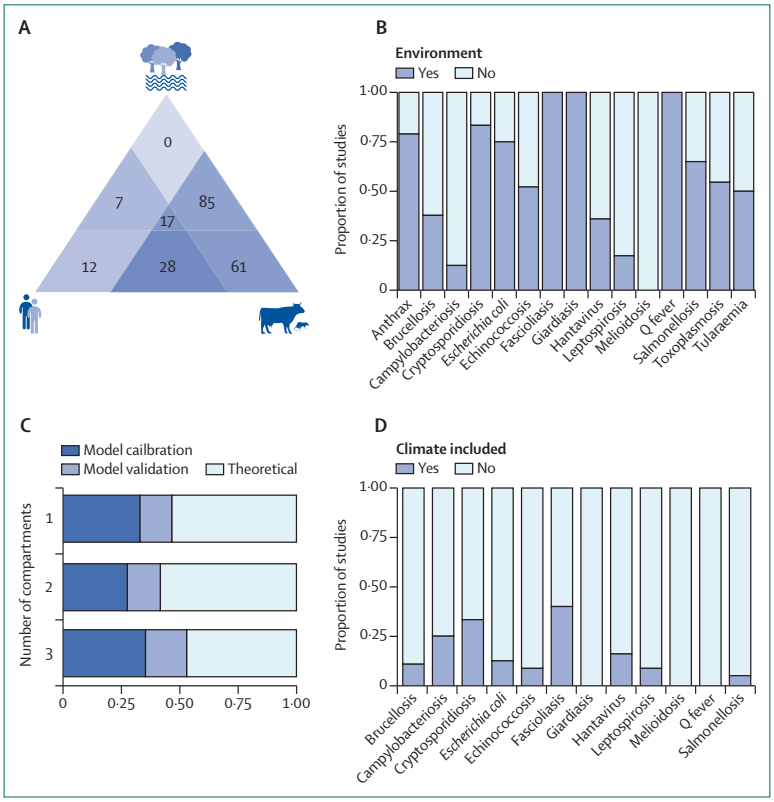

Figure 3: **Models included in systematic review**
(A) Studies by transmission (ie, human, animal, and environmental) factors. The different triangles represent the different components included within the model, with 17 studies including all three components. (B) Proportion of studies that included the environment in their models, by disease (n=210). (C) Proportion of models that validated or calibrated their models by the number of components included within the study (n=210). (D) Proportion of studies that included climate information within their studies (n=178; three diseases excluded because they are not considered to be climate sensitive).

diseases at the human–animal–environment interface, and highlights best practice methodological approaches, which can be applied to lesser studied diseases that have similar transmission dynamics. Environmentally persistent zoonotic diseases vary considerably, occurring in different regions in the world, with different animal hosts and different transmission pathways. However, two key similarities link them together: being a zoonosis, and the capacity of pathogens to survive in the environment for extended periods of time. By contrast with directly transmitted human infections, such as measles, different approaches are required to model this class of human–animal–environment diseases to fully capture the biological processes involved, which could have hindered technical progress. Furthermore, the persistence of pathogens in the environment provides an additional layer of complexity that needs to be considered when studying these diseases. There are many different potential transmission routes; therefore, interventions need to be formulated using a One Health framework to develop effective control programmes, but first this requires a good understanding of the underlying transmission dynamics. The problem is further compounded by the fact that many diseases included in this category are considered to be neglected tropical diseases (NTDs),[73] which typically receive less funding and resources. The transmission process of NTDs is often ambiguous, and, particularly for diseases with wild animal hosts, little is known about the behaviours and environmental interactions exhibited by these animals.

We identified several key areas for progress in the modelling of zoonotic environmental diseases. First, there was substantial variation in the extent of model validation and calibration across pathogens and studies. Overall, less than half of all studies included in this review undertook any kind of model validation (ie, comparing model outputs to observed data), a trend that has not changed over time. This trend can be partly explained by the inclusion of theoretical models in this Review. The aim of such models is to explore transmission dynamics and generate hypotheses, and these models are the foundation for the development of data-driven models. Validating and calibrating models to data is an important step to ensure adequate realism, not only to estimate biological parameters and understand transmission, but also to predict disease outbreaks.[7,8] However, model validation and calibration is a necessary but not sufficient criteria for model realism; the specific choice of data, the implementation methods used, and the model structure are also key decisions. There is substantial future work to be done in this regard, including making testable predictions about real-life epidemics that later be assessed. Additionally, engaging with multidisciplinary and local experts to ensure that the model adequately captures the local environment and situation is an important consideration. The main reason for the lack of extensive model validation is likely to be one of complexity. Some of these diseases have very complex transmission pathways, which means little data exist to understand the full transmission process and, historically, modelling studies have tended to focus on diseases with simpler transmission pathways that are easier to calibrate and validate. In this systematic review, models that included two or three components (ie, animal, human, or environmental) generally included a similar quality of model validation or calibration compared with simpler, and intuitively easier to fit, models that just included one component. Nevertheless, the number of studies validating and calibrating their models was still low, and this highlights the need for more research into these pathogens to provide data to inform models, policy, and important planetary health questions related to landscape change and environmental degradation. This research is likely to require increased transdisciplinary collaboration and coordination between policy makers, mathematical modellers, epidemiologists, ecologists, and veterinarians to overcome the shortfalls of studies to date.

We found that model validation was more common for diseases that affect high-income countries (eg, for example, *E Coli* infection and salmonellosis), and for diseases by which domestic animals are the predominant host. By contrast, fewer models exist for diseases that affect predominantly low and middle-income countries (eg, melioidosis, fascioliasis, giardiasis, and yersinosis) despite a high global burden of disease. This validation discrepancy likely reflects a focus on global research and public health, which in turn means an absence of epidemiological data on the precise number of human cases. Few diseases included within this Review occur primarily in wild animals, most diseases occur in both wild and domestic animals. However, diseases that occur in wild animals (eg, tularaemia and yersinosis), which have low spillover into human populations, tend to be less studied, or do not have model validation and calibration.[9] It is known that wildlife hosts act as major reservoirs of disease, and more effort should be placed on understanding their behaviour and disease transmission potential. However, there are some exceptions. Hantavirus is a disease that is only found in wild animal reservoirs, but there have been a number of outbreaks of hantavirus in Europe, and this is reflected in the number of studies that exist for this disease.[78,79] Additionally, wildlife in national parks are often closely monitored—eg, brucellosis transmission in bison (*Bison bison*) and elk (*Cervus canadensis*) in Yellowstone National Park, USA,[80] and anthrax transmission in Kruger National Park, South Africa.[81,82] A study published in 2020 (ie, after our search was completed), investigated Nipah virus in bats in Bangladesh.[83] Bats were sampled over a 6-year period and a model developed and fitted to seroprevalence data. This study provides a good example of repeated monitoring of a wildlife population and combining this data along with a compartmental model to understand transmission dynamics.

Ideally, data for model validation would be obtained from experiments or field studies specifically designed with modelling as a potential application, with modellers working as part of an interdisciplinary team. There are examples of this collaboration in livestock, such as studies of *Campylobacter* in broiler chickens,[84] *E coli* in pigs[85,86] and cattle,[87,88] *Salmonella* in cattle,[89,90] and examples from wildlife populations, such as echinococcosis in fox populations.[91,92] An illustrative example is a study that originally aimed to look at breeding strategies in female mice.[93] In 2012, there was an outbreak of tularaemia in this study population, allowing for optimal monitoring of this outbreak and a model was subsequently developed using this data. However, often model validation is limited by the data available, and it is not always possible or practical to do experimental studies. For many of these diseases surveillance systems exist, particularly in high-income countries, which monitor the numbers of reported cases in both animals and humans, and these data can then be used to inform and parameterise models. Nevertheless, the existence of surveillance systems varies extensively, not only by disease but also by setting. These surveillance systems tend to focus on human and animal cases, with very little focus on surveillance of the natural environment.

The vast majority of studies that validated their models to data used animal or human data, with few studies including data on the environmental reservoir, which could be explained by the difficulties in collecting such data. Only two diseases included data on the environmental pathogen prevalence, *E coli* and fascioliasis. Some of these studies necessary qualitatively compared their model outputs to environmental data; however, other studies took this further by comparing or fitting their models to observational data. For example, Turner and colleagues[94] compared their model with *Fasciola hepatica* faecal egg counts sampled from dairy cows. Similarly, Mathews and colleagues[95] fitted their model to the prevalence of *E coli* O157 in cow faeces sampled monthly over 1 year. However, transmission to animals and humans is affected by the duration of pathogen survival outside of its host and the extent of spatial dispersal, and for many of these pathogens this is not well understood, highlighting the need for further research and empirical data. For disease systems with little observational epidemic data, experimental estimates (eg, from in vitro or in vivo studies) can be used to parameterise models, which in turn can be used to explore dynamics. There are many examples, but a useful example is Bontje and colleagues[96] who modelled Q fever in Dutch dairy goat herds. The parameters used a wide range of studies, particularly those parameters relating to *Coxiella burnetii*.

By including multiple sources of data within models, it can be possible to estimate the relative contribution and importance of these different transmission routes. For example, Zinstagg and colleagues[97] used demographic and livestock field data from cattle and sheep, and human case data over 9 years, to build a transmission model of brucellosis in Mongolia. This is one of only two examples where human and animal data are used together. The other study, Waters and colleagues,[98] did not fit their model formally, instead they qualitatively compared the model results to the data. Other examples include Gautam and colleagues[99] who combined experimental data in cattle with environmental contamination in faeces, and Ebinger and colleagues[80] who used both bison and elk field data to model brucellosis in Yellowstone National Park.

Another key area for future progress will be consideration of these diseases within a One Health framework, with models exploring the disease transmission system as a whole. Only a small proportion of studies (11%) accounted for the full transmission process (human, animal, and environmental components) within their models, including studies examining the long-term trends of echinococcosis, brucellosis,[100,101] and hantavirus.[78,102] However, including the full transmission

process might not be required for particular research questions, and model parsimony should be considered. Detail and model complexity should not be mistaken for realism; a simple model that explains the data well and answers the question of interest is preferred.[8] There are a number of reasons why some studies have chosen to focus on one element of transmission—eg, it can allow models to focus on particular aspects of transmission for which they have detailed data and a comprehensive understanding. Many of the studies included within this Review did not include the environmental reservoir and the decision to include the environment depends on the context. For example, for *Campylobacter*[3] and hantavirus, the duration of environmental persistence is relatively short (2–14 days for *Campylobacter* and 1–18 days for hantavirus)[19,48] and, depending on the timescale of the model, might not require consideration. Furthermore, although all of these diseases have pathogens that survive in the environment, the importance of the environmental reservoir as a transmission route varies considerably, and in many cases, is unknown. For example, foodborne transmission by *Campylobacter* and *E coli* is considered to be the main transmission route, with environmental transmission a secondary transmission route.[76] The decision of whether or not to include the environment can also be due to the difficulty in understanding the environmental reservoir. For many of these diseases, very little is known about the exact duration of environmental persistence of these pathogens, or the effect of environmental factors on pathogens survival.

However, for some diseases the importance of environmental transmission is well established. For example, transmission of leptospirosis to humans primarily occurs via contaminated water and soil with leptospires surviving long periods in the environment, yet most of the models included humans and animals, without considering the role of the environment (only four of 23 models of leptospirosis considered the environmental reservoir). A better representation of the environmental persistence within these models, particularly with the use of empirical data, would allow for a better understanding and management of these diseases systems, particularly because the environmental burden can pose substantial issues when it comes to control strategies and interventions. Inclusion of environmental data would then lay the groundwork for the development of models that address how environmental change will shape transmission. Many studies also excluded humans from their transmission models, with differences observed between diseases. In diseases with only sporadic human cases (eg, anthrax), human cases provide very little information on the underlying dynamics of transmission. However, when there are outbreaks or endemic transmission in humans, data on humans can help understand the transmission dynamics in the animal hosts even if they are not contributing to transmission directly. Additionally, data collection is usually focussed on human cases, which could aid parameterisation of models that have little or no animal data.

Although there are many valid reasons to focus on particular aspects of transmission when modelling these diseases, there is a need for more models that explore the system as a whole. This approach would allow the transmission dynamics and the effect of climate and anthropogenic change on transmission to be fully explored. Diseases rarely occur in closed, isolated populations and failure to take this complexity into account could result in models being unable to replicate the observed transmission dynamics. This is particularly true for diseases that have an environmental component; failure to take this into account can lead to overestimation of the importance of particular transmission pathways over others, and result in the effect of anthropogenic and climate change being underestimated and unexplored. Furthermore, many of these diseases are climate sensitive, with an increase in cases observed as a result of extreme climatic events. For example, outbreaks of leptospirosis are often associated with heavy rainfall and flooding.[6] The inclusion of climatic data can help to explain observed outbreak dynamics, which was done for hantavirus[78] and brucellosis,[103] and this inclusion can be particularly useful when little is known about the animal population. Furthermore, many of these diseases (eg, anthrax, campylobacteriosis, cryptosporidiosis, and leptospirosis) are expected to expand their range as a result of climate and land-use change and modelling studies incorporating climatic data can help identify the effect of climate change on these diseases, such as campylobacter and cryptosporidium in New Zealand.[104] However, only a small number of models considered the effect of climate variables within their models. It is also important to take into consideration spatially varying covariates, which was done for *E coli*,[105] hantavirus,[79] and echinoccosis.[106] An obvious next step is to combine these dynamic transmission models with other tools, such as ecological niche modelling and geospatial approaches.[107]

Conclusions

This systematic review identified four areas for development in the modelling of zoonotic environmental diseases. First, there is a need for more model validation and calibration for many of these diseases, particularly for models of diseases with wildlife hosts and NTDs that often did not have this important component of the model fitting process. It is known that wildlife hosts act as major reservoirs of diseases; therefore, more effort should be placed on understanding their behaviour and disease transmission potential. Furthermore, most emerging pathogens are zoonotic, with the majority emerging from wildlife reservoirs that then spillover to domestic animals and humans.[2,5,108,109] Second, it is

important for more models to be developed that capture the full transmission process. In particular, the environment as a source of transmission was rarely considered, despite being a major source of transmission to humans for many diseases. This environmental pathogen burden can pose substantial issues when it comes to control strategies and interventions and should be included in more of these disease models using a One Health framework. Third, this Review highlighted how little data exists for the environmental pathogen burden of disease, and often little is known about the environmental burden of these diseases. Finally, it is important to consider the effect of climate variability and climate change on these diseases. Because of the environmental burden, many of these diseases (eg, leptospirosis and melioidosis) are climate sensitive and they are predicted to increase their range in the future.[110] It is essential that we combine these considerations to generate robust models using a One Health approach that are capable of predicting outbreak dynamics and changes in disease risk to inform planning and control.

Contributors

EMR, AJK, and RL conceptualised this Review. EMR, AM, AJK, and RL designed the methodology. EMR did the study search and data analysis. EMR and AM did the screening of studies. All authors contributed equally to the discussion and the editing of the final draft.

Declaration of interests

We declare no competing interests.

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6

Discussion

In this thesis I have explored the complex drivers of infectious disease dynamics. I looked at two different disease case studies, leptospirosis and seasonal HCoVs, both of which have complex infection pathways. Understanding the transmission dynamics and quantifying the strength of transmission drivers requires tools to test these mechanisms, for which mathematical and statistical modelling techniques are ideally suited. Leptospirosis has multiple different animal hosts and leptospires can survive in the environment for long periods of time and go on to cause subsequent human infection. In addition, climate is known to influence the timing and the magnitude of outbreaks in many settings, and this was the focus of Chapter 2. I identified key hydrometeorological and climatic factors influencing leptospirosis risk in Fiji. I found that a climate-driven model was better able to capture the outbreak peaks compared with a baseline random-effects only model, and this is an essential first step towards the development of a climate-driven early warning system in Fiji. Furthermore, infection with *Leptospira* does not confer life-long protection, and the duration of antibody persistence was the focus of Chapter 3. Using serocatalytic models I was able to estimate the duration of antibody persistence following *Leptospira* infection. In addition, I incorporated further data on longitudinal antibody dynamics providing a novel way to estimate the most likely time of infection. Reinfection also occurs with seasonal HCoVs, and due to it being a respiratory virus spread by close contact, social and age mixing patterns are important considerations. Therefore, in Chapter 4 I extended the serocatalytic model to allow for an age-varying FOI, estimating the most likely duration of antibody persistence whilst accounting for differences in FOI by age. The duration of immunity is of key epidemiological importance, as it influences the long-term dynamics of epidemics, but also aids the interpretation of population-wide seroprevalence studies. It is also of clinical im-

portance as it provides information as to how long previously infected individuals may remain immune to reinfection. Finally, in Chapter 5, I explored how climatic drivers and antibody dynamics could be included within a single transmission modelling framework, and provide a more holistic understanding of transmission dynamics.

In this final chapter, I synthesise research from this thesis to show how knowledge from multiple methods (statistical and mathematical models) can provide a greater understanding of transmission dynamics, using leptospirosis and seasonal HCoV as examples. I also highlight the implications of this research, and the remaining challenges that exist.

6.1 Summary of key findings

Quantifying the relationship between hydrometeorological indicators and leptospirosis incidence in Fiji: a modelling study

In Chapter 2 I explored the relationship between different hydrometeorological indicators and leptospirosis incidence in Fiji. Leptospirosis is a neglected zoonotic disease, and there is a high burden of disease in this region. Leptospirosis is a climate-sensitive disease and outbreaks are often reported following heavy rainfall and flooding. However, the relationship between climate factors and leptospirosis incidence has not been well quantified in Fiji or the wider Pacific region. I developed a Bayesian mixed-effect statistical model to explore the role of different hydrometeorological indicators on leptospirosis cases reported in Fiji over 12 years (2006 to 2017) at varying spatial and temporal scales. I also explored different precipitation indicators and identified those that were best able to explain variation in cases. Looking at weekly cases, I found that total rainfall over six weeks, periods of negative SST (i.e. La Niña events) and minimum temperature were all positively associated with leptospirosis cases. Overall, I found that a weekly model which included the climate covariates was better able to capture the seasonal and interannual variation than a model which only included random effects for week and year. These results highlight the potential for creating a climate-based early warning system for leptospirosis in Fiji, and provide a necessary first step. In addition, the results from this study, along with previous studies conducted in Fiji exploring demographic and spatial risk factors [1, 2], bring us closer to a precision public health approach in Fiji by allowing public health interventions to be targeted to the right person, place and time, which is particularly important in settings with limited resources.

Furthermore, in this study I was able to explore the impact of aggregating data to different temporal scales. Statistical-based models exploring climatic factors often use monthly case data. Publicly available surveillance data, gridded climate products and climate forecasts are often only available at the monthly scale. Understanding the implications of aggregating case data was an important addition in this study. With the exception of temperature, I found very little difference in the results between the models using monthly and weekly case data, however, at the monthly scale. However, at the weekly scale minimum temperature was weakly associ-

ated with increased cases, and a short time lag of one week was observed, but this relationship was lost at the monthly scale. These findings demonstrate that higher resolution data may be required to infer relationships that affect cases on short time scales.

Estimating the duration of antibody positivity and likely time of *Leptospira* infection using data from a cross-sectional serological study in Fiji

In Chapter 3, I used data from a large cross-sectional seroprevalence study conducted in Fiji in 2013 [1] to estimate the duration of *Leptospira*-specific antibody persistence (as a proxy for protective immunity). The duration of protective immunity is epidemiologically and clinically important since it was largely unknown for leptospirosis andcan provide insight into the frequency of reinfections, as well as allow for improved interpretation of serosurveys. I used a reverse catalytic model, which allows for comparisons between surveillance and seroprevalence data as it allows estimation of the FOI whilst accounting for waning antibody levels.

I estimated the annual attack rate in Fiji to be 3.15% (2.18% - 5.16%), which suggests there may be as many as 28,000 (19,000 - 46,000) infections annually, assuming a constant FOI. In the five years prior to the seroprevalence survey being conducted there were approximately 1,200 cases reported in total [3] These results highlight the potential extent of unascertained community infections. Possible explanations for this include asymptomatic or mildly symptomatic infections, limited laboratory capacity, and clinical misclassification. I also estimated the duration of antibody persistence to be 8.33 years (4.76–12.50; assuming a constant FOI) and 7.25 years (3.36–11.36; assuming a time-varying FOI). This is longer than previous studies, which estimated antibody persistence to be between three and six years [4, 5]. It is worth noting that in both these previous studies individuals remained seropositive at the conclusion of the follow-up period.

Furthermore, in this study I explored two complementary approaches to estimate the most likely timing of infection at the population level. The first was an extension to the reverse catalytic model which allowed a time-varying FOI, and estimated a large outbreak in 2013. However, there was a lot of uncertainty in this estimate. The second approach combined additional data sources, including longitudinal information on antibody kinetics (from Lupidi *et al.* [4]), to identify the most likely timing of infection. This method estimated that the majority of individuals included within the 2013 serosurvey were most likely the result of a recent infection in the previous two years, and this corresponds to known outbreaks that have occurred in Fiji in 2012 and 2013 [3, 6]. This novel approach estimating the most likely timing of infection allows for richer, longitudinal information to be inferred from cross-sectional studies, and could be applied to other endemic diseases where antibody waning occurs.

Estimating the duration of seropositivity of human seasonal coronaviruses using seroprevalence studies

In Chapter 4, I applied and extended the model I used in Chapter 3 to another disease, seasonal HCoVs. In late 2020 little was known regarding the duration of immunity of SARS-CoV-2. Seasonal HCoVs have been circulating for much longer, and therefore could provide potential insights into SARS-CoV-2 dynamics. I fitted reverse catalytic models to seroprevalence data from six studies covering four different circulating seasonal HCoVs. Due to the differing transmission patterns in children and adults, I extended the reverse catalytic model to allow for a varying FOI (the rate at which susceptible individuals acquire infection and seroconvert) by age.

The results estimated the duration of antibody persistence to last around 1-4 years. This result is in line with the literature from seasonal HCoVs, suggesting that the age-varying reverse catalytic model was able to capture the overall transmission dynamics of seasonal HCoVs. I also found that the FOI in older children (over 8.5 years) and adults was almost twice as high compared with the younger age groups (although there was heterogeneity between studies). This finding has been corroborated with what has been observed during the COVID-19 pandemic [7, 8]. Overall, the results presented in this chapter provide insights into the long-term transmission dynamics of seasonal HCoVs and how these vary by age.

Transmission modelling of environmentally persistent zoonotic diseases: a systematic review.

Finally, in Chapter 5, I explored how compartmental mechanistic transmission models could be used to bring together climatic drivers and immunity dynamics within a single disease framework, providing a more holistic understanding of transmission dynamics. I identified zoonotic diseases that had environmentally persistent pathogens, where indirect transmission can occur from animals to humans via a contaminated environment. I was particularly interested in how previous studies had included and accounted for these complex transmission processes and environmental reservoirs. I identified 20 diseases and systematically reviewed the literature of compartmental transmission models to describe and highlight key themes and best practices, as well as areas for further development. I found that very few studies considered the full transmission process within their models. In particular, the environmental component was often not considered, despite this being a major source of infection for humans for some diseases considered (e.g. leptospirosis). Failure to account for the full transmission framework may result in an overestimation of the importance of particular transmission pathways, and therefore, impact the likely success of different control strategies. I also found that very few studies validated and calibrated their models to data, likely due to the complexity of the transmission systems and the fact that many of these diseases are understudied and neglected. Historically, modelling studies have focused on diseases with simpler transmission pathways (e.g. measles) which are more straightforward to validate and calibrate to data. Due to the environmental burden of disease, many of these diseases are also climate sensitive, yet few studies considered the impact of climate on transmission. Overall, this review highlighted the need for more data-driven

transmission models which consider the full transmission system within a holistic One Health framework, and use this to inform disease prevention and control strategies.

6.2 Progress towards a leptospirosis mechanistic transmission model

Leptospirosis is an example of a zoonotic disease with an environmentally persistent pathogen. It has multiple different animal hosts and numerous circulating serovars. Leptospires can survive in the environment for weeks or months, and transmission is influenced by climatic factors. The complex disease dynamics of leptospirosis, in part, motivated the systematic review I conducted in Chapter 5. Mechanistic transmission models can be used as a tool to study and test theories regarding the transmission dynamics of a pathogen. However, when considering a pathogen as complex as leptospirosis, it can be useful to break down the overall transmission model, and to think about it in smaller sub-component parts.

In Chapter 1 I introduced a leptospirosis compartmental transmission model and in this thesis I have made progress towards understanding some of the sub-component parts that could then be used to inform the development of a more complete transmission model. I have updated and expanded the transmission model introduced in Chapter 1, highlighting the new knowledge gained from this thesis (Fig. 6.1).

In Chapter 2 I sought to understand the seasonal and inter-annual climatic drivers of leptospirosis in Fiji. This information could be incorporated within the FOI (λ_H and λ_A) from the environmental reservoir (L) to humans and to animals, via the parameter ρ (Fig. 6.1), as previously described by Henderson *et al.* 2021 [9]. In Chapter 3 I estimated the duration of antibody persistence, which can act as a proxy for waning immunity, and therefore can inform the rate at which humans move from the recovered to susceptible compartment. Finally, in Chapter 5 I reviewed the literature to identify transmission models that share similar transmission characteristics. This highlighted the challenges associated with developing models for diseases with such complex transmission pathways, and particularly highlighted the gaps in our knowledge regarding leptospirosis transmission.

6.3 Contribution to the field and strengths of this research

6.3.1 Adapting methodology to more complex disease dynamics and overall contribution to the literature

One of the strengths of this work is that leptospirosis is an under-studied disease and there remain many unanswered questions regarding the transmission dynamics. As such, this thesis has made a distinct contribution to furthering our understanding of disease transmission dynamics and drivers of leptospirosis, by adapting and bringing together disparate datasets and

methods for this purpose. In addition, I was able to apply the methodology from Chapter 3 to another understudied disease, seasonal HCoVs.

For example, in Chapter 2 I brought together multiple datasets from different sources, including national Fiji leptospirosis surveillance case data, meteorological data obtained from the Fiji Meterological Office, and data on Sea Surface Temperatures from the National Oceanic and Atmospheric Administration (NOAA) [10]. Given the close association between rainfall, flooding, and leptospirosis cases, I explored five different extreme precipitation indicators defined by the World Meteorological Organisation Expert Team on Climate Change Detection and Indices [11], as well as standardisation measures such as the Standardised Precipitation Index (SPI), and the Standardised Precipitation Evapotranspiration Index (SPEI) [12]. I explored these precipitation indicators in terms of the time period that the indicator measures, and also at different lags to account for the lagged relationship between climate and the observed effect on leptospirosis cases. Many previous studies have only considered total precipitation (usually over one month) within a model, without considering whether there may be better precipitation indicators or time periods to use. In addition, I had access to individual case data, which enabled me to explore the impact of aggregating case data to the monthly or the weekly level. Many studies which explore spatio-temporal risk factors only have monthly data available, and the data used here provides a unique opportunity to explore the advantages and disadvantages of aggregating data to different temporal scales. In this study, as well as precipitation indicators, I explored the role of ENSO and temperature on leptospirosis incidence in Fiji. There are very few studies which have aimed to quantify the relationship between climate and leptospirosis in the South Pacific region, and this study adds to our understanding of the role of climate. Such work is of benefit as it may allow for the development of a clinically useful climate-based early warning system in Fiji in the future.

In Chapter 3 I explored the antibody duration of *Leptospira* infection using serocatalytic models fitted to a large seroprevalence dataset. A literature search did not reveal any serocatalytic models for leptospirosis and therefore this research makes an important contribution to the understanding of the duration of antibody persistence. I also estimated the most likely timing of infection from the seroprevalence study by bringing together longitudinal data on antibody kinetics. This study proposes a novel method for obtaining longitudinal information from seroprevalence surveys, and could be applied to other endemic diseases where antibody waning occurs. This may allow for richer data to be gained from studies of neglected and under-studied diseases where resources are often limited. In Chapter 4, I applied a similar method to seasonal HCoVs, and to my knowledge this is the only study to estimate the duration of antibody persistence for seasonal HCoVs using serocatalytic models. Seasonal HCoVs are transmitted via direct human-to-human contact, and because of this, social networks are considered to be important. Given that there are differences in social mixing by age, I extended the reverse catalytic model to allow for an age-varying FOI. This allowed us to explore assumptions regarding the transmission dynamics by age. In addition to providing new insights into seasonal HCoVs dynamics, this study also demonstrates the transferability of the model I developed to understand leptospirosis in Chapter 2 and its application to a different disease framework.

Finally, in Chapter 5, I conducted a systematic review of transmission models of zoonotic diseases with environmentally persistent pathogens. This provides a novel way of grouping these diseases and brings a new perspective on how information and knowledge can be shared across environmentally persistent zoonotic diseases. Previous transmission modelling reviews have focused on vector-borne diseases or zoonotic disease more generally [13–15], but in this review I was able to focus specifically on the environmental burden of disease, and how this had been included and accounted for within models. Furthermore, this approach allows the sharing of knowledge between well-studied zoonoses affecting domestic animals in high income countries, and less studied neglected diseases in resource-poor settings, particularly those affecting wild animals. This framework will become more important as climate change increases the significance of the environment as a driver of many of these diseases.

6.3.2 Data

Another of the key strengths of this thesis is the data used to inform and fit the models in Chapters 2, 3 and 4. The seroprevalence survey data used in Chapter 3 was a particularly comprehensive dataset. Population proportionate sampling was used and this is a real strength of this data as it aims to be representative of the whole population, and differs from many other seroprevalence studies which use convenience sampling. In addition, a large number of children were included in this study (566 individuals $\leq$ 18 out of 2152 total individuals). The inclusion of children allows for the inference of the FOI in this population as children have been exposed for a fewer number of years, thus showing how seroprevalence accumulates over time, and therefore age, in a population. However, due to ethical considerations and difficulties with sampling, many seroprevalence studies choose not to include children, and therefore lack this ability.

In Chapter 4, I was able to bring together data covering the four different seasonal HCoV strains, from six different seroprevalence studies. The studies varied in both the time they were carried out, but also the geographical setting. Combining information from six different studies strengthens the estimates of antibody persistence allows for greater generalisability of our results. It also allows the comparison of how the estimates of antibody persistence vary by strain and the impact of assay and geographical setting on our results.

6.3.3 Reproducibility and replicability

Finally, throughout this PhD thesis I have endeavoured to make my research as reproducible and replicable as possible. Reproducibility refers to the ability for the results of a study to be duplicated using the same materials as the original investigator and obtain the same results [16, 17]. For epidemiological studies, this requires code and analytical data to be made publicly available, and for the use of open source software [17, 18]. However, these data sharing processes must respect individual anonymity and ethical considerations. Replicability refers to the ability of a researcher to use new data to duplicate the results of a prior study following the same procedures [16, 17]. In Chapters 3 and 4 I have shared my code in publicly available

Github repositories in order to be transparent and enable replicability, and to make extensions and adaptations to the code as easy as possible. This is planned following submission for publication of Chapter 2. In Chapter 4, the data used was publicly available, and this allowed me to share all the raw data, allowing for this chapter to be fully reproducible. In order to respect the anonymity of study participants, in Chapter 3, I publicly shared de-identified data aggregated by five-year age groups. The full dataset is available on request with appropriate ethical approval. This does not allow the full results to be reproduced by sex, division and serovar, but did allow the main reverse catalytic model to be reproduced, albeit with slight differences in the results due to the use of aggregate data. I also created simulated individual-level MAT data which allowed users to replicate the most likely time of infection using simulated data. Chapter 5 was different, as it described a systematic review, and did not have any data analysis associated with it. However, I set out my search criteria and databases used as clearly as possible, so that someone could repeat or replicate the search.

6.4 Limitations and challenges

6.4.1 Data

Whilst this thesis benefits from the data used, it is not without its limitations. The conclusions from this thesis rely heavily on the quality of the seroprevalence and surveillance data used throughout this research, and the models are only as good at the available data used to inform them.

The leptospirosis seroprevalence data is a rich dataset, which included many participants and used population-proportionate sampling [1]. However, there are still limitations associated with this data. Seropositivity was determined using the MAT diagnostic test. The MAT is expensive and difficult to perform, and as such only six serovars were included in the final panel used in the seroprevalence study. Given that there are known to be over 15 different serogroups circulating in Fiji in animals and humans [19, 20], the seroprevalence of leptospirosis in Fiji may have been under-estimated. However, every effort was made to limit this in the original study design. An initial panel of 21 serovars was used on a randomly selected 10% of samples collected in the seroprevalence survey, and the most common serovars included in the panel. In addition, during outbreaks of leptospirosis in Fiji in 2012 and 2013, this same 21 serovar panel was used on approximately 200 *Leptospira* ELISA-positive samples collected from patients with suspected clinical leptospirosis. This will have ensured that both commonly circulating serovars, as well as those serovars responsible for more severe disease (as evidenced by hospitalisation), will have been included in the final panel. In addition, although the MAT is considered to be the gold-standard test for the diagnosis of leptospirosis, it is not without limitations. The results can be difficult to interpret and there is a lack of standardisation between laboratories [21]. While the MAT is able to distinguish between serogroups, cross-reaction between serogroups is common [21]. Finally, the catalytic model requires a cut-off titre to be selected. In the seroprevalence study a low cut-off titre of 1:50 was chosen, as we were interested in any evidence of past infec-

tion, however, depending on the research question, different cut-offs may be chosen. Since we only had seven dilution titres, this did not allow for the use of a mixture model to inform the cut off point [22, 23]; nor did it allow for the use of an antibody acquisition model which fully utilises the antibody titre data and has previously been used for other diseases such as malaria and trachoma [24, 25].

Seroprevalence studies were also used to estimate the duration of antibody persistence for seasonal HCoV. Six studies were used in this analysis [26–31], and although we were able to compare and pool results across multiple settings, there were limitations. The seroprevalence studies were conducted at different points in time, in different settings, using different diagnostic tests. These diagnostic tests had different cut-off points. We attempted to understand the impact of this by conducting a number of different sensitivities (e.g. looking at the results by the type of diagnostic test used). We were also limited by the age brackets authors chose to report.

A further limitation with the interpretation of seroprevalence studies is how well antibody response correlates with protective immunity, and this applies to both leptospirosis and seasonal HCoVs. Relating the seroprevalence level in a population to population immunity is complicated. Therefore, I have been careful throughout this thesis not to equate the duration of antibody persistence with the duration of immunity. However, antibodies can act as a marker of protection, and in the absence of longitudinal reinfection studies they can be a useful strategy to understand infection dynamics.

There are also limitations with the leptospirosis surveillance data. In Chapter 2 we only had reported ELISA-positive cases, and had no information on the underlying infection patterns. ELISA-positive cases are only ascertained if individuals feel unwell enough to report to healthcare, the clinician suspects leptospirosis, and there is diagnostic capacity for testing. Given that many cases are asymptomatic and mildly symptomatic, the cases reported to surveillance are likely to be a small fraction of the true cases. During declared outbreaks, it is recommended that diagnosis is performed based on case definitions and clinical assessment to conserve testing capabilities [32]. Therefore, there is variation in the case definition over time and the surveillance data may not capture the true scale of the outbreaks. In addition, it is known that testing strategies have also changed over the study time period. There was a large outbreak in 2012 in the Western division [6] which resulted in a number of deaths, and it is likely that this brought renewed attention to the disease, and as a result, may have increased clinical suspicion and awareness. Furthermore, in 2016 new guidelines were released [33], which raised the index of suspicion and recommendations of when to test. There is also thought to have been an increase in laboratory capacity over time. Whilst this is all likely to have led to an increase in reported cases, there is evidence that the number of cases of leptospirosis admitted to intensive care units in Fiji is increasing. This implies there is a true increase in the burden of disease and this is not just an artefact of the data reporting and laboratory capacity.

Limitations associated with the ELISA test may have also impacted our results [21, 34, 35]. Firstly, the timing of the test is very important. During the early stages of infection (5-7 days),

antibody titres may have not yet risen, and if samples are taken too early following onset of disease they may be falsely declared as *Leptospira*-negative. Secondly, if the ELISA test is conducted too late following the administration of antibiotics, individuals may also be falsely declared as *Leptospira*-negative. Finally, the ELISA test does not differentiate between serovars. Different animals are known to be associated with certain serovars [36] and that pathogenicity can vary by serovar. Therefore, transmission mechanisms may differ by serovar, and this could not be accounted for within the model.

6.4.2 Limited research interest and investment

Leptospirosis is under-studied, and there remain large gaps in our knowledge of the transmission dynamics. A study by Costa *et al.* [37] estimated the annual global burden of disease to be 1.03 million cases and 58,900 deaths, and this estimate puts leptospirosis as a leading zoonotic cause of morbidity and mortality. However, despite this, research interest in leptospirosis is minimal, and it is not considered by the WHO to be one of the key neglected tropical diseases. The cycle of neglect was highlighted by Goarant *et al.* [38] who found evidence of insufficient research attention in relation to burden of disease, demonstrating that leptospirosis research is significantly under-resourced. As a consequence of this, there remain large gaps in our current knowledge and understanding of leptospirosis transmission dynamics, and progress in leptospirosis research is slow. The body of work presented here enhances the knowledge base in the field, but is also limited by the lack of prior studies to inform model design. There are a limited number of researchers with whom it is possible to discuss ideas. Moreover, leptospirosis is often not discussed at conferences, and leptospirosis papers tend to be published in less high impact journals, and therefore may reach a smaller audience. This lack of peer-to-peer discussion and research interest compounds challenges in interpretation of the results and comparisons to other settings.

Despite seasonal HCoVs first being identified in the 1960's [39], they are also little studied. Seasonal HCoVs were traditionally not deemed to be clinically important, as they predominantly cause mild or asymptomatic disease. Therefore, many unanswered questions remain regarding the transmission dynamics of seasonal HCoVs. Following the emergence of SARS-CoV-1 and MERS-CoV there was renewed interest, which led to the identification of two new strains. Once again, the emergence of SARS-CoV-2 renewed interest in seasonal HCoVs, but there are still many unknowns and gaps in our knowledge, and this limits the interpretation and contextualisation of these results.

6.4.3 Model limitations

Infectious disease dynamics are hugely complex and inter-woven, and we cannot aim to include every element of transmission as the complexity and detail required would be vast. Furthermore, the limited prior knowledge and understanding of the disease system, as well as the limitations with the data available, can result in the development of simpler models, as the knowledge or data to support a more complex model is absent. For example, during the emergence

and global spread of SARS-CoV-2, a wealth of knowledge and data was generated very quickly, aided by the development of accurate and rapid diagnostic tests. This enabled the development of much more complex and detailed models, and a greater understanding of the underlying transmission dynamics. However, for other diseases such as leptospirosis, the knowledge base, diagnostic capability and data lag behind, often necessitating simplifying assumptions. This was highlighted in Chapters 3 and 4, where I used serocatalytic models to estimate the duration of antibody persistence in leptospirosis and seasonal HCoVs and made several simplifying assumptions. Firstly, I did not consider seasonality within the model. Previous studies had found that regular epidemics do not strongly bias the catalytic model, which suggests that the effect of not considering seasonality may have been marginal. Secondly, I did not consider the role of cross-protection and cross-reactivity between strains (seasonal HCoVs) and serovars (leptospirosis). Cross-reactivity may result in false-positives, and this would lead to a higher plateau in older ages and result in an over-estimation of both the FOI and waning rate. However, the role of cross-protection and cross-reactivity is not well understood, particularly for leptospirosis, and a greater understanding or improved data is required before this may be considered within models. Furthermore, in Chapter 2, model complexity was limited by the data that was available. Therefore it was not possible to include more spatially-explicit data, nor any information on socio-economic factors such as access to sanitation or poverty indicators, and this is discussed further in Section 6.5.

6.4.4 Generalisability

A final limitation is how generalisable these findings are. Leptospirosis transmission appears to show strong heterogeneity around the world, with different risk factors identified. Whilst the methods themselves are generalisable, the variation in transmission of leptospirosis in different settings limits the generalisability of these results. As such, these results may be context-specific. In particular, the seroprevalence study was conducted in an endemic context, and re-infections are likely to have occurred. Therefore, the estimated duration of antibody persistence may be longer than in a setting with no re-infections. To the best of my knowledge, this is the first study that aimed to estimate the duration of antibody persistence from seroprevalence studies in this way, and it would be useful for future studies to explore this in other settings. However, seroprevalence studies are expensive and time-consuming to implement, and if expected prevalence is low, large sample sizes are required. In addition, this requires sampling of children, and often seroprevalence studies choose to include only adults. Because of their limited natural exposure times, children are invaluable to understanding the FOI of different diseases, and should be considered for inclusion within future seroprevalence studies.

In addition, the results from Chapter 2 exploring the role of the climate in Fiji may not be generalisable to other settings. Other settings have been found to have one predominant serovar and one primary animal host driving transmission [40]. Conversely, in Fiji there are many different animal hosts, multiple circulating serovars, and various transmission pathways influencing infection. Therefore, climate may contribute to transmission differently in other settings. For example, the climatic factors influencing transmission in urban slum environments may be

different than in rural agricultural settings. However, other Pacific Island Countries also have a large number of circulating serovars and animal hosts [20, 41], and this study may help inform studies in these settings. Care must be taken however to account for different laboratory diagnostic capabilities between settings. Furthermore, in Chapter 4, I combined data from multiple different settings. This is at once a strength and a limitation. Pooling data from across settings may allow for the results to be more generalisable. However, this study used data from a number of different settings across a range of times. Seasonal HCoV transmission is strongly influenced by social contact patterns. These can differ across settings, but also have changed over time due to changes in household structure. For example, the data used spans 43 years from 1970 to 2013, during which time, community structures have changed and multi-generational households are less common in some settings [42].

6.5 Implications, remaining challenges and future work

The results from Chapter 2 demonstrate the important role that climate plays on leptospirosis incidence in Fiji. Outbreaks in Fiji have been increasing in size and frequency in recent years, and it is not clear what is driving this, but it is likely that climate has an important role. However, there remain questions regarding the role of climate on leptospirosis in Fiji. In order to begin to address some of these questions, additional years of surveillance data are required, particularly when considering events such as ENSO which only occur on average every four years. In addition, more spatially-explicit surveillance data is required, which currently is not routinely collected in Fiji. Transmission appears to differ by setting in Fiji, and it is likely that the way that climate influences transmission also differs according to the local socio-ecological context. Spatially-explicit data would enable the development of models which could be used to explore socio-economic factors driving transmission, such as poverty, access to sanitation and housing infrastructure, and these are likely to be inter-connected with climate. Local environmental drivers of transmission could also be explored, such as proximity to rivers and floodplains. Furthermore, in Fiji there are numerous animal hosts and many different circulating serovars, and it is likely that the importance of animal hosts varies geographically, and therefore climate may impact these differently.

In addition, Chapter 2 highlights the potential for the development of a climate-based early warning system for leptospirosis. This is of key importance for Fiji given the effects of climate change are already being felt, and it is thought that this will further increase the number of outbreaks going forward. Early warning systems have been developed for other climate-sensitive diseases such as dengue and malaria [43–45], however, these require a good understanding of the climatic drivers and transmission mechanisms, as well as robust surveillance data. An early warning system would be of benefit to policy makers as it would enable the deployment of preventative interventions. When developing an early warning system care must be taken to minimise false alarms (predicting an outbreak that does not occur) and missed events (failing to predict an outbreak).

In Chapters 3 and 4 I estimated the duration of antibody persistence for both leptospirosis and seasonal HCoVs. This is important as the duration of antibody persistence may influence the timing and likelihood of outbreaks. Knowledge of whether immunity is life-long or of short duration is also important for planning and preparedness as it can provide insight as to the likelihood of re-infection as well as inform vaccine development. In addition, it can help determine if a disease will become a seasonal epidemic, or more likely, have longer periods between epidemics (e.g. if the duration of protective immunity is long-lasting, it can take a while for a build-up of susceptible individuals in the population); although this does not consider other driving factors of epidemics, such as climate. Moreover, there remain questions regarding antibody dynamics, and how antibodies correlate with protection against infection. In addition, the role of cross-protection between serovars (leptospirosis) and strains (seasonal HCoVs) is not well understood. Further work exploring antibody persistence in other settings would be of benefit, as well as more longitudinal studies following individuals up over time.

In Chapter 5 I highlighted the challenges of developing a mechanistic transmission model for zoonotic environmentally persistent pathogens, however, the development of such a model would allow for disease transmission to be considered within a holistic disease framework. The review highlighted that there was a need for more data-driven modelling. In particular it was found that little is known about the pathogen disease burden of many environmentally-persistent diseases, despite this being an important source of transmission to humans for many of these diseases. Although there has been an increase in studies recently which have started exploring the duration of *Leptospira* survival in the environment [46, 47], there are still many gaps in our knowledge and understanding.

Due to the complex pathways driving leptospirosis transmission in Fiji, with multiple interacting and interconnected components, future work, which combines knowledge and data from multiple sources and sectors, will be key. Specifically, a multi-pronged approach, which brings together enhanced surveillance case data, seroprevalence data in humans, and seroprevalence data in animal hosts would allow for an improved understanding of leptospirosis transmission dynamics. Repeated seroprevalence sampling during outbreak and non-outbreak periods, across different geographical settings in Fiji, would provide population level data of the serovars driving transmission, and how these change over time. Furthermore, seroprevalence studies of animals may help untangle the importance of different animal hosts across geographical settings, and identify which animal hosts may be driving large outbreaks. Moreover, multi-sectoral control strategies have been proposed for the control of leptospirosis, but there is limited evidence regarding the effectiveness of such interventions. There is a need for data and models which can assess not only the effectiveness of these control strategies, but also the environmental and human impact. This would require the development of cross-sectoral models to synergise decision making between sectors (e.g. health and environment) [48]. Enhanced data collection and cross-sectoral work would provide a greater understanding of leptospirosis transmission, allowing for the development of models which consider the full transmission pathway within a One Health framework.

6.6 Concluding remarks

This thesis brings together diverse modelling approaches, which aimed to understand the complex drivers of disease transmission dynamics applied to two diseases, leptospirosis and seasonal HCoVs. Despite the many limitations and challenges associated with studying these diseases, this research highlights the importance of conducting epidemiological research, and particularly for leptospirosis, bringing attention and better evidence base to this understudied neglected zoonotic disease.

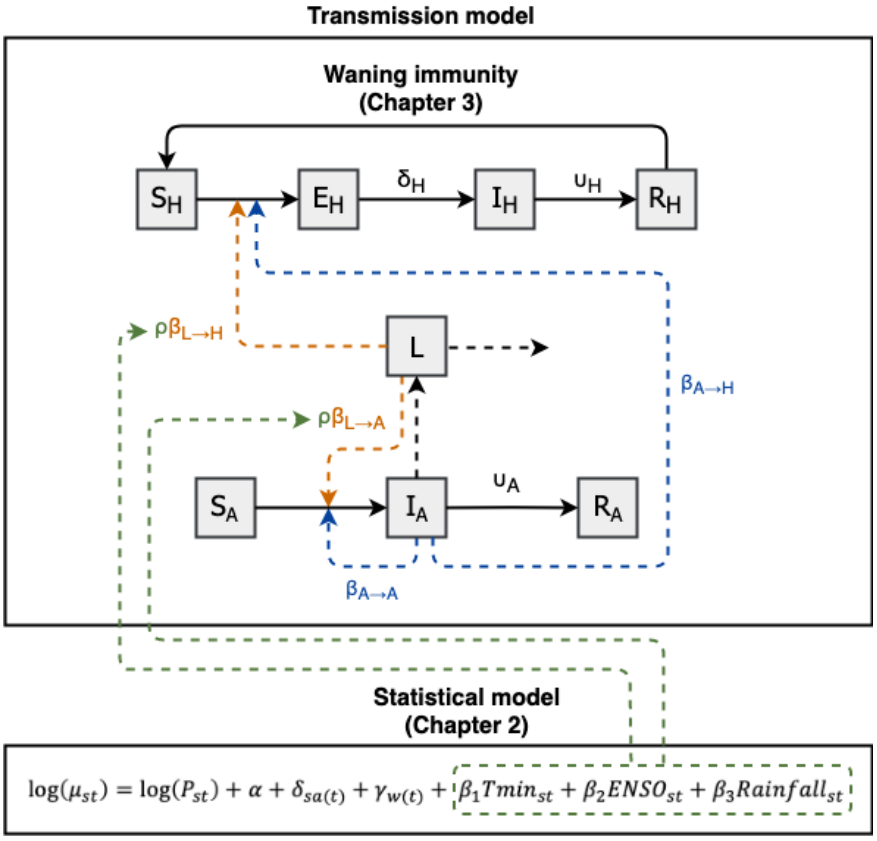

Figure 6.1: Schematic representation of a theoretical leptospirosis mechanistic transmission model. The force of infection (FOI) to humans (λ_H) includes both infection via the environment (L) or via an infected animal (I_A). In humans, transmission can occur via indirect transmission from the environment, with coefficient $\beta_{L\rightarrow H}$, where the risk of infection increases linearly with the number of free-living leptospires. Climate is considered to impact environmental transmission, and therefore can be incorporated via a seasonality coefficient (ρ), informed by the results from Chapter 2. Transmission can also occur via direct transmission from an infected animal (I_A), at an effective contact rate $\beta_{A\rightarrow H}$. Once infected, humans move from susceptible (S_H) to latently infected (E_H), to infected (I_H, at a rate of δ_H) and finally to recovered (R_H, at a rate of U_H). Once recovered they lose immunity at a waning rate and return to the susceptible compartment(S_H), where they can once more become infected. This waning rate is informed by the results from Chapter 3. Animals are infected either indirectly via the environment, $\rho\beta_{L\rightarrow A}$, or directly from another infectious animal, $\beta_{A\rightarrow A}$. No vertical transmission is included within this model framework. Once infected, animals move from susceptible (S_A), to infected (I_A) and finally to recovered (R_A, at a rate of U_A). It is assumed that there is no waning immunity due to the shorter animal lifespan. Infected animals release leptospires (L) into the environment. Once in the environment leptospires decay based on a decay rate. While in reality there are many different animal hosts, this theoretical model is based on cattle given they are thought to be one of the predominant sources of infection to humans in Fiji. The statistical model developed in Chapter 2 is shown below the transmission model. $\beta_1 Tmin_{st}+\beta_2 ENSO_{st}+\beta_3 Rainfall_{st}$ are the climatic coefficients from the statistical model, which can be incorporated within the transmission model via the ρ parameter.

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A

Supplementary Material Ethical Approval

Appendix A: Ethical Approval

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Miss Eleanor Rees
LSHTM

28 January 2019

Dear Eleanor,

Study Title: Characterising leptospirosis transmission dynamics and implications for outbreaks

LSHTM ethics ref: 16171

Thank you for your application for the above research, which has now been considered by the Observational Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	CV REES	11/12/2018	1
Protocol / Proposal	Study protocol REES V2	11/12/2018	2
Consent form	Combi lepto typhoid forms_questionnaire v014	11/12/2018	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Appendix A: Ethical Approval

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
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Research Ethics Committee

Miss Eleanor Rees
6 January 2022

Dear Miss Eleanor Rees,

Study Title: Characterising leptospirosis transmission dynamics and implications for outbreaks

LSHTM Ethics ref: 16171 - 1

Thank you for submitting your amendment for the above research project.

Your amendment has been assessed by the Research Governance & Integrity Office and has been approved as a non-substantial change. The amendment does not require further ethical approval from the observational ethics committee.

List of documents reviewed:

Document Type	File Name	Date	Version
Local Approval	Approval Letter_Eleanor Rees_24th June 2019_New		
Other	Study protocol REES V2-1		

Any subsequent changes to the application must be submitted to the Committee via an Amendment form on the ethics online applications website: http://leo.lshtm.ac.uk .

Best of luck with your project.

Yours sincerely,

Rebecca Carter

Ethics Facilitator

Ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Fiji National Health Research and Ethics Review Committee

MINISTRY OF HEALTH AND MEDICAL SERVICES

Date: 21/06/2019

Eleanor Rees
London School of Hygiene &
Tropical Medicine
London

Project Title: "Understanding drivers of leptospirosis outbreaks in Fiji."

FNHRERC Number:	2019.72.NW
Primary Investigator(s):	Eleanor Rees, London School of Hygiene & Tropical Medicine, London.
Co- Investigator(s):	Adam Kucharski, EPH, LSHTM. Rachel Lowe, EPH, LSHTM. Colleen Lau, Australian National University.
Local Collaborator(s):	Dr Daniel Faktaufon, MOHMS, Fiji.

Dear Ms Eleanor

This is to inform you that the Fiji National Health Research Ethics Review Committee (FNHRERC) has granted scientific, technical and ethical **approval** to your proposal titled *"Understanding drivers of leptospirosis outbreaks in Fiji".*

As the Principle Investigator, it is **your responsibility to ensure that all the people associated with this particular project area aware of the conditions of this approval and copy of the final report is also submitted to the Ministry of Health and Medical Services at the conclusion of your project for our records.**

The following conditions apply to your approval. Failure to abide by these conditions may result in suspension or discontinuation of approval and/or disciplinary action.

1. **Variation to the project:** Any subsequent variation s or modifications you may wish to make to your project must be notified formally to the Chair, FNHRERC for further considerations and approval. If the Chair considers that the proposed changes are significant, you may be required to submit a new application for approval of the revised project.

2. **Incidence or adverse events:** Researchers must report immediately to the Chair FNHRERC anything which may affect the ethical acceptance of the protocol including adverse effects on subjects or unforeseen events that may affect continued ethical acceptability of the project. Failure to do so may result in suspension or cancellation of approval.

3. **Monitoring:** Projects are subject to monitoring at any time by the Committee.

4. **Annual/Final Report:** You must submit a progress report at 6 months of your study and an annual/final report at the end of the year or at the conclusion of the project if it continues for less than or more than a year. Also you are to present the evidence back to the participating institutions.

Please quote the FNHRERC number and the name of the project in any future correspondence.

If you have any further queries or require any additional information, please do not hesitate to contact the Secretariat on telephone: (679) 3306177 ext. 340170 or email: anjana.deo@govnet.gov.fj.

We wish you all the best in your study.

Dr Eric Rafai
Head of Research Innovation
Ministry of Health and Medical Services

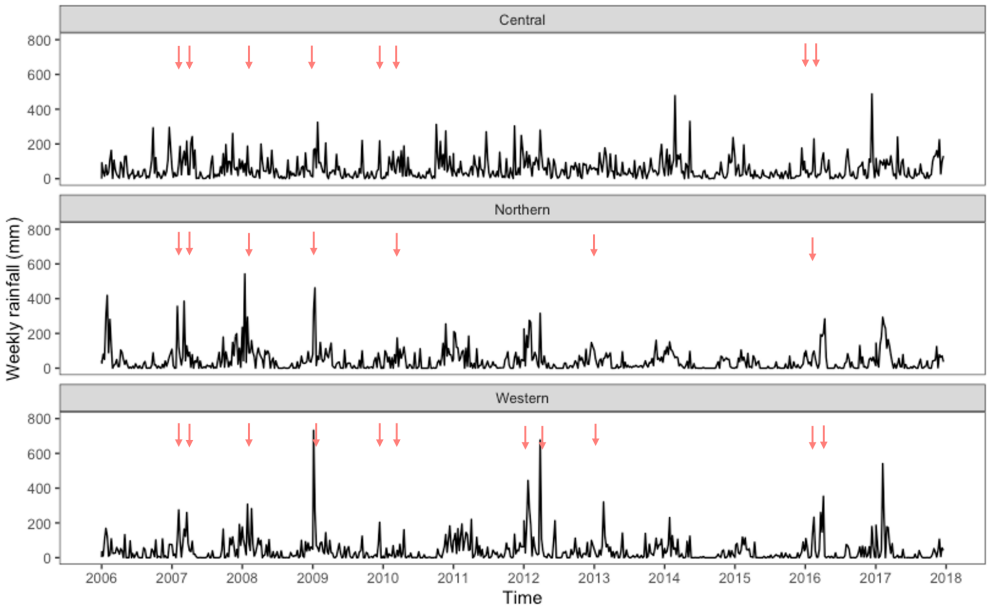
B

Supplementary Material Chapter 2

Supplementary material

Supplementary Table 1. Flooding and Tropical Cyclones recorded in Fiji (Central, Western and Northern Division) by the Emergency Events Database (EM-DAT).

Year	Date	Disaster Type	Division
2007	3/02/2007 - 20/02/2007	Riverine flood (origin heavy rain)	Central, Northern, Western
2007	9/03/2007 - 12/03/2007	Flash flood	Central, Northern, Western
2008	28/01/2008 - 29/01/2008	Cyclone "Gene" (associated disaster flooding)	Central, Northern, Western
2009	8/01/2009 - 19/01/2009	Riverine flood (origin heavy rain)	Central, Northern, Western
2009	14/12/2009 - 15/12/2009	Cyclone "Mick" (associated disaster flooding)	Central, Western
2010	14/03/2010 - 16/03/2010	Cyclone "Tomas" (associated disaster flooding)	Central, Northern, Western
2012	22/01/2012 - 06/02/2012	Riverine flood (origin heavy rain & tropical depression)	Western
2012	29/03/2012 - 30/03/2012	Riverine flood (origin heavy rain & tropical depression)	Western
2012	16/12/2012 - 18/12/2012	Cyclone "Evan"	Northern, Western
2016	20/02/2016 - 21/02/2016	Cyclone "Winston" (associated disaster flooding)	Central, Northern, Western
2016	04/04/2016 - 07/04/2016	Cyclone "Zena" (associated disaster flooding)	Central, Western



Supplementary Figure 1. Weekly rainfall from Laucala Bay (Central division), Nadi Airport (Western Division) and Labasa Airfield (Northern Division) between 2006-2017. Red arrows indicate flooding and tropical cyclones recorded in Fiji by the Emergency Events Database (EM-DAT).

Model	Variable	TimePeriod	Lag	Mean	LCI	UCI	WAIC	CVLogScore	RsqNull
0	**RE**	**-**	**-**	**-**	**-**	**-**	**5328**	**1.426**	**0.458**
1	prcp	-	0	0.073	0.003	0.144	5327	1.426	0.46
2	prcp	-	1	0.081	0.01	0.153	5326	1.425	0.459
3	prcp	-	2	0.147	0.079	0.219	5314	1.422	0.462
4	prcp	-	3	0.093	0.028	0.16	5323	1.425	0.46
5	prcp	-	4	0.09	0.026	0.156	5323	1.425	0.46
6	prcp	-	5	0.047	-0.017	0.112	5329	1.426	0.459
7	prcp	-	6	0.082	0.013	0.153	5326	1.425	0.459
8	prcp	-	7	-0.009	-0.076	0.06	5330	1.426	0.458
9	prcp	-	8	0.007	-0.062	0.078	5330	1.426	0.458
10	prcp	-	9	0.024	-0.044	0.093	5330	1.426	0.458
11	prcp	-	10	0.04	-0.029	0.11	5330	1.426	0.458
12	prcp	-	11	0.005	-0.063	0.074	5330	1.426	0.458
13	prcp	-	12	0.118	0.052	0.185	5318	1.423	0.462
14	prcp	-	13	0.067	-0.002	0.138	5327	1.426	0.459
15	prcp	-	14	0.014	-0.053	0.083	5330	1.426	0.458
16	prcp	-	15	0.02	-0.049	0.09	5330	1.427	0.458
17	prcp	-	16	0.019	-0.053	0.092	5330	1.426	0.458
18	tmin	-	0	0.006	-0.138	0.15	5330	1.427	0.458
19	**tmin**	**-**	**1**	**0.172**	**0.022**	**0.321**	**5325**	**1.425**	**0.459**
20	tmin	-	2	-0.023	-0.171	0.123	5330	1.426	0.458
21	tmin	-	3	-0.055	-0.204	0.094	5329	1.426	0.459
22	tmin	-	4	0.017	-0.137	0.17	5331	1.427	0.458
23	tmin	-	5	-0.029	-0.181	0.123	5330	1.426	0.458
24	tmin	-	6	-0.053	-0.198	0.092	5329	1.426	0.459
25	tmin	-	7	-0.046	-0.192	0.099	5330	1.426	0.459
26	tmin	-	8	0.056	-0.095	0.207	5330	1.426	0.458
27	tmin	-	9	-0.126	-0.275	0.022	5326	1.425	0.46
28	tmin	-	10	-0.185	-0.332	-0.038	5322	1.424	0.462
29	tmin	-	11	-0.045	-0.195	0.104	5330	1.426	0.459
30	tmin	-	12	-0.081	-0.228	0.065	5329	1.426	0.459
31	tmin	-	13	0.012	-0.135	0.159	5330	1.427	0.458
32	tmin	-	14	0.016	-0.134	0.164	5330	1.427	0.458
33	tmin	-	15	-0.065	-0.211	0.08	5329	1.426	0.459
34	tmin	-	16	-0.111	-0.254	0.032	5327	1.426	0.459
35	tmax	-	0	-0.094	-0.211	0.022	5326	1.425	0.46
36	tmax	-	1	0.04	-0.076	0.156	5330	1.427	0.458
37	tmax	-	2	-0.096	-0.212	0.019	5326	1.425	0.46
38	tmax	-	3	-0.018	-0.133	0.096	5330	1.426	0.459
39	tmax	-	4	-0.067	-0.183	0.049	5327	1.426	0.459
40	tmax	-	5	0.071	-0.043	0.185	5330	1.426	0.458
41	tmax	-	6	-0.002	-0.118	0.113	5330	1.426	0.458
42	tmax	-	7	-0.004	-0.119	0.11	5330	1.426	0.458
43	tmax	-	8	0.001	-0.114	0.116	5330	1.427	0.458
44	tmax	-	9	0.104	-0.014	0.222	5330	1.426	0.458

45	tmax	-	10	0.096	-0.019	0.211	5330	1.426	0.458
46	tmax	-	11	0.006	-0.109	0.12	5330	1.427	0.458
47	tmax	-	12	-0.028	-0.143	0.086	5329	1.426	0.459
48	tmax	-	13	0.116	0.005	0.227	5328	1.426	0.458
49	tmax	-	14	0.179	0.067	0.291	5324	1.425	0.458
50	tmax	-	15	0.051	-0.06	0.161	5330	1.426	0.458
51	tmax	-	16	0.068	-0.044	0.181	5330	1.426	0.458
52	sst.34	-	0	-0.252	-0.346	-0.158	5302	1.419	0.468
53	sst.34	-	1	-0.272	-0.364	-0.179	5297	1.418	0.469
54	sst.34	-	2	-0.263	-0.355	-0.171	5298	1.418	0.469
55	sst.34	-	3	-0.249	-0.34	-0.158	5301	1.419	0.468
56	**sst.34**	**-**	**4**	**-0.238**	**-0.328**	**-0.148**	**5302**	**1.419**	**0.468**
57	sst.34	-	5	-0.238	-0.326	-0.149	5301	1.419	0.468
58	sst.34	-	6	-0.232	-0.32	-0.144	5302	1.419	0.468
59	sst.34	-	7	-0.204	-0.292	-0.116	5309	1.421	0.465
60	sst.34	-	8	-0.202	-0.29	-0.114	5309	1.421	0.465
61	sst.34	-	9	-0.205	-0.292	-0.118	5308	1.421	0.465
62	sst.34	-	10	-0.222	-0.31	-0.134	5304	1.42	0.466
63	sst.34	-	11	-0.243	-0.331	-0.154	5299	1.418	0.468
64	sst.34	-	12	-0.211	-0.302	-0.121	5307	1.42	0.466
65	sst.34	-	13	-0.194	-0.285	-0.102	5311	1.421	0.465
66	sst.34	-	14	-0.207	-0.298	-0.117	5307	1.42	0.466
67	sst.34	-	15	-0.193	-0.282	-0.103	5310	1.421	0.465
68	sst.34	-	16	-0.139	-0.231	-0.047	5320	1.424	0.462
69	sst.34	-	17	-0.112	-0.206	-0.019	5323	1.425	0.461
70	sst.34	-	18	-0.13	-0.223	-0.036	5321	1.424	0.461
71	sst.34	-	19	-0.138	-0.233	-0.043	5320	1.424	0.462
72	sst.34	-	20	-0.103	-0.2	-0.007	5324	1.425	0.46
73	sst.4	-	0	-0.292	-0.402	-0.182	5300	1.419	0.469
74	sst.4	-	1	-0.321	-0.43	-0.212	5294	1.417	0.47
75	sst.4	-	2	-0.259	-0.367	-0.15	5307	1.42	0.467
76	sst.4	-	3	-0.212	-0.32	-0.105	5314	1.422	0.464
77	sst.4	-	4	-0.189	-0.296	-0.082	5317	1.423	0.463
78	sst.4	-	5	-0.209	-0.316	-0.103	5314	1.422	0.464
79	sst.4	-	6	-0.23	-0.337	-0.122	5310	1.421	0.465
80	sst.4	-	7	-0.188	-0.296	-0.08	5317	1.423	0.463
81	sst.4	-	8	-0.175	-0.284	-0.065	5319	1.423	0.462
82	sst.4	-	9	-0.164	-0.275	-0.054	5321	1.424	0.462
83	sst.4	-	10	-0.176	-0.289	-0.063	5319	1.424	0.462
84	sst.4	-	11	-0.218	-0.331	-0.104	5314	1.422	0.464
85	sst.4	-	12	-0.2	-0.315	-0.084	5317	1.423	0.463
86	sst.4	-	13	-0.091	-0.211	0.029	5327	1.426	0.46
87	sst.4	-	14	-0.097	-0.217	0.023	5327	1.426	0.46
88	sst.4	-	15	-0.12	-0.239	-0.001	5325	1.425	0.46
89	sst.4	-	16	-0.083	-0.204	0.038	5328	1.426	0.459
90	sst.4	-	17	-0.048	-0.171	0.075	5329	1.426	0.459

91	sst.4	-	18	-0.063	-0.187	0.061	5329	1.426	0.459
92	sst.4	-	19	-0.047	-0.173	0.079	5330	1.426	0.458
93	sst.4	-	20	-0.016	-0.144	0.112	5330	1.427	0.458
94	totalPrcp	2	0	0.114	0.037	0.192	5322	1.424	0.46
95	totalPrcp	2	1	0.164	0.09	0.24	5313	1.422	0.462
96	totalPrcp	2	2	0.168	0.098	0.241	5311	1.421	0.463
97	totalPrcp	2	3	0.131	0.062	0.202	5318	1.423	0.461
98	totalPrcp	2	4	0.098	0.03	0.167	5324	1.425	0.46
99	totalPrcp	2	5	0.087	0.017	0.158	5326	1.425	0.459
100	totalPrcp	2	6	0.05	-0.022	0.122	5329	1.426	0.458
101	totalPrcp	2	7	-0.001	-0.074	0.073	5330	1.426	0.458
102	totalPrcp	2	8	0.022	-0.05	0.095	5330	1.426	0.458
103	totalPrcp	4	0	0.227	0.144	0.311	5303	1.419	0.465
104	totalPrcp	4	1	0.236	0.155	0.318	5301	1.419	0.465
105	totalPrcp	4	2	0.218	0.138	0.299	5306	1.42	0.464
106	totalPrcp	4	3	0.176	0.097	0.256	5315	1.422	0.462
107	totalPrcp	4	4	0.12	0.041	0.201	5324	1.425	0.46
108	totalPrcp	4	5	0.072	-0.009	0.153	5329	1.426	0.458
109	totalPrcp	4	6	0.057	-0.025	0.14	5329	1.426	0.458
110	totalPrcp	4	7	0.036	-0.048	0.12	5330	1.426	0.458
111	totalPrcp	4	8	0.043	-0.04	0.127	5330	1.426	0.458
112	totalPrcp	6	0	0.286	0.195	0.378	5296	1.417	0.467
113	**totalPrcp**	**6**	**1**	**0.283**	**0.193**	**0.373**	**5298**	**1.418**	**0.466**
114	totalPrcp	6	2	0.239	0.15	0.329	5309	1.421	0.463
115	totalPrcp	6	3	0.165	0.076	0.255	5322	1.424	0.46
116	totalPrcp	6	4	0.128	0.038	0.218	5325	1.425	0.459
117	totalPrcp	6	5	0.097	0.007	0.188	5328	1.426	0.458
118	totalPrcp	6	6	0.077	-0.016	0.17	5329	1.426	0.458
119	totalPrcp	6	7	0.102	0.01	0.195	5327	1.426	0.458
120	totalPrcp	6	8	0.138	0.047	0.23	5323	1.425	0.46
121	totalPrcp	8	0	0.318	0.218	0.418	5298	1.418	0.466
122	totalPrcp	8	1	0.286	0.186	0.387	5307	1.42	0.463
123	totalPrcp	8	2	0.258	0.158	0.358	5312	1.422	0.462
124	totalPrcp	8	3	0.195	0.096	0.295	5321	1.424	0.46
125	totalPrcp	8	4	0.153	0.052	0.254	5325	1.425	0.459
126	totalPrcp	8	5	0.169	0.068	0.272	5323	1.424	0.459
127	totalPrcp	8	6	0.177	0.075	0.28	5321	1.424	0.46
128	totalPrcp	8	7	0.14	0.039	0.241	5325	1.425	0.459
129	totalPrcp	8	8	0.149	0.05	0.249	5324	1.425	0.459
130	totalPrcp	12	0	0.355	0.24	0.471	5303	1.419	0.463
131	totalPrcp	12	1	0.379	0.264	0.493	5298	1.418	0.464
132	totalPrcp	12	2	0.374	0.259	0.489	5298	1.418	0.465
133	totalPrcp	12	3	0.306	0.192	0.421	5311	1.421	0.462
134	totalPrcp	12	4	0.266	0.151	0.381	5316	1.423	0.461
135	totalPrcp	12	5	0.223	0.107	0.339	5321	1.424	0.46
136	totalPrcp	12	6	0.177	0.062	0.293	5324	1.425	0.459

137	totalPrcp	12	7	0.119	0.005	0.233	5328	1.426	0.458
138	totalPrcp	12	8	0.111	-0.002	0.225	5328	1.426	0.458
139	totalPrcp	16	0	0.508	0.366	0.625	5296	1.417	0.463
140	totalPrcp	16	1	0.455	0.325	0.58	5296	1.417	0.464
141	totalPrcp	16	2	0.393	0.266	0.519	5304	1.419	0.463
142	totalPrcp	16	3	0.296	0.169	0.422	5316	1.423	0.461
143	totalPrcp	16	4	0.233	0.106	0.361	5322	1.424	0.459
144	totalPrcp	16	5	0.148	0.019	0.276	5328	1.426	0.458
145	totalPrcp	16	6	0.113	-0.014	0.241	5329	1.426	0.458
146	totalPrcp	16	7	0.064	-0.062	0.191	5330	1.426	0.458
147	totalPrcp	16	8	0.069	-0.058	0.195	5330	1.426	0.458
148	RR10	2	0	0.123	0.039	0.208	5322	1.424	0.46
149	RR10	2	1	0.189	0.107	0.273	5312	1.422	0.462
150	RR10	2	2	0.186	0.105	0.269	5313	1.422	0.462
151	RR10	2	3	0.131	0.051	0.213	5322	1.424	0.46
152	RR10	2	4	0.085	0.006	0.164	5327	1.426	0.459
153	RR10	2	5	0.06	-0.018	0.137	5330	1.426	0.458
154	RR10	2	6	0.024	-0.056	0.104	5330	1.427	0.458
155	RR10	2	7	-0.005	-0.086	0.076	5330	1.426	0.458
156	RR10	2	8	0.02	-0.061	0.1	5330	1.426	0.458
157	RR10	4	0	0.245	0.149	0.342	5307	1.42	0.463
158	RR10	4	1	0.251	0.157	0.345	5307	1.42	0.463
159	RR10	4	2	0.211	0.119	0.305	5314	1.422	0.461
160	RR10	4	3	0.147	0.057	0.239	5324	1.425	0.459
161	RR10	4	4	0.086	-0.005	0.177	5329	1.426	0.458
162	RR10	4	5	0.044	-0.046	0.135	5331	1.427	0.458
163	RR10	4	6	0.034	-0.058	0.126	5331	1.427	0.458
164	RR10	4	7	0.03	-0.063	0.124	5330	1.427	0.458
165	RR10	4	8	0.058	-0.036	0.152	5330	1.426	0.458
166	RR10	6	0	0.273	0.169	0.377	5308	1.42	0.463
167	RR10	6	1	0.256	0.155	0.358	5312	1.421	0.461
168	RR10	6	2	0.201	0.099	0.303	5321	1.424	0.46
169	RR10	6	3	0.125	0.025	0.225	5328	1.426	0.458
170	RR10	6	4	0.087	-0.013	0.187	5330	1.426	0.458
171	RR10	6	5	0.068	-0.032	0.169	5330	1.427	0.458
172	RR10	6	6	0.067	-0.036	0.17	5330	1.426	0.458
173	RR10	6	7	0.078	-0.026	0.182	5329	1.426	0.458
174	RR10	6	8	0.141	0.038	0.245	5325	1.425	0.459
175	RR10	8	0	0.271	0.158	0.384	5314	1.422	0.461
176	RR10	8	1	0.236	0.126	0.347	5319	1.423	0.46
177	RR10	8	2	0.199	0.089	0.309	5323	1.425	0.459
178	RR10	8	3	0.148	0.038	0.259	5328	1.426	0.458
179	RR10	8	4	0.12	0.009	0.232	5329	1.426	0.458
180	RR10	8	5	0.114	0.002	0.226	5329	1.426	0.458
181	RR10	8	6	0.151	0.038	0.265	5327	1.425	0.459
182	RR10	8	7	0.13	0.017	0.242	5327	1.426	0.458

183	RR10	8	8	0.142	0.03	0.253	5327	1.426	0.458
184	RR10	12	0	0.298	0.17	0.425	5317	1.423	0.459
185	RR10	12	1	0.296	0.17	0.422	5317	1.423	0.46
186	RR10	12	2	0.307	0.18	0.433	5317	1.423	0.46
187	RR10	12	3	0.24	0.114	0.365	5323	1.424	0.459
188	RR10	12	4	0.203	0.077	0.329	5326	1.425	0.458
189	RR10	12	5	0.188	0.061	0.314	5326	1.425	0.458
190	RR10	12	6	0.172	0.046	0.298	5326	1.425	0.459
191	RR10	12	7	0.139	0.014	0.264	5327	1.426	0.459
192	RR10	12	8	0.153	0.028	0.278	5326	1.425	0.459
193	RR10	16	0	0.399	0.252	0.545	5313	1.422	0.459
194	RR10	16	1	0.384	0.241	0.525	5313	1.422	0.46
195	RR10	16	2	0.34	0.201	0.477	5317	1.423	0.46
196	RR10	16	3	0.258	0.121	0.395	5323	1.424	0.459
197	RR10	16	4	0.223	0.085	0.361	5325	1.425	0.459
198	RR10	16	5	0.167	0.029	0.304	5328	1.426	0.458
199	RR10	16	6	0.148	0.01	0.285	5328	1.426	0.458
200	RR10	16	7	0.115	-0.023	0.253	5329	1.426	0.458
201	RR10	16	8	0.093	-0.045	0.231	5329	1.426	0.458
202	RR20	2	0	0.077	0	0.156	5327	1.426	0.459
203	RR20	2	1	0.146	0.071	0.222	5318	1.423	0.461
204	RR20	2	2	0.148	0.074	0.223	5317	1.423	0.462
205	RR20	2	3	0.131	0.057	0.205	5320	1.424	0.461
206	RR20	2	4	0.127	0.057	0.199	5320	1.424	0.461
207	RR20	2	5	0.121	0.051	0.193	5321	1.424	0.461
208	RR20	2	6	0.08	0.008	0.153	5327	1.426	0.459
209	RR20	2	7	0.028	-0.046	0.103	5330	1.426	0.458
210	RR20	2	8	0.044	-0.029	0.118	5329	1.426	0.458
211	RR20	4	0	0.174	0.089	0.26	5316	1.423	0.461
212	RR20	4	1	0.21	0.127	0.294	5309	1.421	0.463
213	RR20	4	2	0.208	0.127	0.29	5308	1.421	0.464
214	RR20	4	3	0.187	0.107	0.268	5312	1.422	0.463
215	RR20	4	4	0.16	0.08	0.242	5318	1.423	0.461
216	RR20	4	5	0.116	0.036	0.198	5325	1.425	0.459
217	RR20	4	6	0.095	0.013	0.178	5327	1.426	0.459
218	RR20	4	7	0.057	-0.026	0.14	5330	1.426	0.458
219	RR20	4	8	0.059	-0.025	0.143	5329	1.426	0.458
220	RR20	6	0	0.235	0.145	0.325	5307	1.42	0.463
221	**RR20**	**6**	**1**	**0.254**	**0.167**	**0.343**	**5302**	**1.419**	**0.465**
222	RR20	6	2	0.232	0.144	0.32	5308	1.421	0.464
223	RR20	6	3	0.183	0.096	0.271	5317	1.423	0.461
224	RR20	6	4	0.169	0.081	0.258	5320	1.424	0.46
225	RR20	6	5	0.134	0.045	0.223	5325	1.425	0.459
226	RR20	6	6	0.107	0.016	0.199	5327	1.426	0.458
227	RR20	6	7	0.097	0.005	0.189	5327	1.426	0.458
228	RR20	6	8	0.13	0.039	0.221	5324	1.425	0.459

229	RR20	8	0	0.27	0.174	0.368	5305	1.42	0.464
230	RR20	8	1	0.263	0.167	0.36	5308	1.42	0.463
231	RR20	8	2	0.248	0.153	0.345	5310	1.421	0.463
232	RR20	8	3	0.207	0.111	0.303	5318	1.423	0.46
233	RR20	8	4	0.19	0.092	0.289	5321	1.424	0.46
234	RR20	8	5	0.179	0.079	0.279	5322	1.424	0.46
235	RR20	8	6	0.179	0.08	0.28	5321	1.424	0.46
236	RR20	8	7	0.129	0.031	0.228	5326	1.425	0.459
237	RR20	8	8	0.124	0.027	0.221	5326	1.425	0.459
238	RR20	12	0	0.315	0.204	0.427	5308	1.42	0.462
239	RR20	12	1	0.335	0.223	0.447	5304	1.419	0.463
240	RR20	12	2	0.341	0.23	0.453	5303	1.419	0.464
241	RR20	12	3	0.284	0.174	0.394	5312	1.422	0.461
242	RR20	12	4	0.255	0.145	0.365	5316	1.423	0.461
243	RR20	12	5	0.224	0.113	0.334	5319	1.423	0.46
244	RR20	12	6	0.181	0.072	0.291	5323	1.425	0.459
245	RR20	12	7	0.11	0.003	0.218	5328	1.426	0.459
246	RR20	12	8	0.104	-0.004	0.212	5328	1.426	0.459
247	RR20	16	0	0.406	0.278	0.533	5302	1.419	0.463
248	RR20	16	1	0.399	0.275	0.523	5301	1.419	0.463
249	RR20	16	2	0.36	0.239	0.48	5305	1.42	0.463
250	RR20	16	3	0.273	0.153	0.392	5316	1.423	0.461
251	RR20	16	4	0.241	0.121	0.361	5319	1.424	0.46
252	RR20	16	5	0.178	0.058	0.298	5325	1.425	0.459
253	RR20	16	6	0.147	0.028	0.267	5326	1.425	0.459
254	RR20	16	7	0.096	-0.023	0.216	5329	1.426	0.458
255	RR20	16	8	0.082	-0.038	0.202	5329	1.426	0.458
256	wetDays	2	0	0.151	0.055	0.248	5320	1.424	0.461
257	wetDays	2	1	0.239	0.142	0.335	5308	1.42	0.464
258	wetDays	2	2	0.219	0.124	0.314	5311	1.421	0.462
259	wetDays	2	3	0.155	0.06	0.249	5321	1.424	0.461
260	wetDays	2	4	0.061	-0.034	0.155	5329	1.426	0.458
261	wetDays	2	5	0.021	-0.073	0.114	5331	1.427	0.458
262	wetDays	2	6	0.091	-0.003	0.186	5328	1.426	0.459
263	wetDays	2	7	0.053	-0.042	0.149	5330	1.426	0.458
264	wetDays	2	8	0.033	-0.062	0.129	5330	1.426	0.458
265	wetDays	4	0	0.301	0.186	0.416	5304	1.419	0.465
266	wetDays	4	1	0.314	0.2	0.428	5302	1.419	0.465
267	wetDays	4	2	0.223	0.11	0.336	5317	1.423	0.461
268	wetDays	4	3	0.139	0.027	0.251	5326	1.425	0.459
269	wetDays	4	4	0.12	0.008	0.231	5328	1.426	0.459
270	wetDays	4	5	0.057	-0.054	0.168	5331	1.427	0.458
271	wetDays	4	6	0.1	-0.013	0.214	5329	1.426	0.458
272	wetDays	4	7	0.141	0.026	0.256	5326	1.425	0.458
273	wetDays	4	8	0.147	0.031	0.263	5326	1.425	0.458
274	wetDays	6	0	0.308	0.18	0.436	5309	1.421	0.464

275	wetDays	6	1	0.29	0.164	0.417	5313	1.422	0.462
276	wetDays	6	2	0.257	0.132	0.382	5317	1.423	0.461
277	wetDays	6	3	0.154	0.031	0.278	5326	1.425	0.459
278	wetDays	6	4	0.125	0.001	0.248	5328	1.426	0.459
279	wetDays	6	5	0.132	0.007	0.257	5329	1.426	0.458
280	wetDays	6	6	0.192	0.064	0.319	5325	1.425	0.459
281	wetDays	6	7	0.185	0.057	0.313	5325	1.425	0.459
282	wetDays	6	8	0.207	0.078	0.336	5323	1.424	0.459
283	wetDays	8	0	0.342	0.204	0.48	5309	1.421	0.464
284	wetDays	8	1	0.295	0.159	0.43	5316	1.422	0.461
285	wetDays	8	2	0.253	0.118	0.388	5320	1.424	0.46
286	wetDays	8	3	0.218	0.083	0.354	5324	1.425	0.459
287	wetDays	8	4	0.21	0.073	0.346	5325	1.425	0.459
288	wetDays	8	5	0.181	0.043	0.319	5327	1.425	0.458
289	wetDays	8	6	0.252	0.112	0.392	5321	1.424	0.46
290	wetDays	8	7	0.215	0.075	0.355	5324	1.425	0.459
291	wetDays	8	8	0.211	0.069	0.353	5325	1.425	0.458
292	wetDays	12	0	0.417	0.262	0.571	5308	1.42	0.462
293	wetDays	12	1	0.4	0.244	0.554	5311	1.421	0.462
294	wetDays	12	2	0.397	0.24	0.552	5312	1.421	0.461
295	wetDays	12	3	0.302	0.145	0.459	5322	1.424	0.459
296	wetDays	12	4	0.284	0.125	0.441	5324	1.425	0.458
297	wetDays	12	5	0.233	0.073	0.393	5326	1.425	0.458
298	wetDays	12	6	0.264	0.103	0.425	5323	1.425	0.459
299	wetDays	12	7	0.249	0.087	0.411	5323	1.425	0.459
300	wetDays	12	8	0.255	0.092	0.418	5323	1.425	0.459
301	wetDays	16	0	0.501	0.324	0.671	5307	1.42	0.462
302	wetDays	16	1	0.466	0.287	0.64	5311	1.421	0.461
303	wetDays	16	2	0.424	0.246	0.598	5314	1.422	0.46
304	wetDays	16	3	0.346	0.17	0.52	5321	1.424	0.459
305	wetDays	16	4	0.335	0.158	0.511	5321	1.424	0.459
306	wetDays	16	5	0.277	0.1	0.453	5324	1.425	0.459
307	wetDays	16	6	0.283	0.105	0.461	5322	1.424	0.459
308	wetDays	16	7	0.242	0.063	0.421	5325	1.425	0.459
309	wetDays	16	8	0.182	0.002	0.362	5327	1.426	0.458
310	consecWetDays	2	0	0.072	-0.009	0.155	5328	1.426	0.459
311	consecWetDays	2	1	0.08	0.004	0.16	5327	1.426	0.459
312	consecWetDays	2	2	0.07	-0.003	0.147	5327	1.426	0.459
313	consecWetDays	2	3	0.064	-0.008	0.138	5328	1.426	0.458
314	consecWetDays	2	4	0.053	-0.017	0.126	5329	1.426	0.459
315	consecWetDays	2	5	0.057	-0.015	0.131	5329	1.426	0.459
316	consecWetDays	2	6	0.055	-0.02	0.133	5329	1.426	0.459
317	consecWetDays	2	7	0.021	-0.054	0.098	5330	1.426	0.458
318	consecWetDays	2	8	0.057	-0.021	0.138	5329	1.426	0.458
319	consecWetDays	4	0	0.082	0.003	0.164	5327	1.426	0.459
320	consecWetDays	4	1	0.077	0	0.156	5328	1.426	0.458

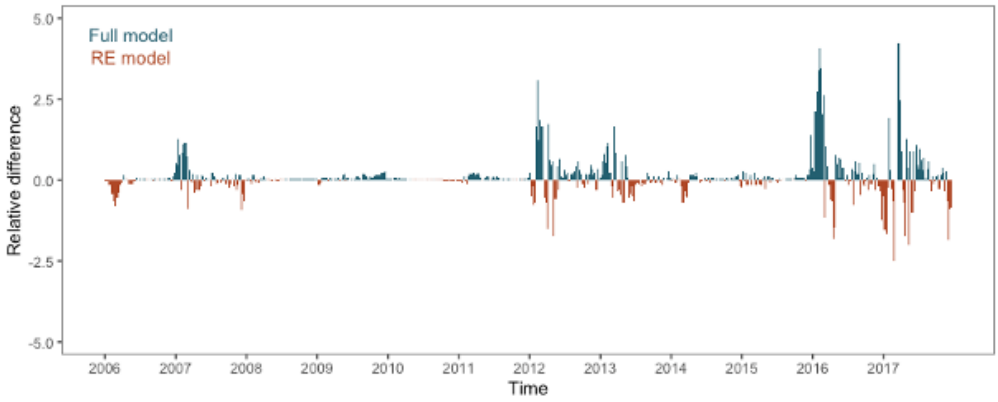
321	consecWetDays	4	2	0.071	-0.003	0.148	5328	1.426	0.459
322	consecWetDays	4	3	0.078	0.003	0.155	5327	1.426	0.459
323	consecWetDays	4	4	0.06	-0.014	0.137	5329	1.426	0.459
324	consecWetDays	4	5	0.042	-0.033	0.119	5330	1.426	0.458
325	consecWetDays	4	6	0.054	-0.024	0.134	5329	1.426	0.458
326	consecWetDays	4	7	0.056	-0.023	0.138	5329	1.426	0.458
327	consecWetDays	4	8	0.106	0.025	0.19	5325	1.425	0.459
328	consecWetDays	6	0	0.073	-0.005	0.154	5328	1.426	0.458
329	consecWetDays	6	1	0.085	0.007	0.166	5327	1.426	0.459
330	consecWetDays	6	2	0.07	-0.008	0.149	5328	1.426	0.459
331	consecWetDays	6	3	0.053	-0.023	0.131	5329	1.426	0.458
332	consecWetDays	6	4	0.053	-0.024	0.133	5329	1.426	0.458
333	consecWetDays	6	5	0.067	-0.013	0.149	5329	1.426	0.458
334	consecWetDays	6	6	0.099	0.017	0.184	5326	1.425	0.459
335	consecWetDays	6	7	0.081	-0.001	0.166	5328	1.426	0.458
336	consecWetDays	6	8	0.093	0.01	0.179	5327	1.426	0.459
337	consecWetDays	8	0	0.069	-0.011	0.152	5329	1.426	0.458
338	consecWetDays	8	1	0.056	-0.024	0.137	5329	1.426	0.458
339	consecWetDays	8	2	0.05	-0.028	0.131	5330	1.426	0.458
340	consecWetDays	8	3	0.072	-0.008	0.154	5328	1.426	0.459
341	consecWetDays	8	4	0.103	0.02	0.187	5325	1.425	0.459
342	consecWetDays	8	5	0.094	0.01	0.179	5327	1.426	0.458
343	consecWetDays	8	6	0.095	0.011	0.182	5327	1.426	0.459
344	consecWetDays	8	7	0.08	-0.003	0.165	5328	1.426	0.458
345	consecWetDays	8	8	0.093	0.01	0.179	5327	1.426	0.459
346	consecWetDays	12	0	0.068	-0.017	0.154	5329	1.426	0.458
347	consecWetDays	12	1	0.074	-0.011	0.16	5329	1.426	0.458
348	consecWetDays	12	2	0.076	-0.008	0.161	5329	1.426	0.458
349	consecWetDays	12	3	0.083	0	0.167	5328	1.426	0.458
350	consecWetDays	12	4	0.098	0.013	0.184	5327	1.426	0.459
351	consecWetDays	12	5	0.095	0.011	0.182	5327	1.426	0.459
352	consecWetDays	12	6	0.087	0.001	0.174	5327	1.426	0.458
353	consecWetDays	12	7	0.092	0.006	0.182	5327	1.426	0.459
354	consecWetDays	12	8	0.11	0.022	0.201	5325	1.425	0.459
355	consecWetDays	16	0	0.049	-0.048	0.146	5330	1.426	0.458
356	consecWetDays	16	1	0.046	-0.05	0.141	5330	1.426	0.458
357	consecWetDays	16	2	0.032	-0.063	0.127	5330	1.427	0.458
358	consecWetDays	16	3	0.063	-0.033	0.158	5330	1.426	0.458
359	consecWetDays	16	4	0.061	-0.034	0.156	5330	1.426	0.458
360	consecWetDays	16	5	0.051	-0.044	0.146	5330	1.426	0.458
361	consecWetDays	16	6	0.033	-0.062	0.128	5330	1.426	0.458
362	consecWetDays	16	7	0.032	-0.061	0.126	5330	1.426	0.458
363	consecWetDays	16	8	0.053	-0.04	0.148	5329	1.426	0.458
364	spi.1	-	0	0.17	0.096	0.244	5309	1.421	0.465
365	spi.1	-	1	0.065	-0.008	0.138	5328	1.426	0.459
366	spi.1	-	2	0.014	-0.06	0.087	5330	1.426	0.458

367	spi.1	-	3	0.097	0.024	0.171	5323	1.425	0.46
368	spi.1	-	4	0.05	-0.025	0.124	5329	1.426	0.459
369	spi.1	-	5	-0.017	-0.092	0.058	5330	1.426	0.458
370	spi.1	-	6	-0.062	-0.135	0.011	5328	1.426	0.459
371	spi.1	-	7	0.006	-0.066	0.079	5331	1.427	0.458
372	spi.1	-	8	-0.052	-0.124	0.02	5329	1.426	0.458
373	spi.1	-	9	-0.074	-0.148	0	5327	1.426	0.459
374	spi.1	-	10	0	-0.076	0.076	5330	1.427	0.458
375	spi.1	-	11	0.039	-0.039	0.117	5329	1.426	0.458
376	spi.1	-	12	0.059	-0.019	0.137	5328	1.426	0.459
377	spi.1	-	13	0.035	-0.042	0.112	5329	1.426	0.459
378	spi.1	-	14	0.028	-0.051	0.106	5330	1.426	0.458
379	spi.1	-	15	0.066	-0.011	0.143	5327	1.426	0.459
380	spi.1	-	16	0.018	-0.058	0.094	5330	1.426	0.458
381	spi.3	-	0	0.191	0.104	0.278	5313	1.422	0.464
382	spi.3	-	1	0.141	0.055	0.228	5321	1.424	0.461
383	spi.3	-	2	0.115	0.03	0.199	5323	1.425	0.46
384	spi.3	-	3	0.115	0.029	0.2	5324	1.425	0.46
385	spi.3	-	4	-0.001	-0.087	0.086	5330	1.426	0.458
386	spi.3	-	5	-0.05	-0.136	0.037	5329	1.426	0.458
387	spi.3	-	6	-0.055	-0.139	0.029	5329	1.426	0.458
388	spi.3	-	7	-0.032	-0.118	0.054	5330	1.426	0.458
389	spi.3	-	8	-0.053	-0.137	0.031	5329	1.426	0.458
390	spi.3	-	9	-0.02	-0.108	0.068	5330	1.426	0.458
391	spi.3	-	10	0.011	-0.076	0.097	5330	1.426	0.458
392	spi.3	-	11	0.038	-0.05	0.126	5330	1.426	0.459
393	spi.3	-	12	0.052	-0.038	0.142	5328	1.426	0.459
394	spi.3	-	13	0.031	-0.056	0.119	5329	1.426	0.458
395	spi.3	-	14	0.034	-0.052	0.121	5329	1.426	0.458
396	spi.3	-	15	0.04	-0.046	0.127	5329	1.426	0.458
397	spi.3	-	16	-0.051	-0.135	0.034	5329	1.426	0.459
398	spi.6	-	0	0.281	0.173	0.389	5306	1.42	0.466
399	spi.6	-	1	0.156	0.049	0.262	5323	1.425	0.461
400	spi.6	-	2	0.144	0.036	0.252	5324	1.425	0.46
401	spi.6	-	3	0.148	0.038	0.258	5323	1.425	0.461
402	spi.6	-	4	-0.025	-0.135	0.085	5330	1.426	0.458
403	spi.6	-	5	-0.048	-0.162	0.065	5330	1.426	0.458
404	spi.6	-	6	0.003	-0.11	0.115	5330	1.426	0.458
405	spi.6	-	7	0.007	-0.1	0.113	5330	1.426	0.458
406	spi.6	-	8	-0.049	-0.151	0.054	5330	1.426	0.458
407	spi.6	-	9	-0.052	-0.158	0.053	5330	1.426	0.458
408	spi.6	-	10	0	-0.106	0.106	5330	1.427	0.458
409	spi.6	-	11	0.003	-0.103	0.109	5330	1.427	0.458
410	spi.6	-	12	-0.009	-0.117	0.099	5330	1.427	0.458
411	spi.6	-	13	-0.038	-0.146	0.07	5330	1.427	0.458
412	spi.6	-	14	0.004	-0.1	0.108	5330	1.426	0.458

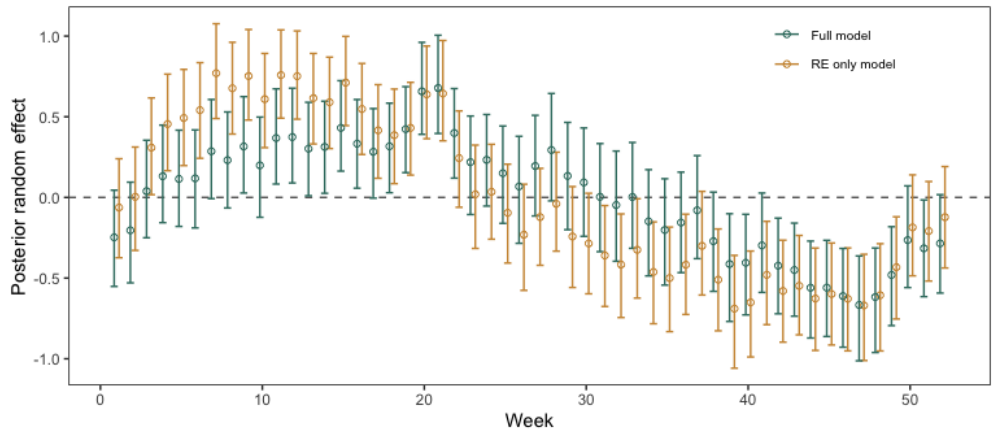
413	spi.6	-	15	0.028	-0.073	0.13	5330	1.426	0.458
414	spi.6	-	16	-0.106	-0.206	-0.005	5327	1.426	0.459
415	spei.1	-	0	0.17	0.096	0.244	5309	1.421	0.465
416	spei.1	-	1	0.065	-0.008	0.138	5328	1.426	0.459
417	spei.1	-	2	0.014	-0.06	0.087	5330	1.426	0.458
418	spei.1	-	3	0.097	0.024	0.171	5323	1.425	0.46
419	spei.1	-	4	0.05	-0.025	0.124	5329	1.426	0.459
420	spei.1	-	5	-0.017	-0.092	0.058	5330	1.426	0.458
421	spei.1	-	6	-0.062	-0.135	0.011	5328	1.426	0.459
422	spei.1	-	7	0.006	-0.066	0.079	5331	1.427	0.458
423	spei.1	-	8	-0.052	-0.124	0.02	5329	1.426	0.458
424	spei.1	-	9	-0.074	-0.148	0	5327	1.426	0.459
425	spei.1	-	10	0	-0.076	0.076	5330	1.427	0.458
426	spei.1	-	11	0.039	-0.039	0.117	5329	1.426	0.458
427	spei.1	-	12	0.059	-0.019	0.137	5328	1.426	0.459
428	spei.1	-	13	0.035	-0.042	0.112	5329	1.426	0.459
429	spei.1	-	14	0.028	-0.051	0.106	5330	1.426	0.458
430	spei.1	-	15	0.066	-0.011	0.143	5327	1.426	0.459
431	spei.1	-	16	0.018	-0.058	0.094	5330	1.426	0.458
432	spei.3	-	0	0.191	0.104	0.278	5313	1.422	0.464
433	spei.3	-	1	0.141	0.055	0.228	5321	1.424	0.461
434	spei.3	-	2	0.115	0.03	0.199	5323	1.425	0.46
435	spei.3	-	3	0.115	0.029	0.2	5324	1.425	0.46
436	spei.3	-	4	-0.001	-0.087	0.086	5330	1.426	0.458
437	spei.3	-	5	-0.05	-0.136	0.037	5329	1.426	0.458
438	spei.3	-	6	-0.055	-0.139	0.029	5329	1.426	0.458
439	spei.3	-	7	-0.032	-0.118	0.054	5330	1.426	0.458
440	spei.3	-	8	-0.053	-0.137	0.031	5329	1.426	0.458
441	spei.3	-	9	-0.02	-0.108	0.068	5330	1.426	0.458
442	spei.3	-	10	0.011	-0.076	0.097	5330	1.426	0.458
443	spei.3	-	11	0.038	-0.05	0.126	5330	1.426	0.459
444	spei.3	-	12	0.052	-0.038	0.142	5328	1.426	0.459
445	spei.3	-	13	0.031	-0.056	0.119	5329	1.426	0.458
446	spei.3	-	14	0.034	-0.052	0.121	5329	1.426	0.458
447	spei.3	-	15	0.04	-0.046	0.127	5329	1.426	0.458
448	spei.3	-	16	-0.051	-0.135	0.034	5329	1.426	0.459
449	spei.6	-	0	0.277	0.17	0.383	5306	1.42	0.466
450	spei.6	-	1	0.159	0.052	0.266	5323	1.425	0.461
451	spei.6	-	2	0.124	0.017	0.231	5326	1.425	0.46
452	spei.6	-	3	0.11	0.001	0.219	5326	1.425	0.46
453	spei.6	-	4	-0.076	-0.184	0.032	5328	1.426	0.459
454	spei.6	-	5	-0.103	-0.214	0.007	5327	1.426	0.459
455	spei.6	-	6	-0.02	-0.129	0.09	5330	1.426	0.458
456	spei.6	-	7	0.009	-0.096	0.113	5330	1.426	0.458
457	spei.6	-	8	-0.042	-0.143	0.059	5330	1.426	0.458
458	spei.6	-	9	-0.043	-0.147	0.061	5330	1.426	0.458

459	spei.6	-	10	0.009	-0.096	0.115	5330	1.427	0.458
460	spei.6	-	11	0.018	-0.087	0.124	5330	1.426	0.458
461	spei.6	-	12	0.023	-0.085	0.132	5330	1.426	0.458
462	spei.6	-	13	-0.019	-0.128	0.09	5331	1.427	0.458
463	spei.6	-	14	0.001	-0.103	0.107	5330	1.426	0.458
464	spei.6	-	15	0.03	-0.072	0.132	5330	1.426	0.458
465	spei.6	-	16	-0.107	-0.208	-0.006	5327	1.426	0.459

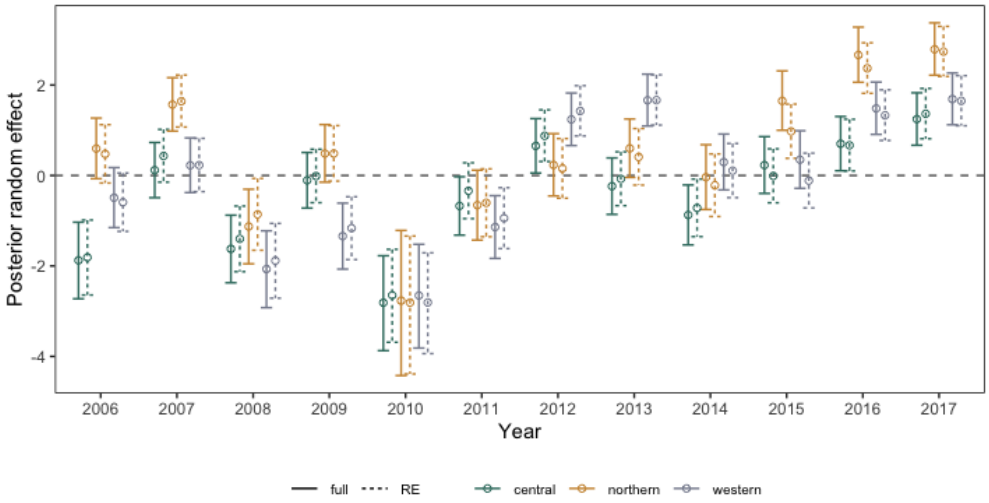
Supplementary Table 2. Model goodness of fit results from the hydrometeorological indicators and lags included within the study.



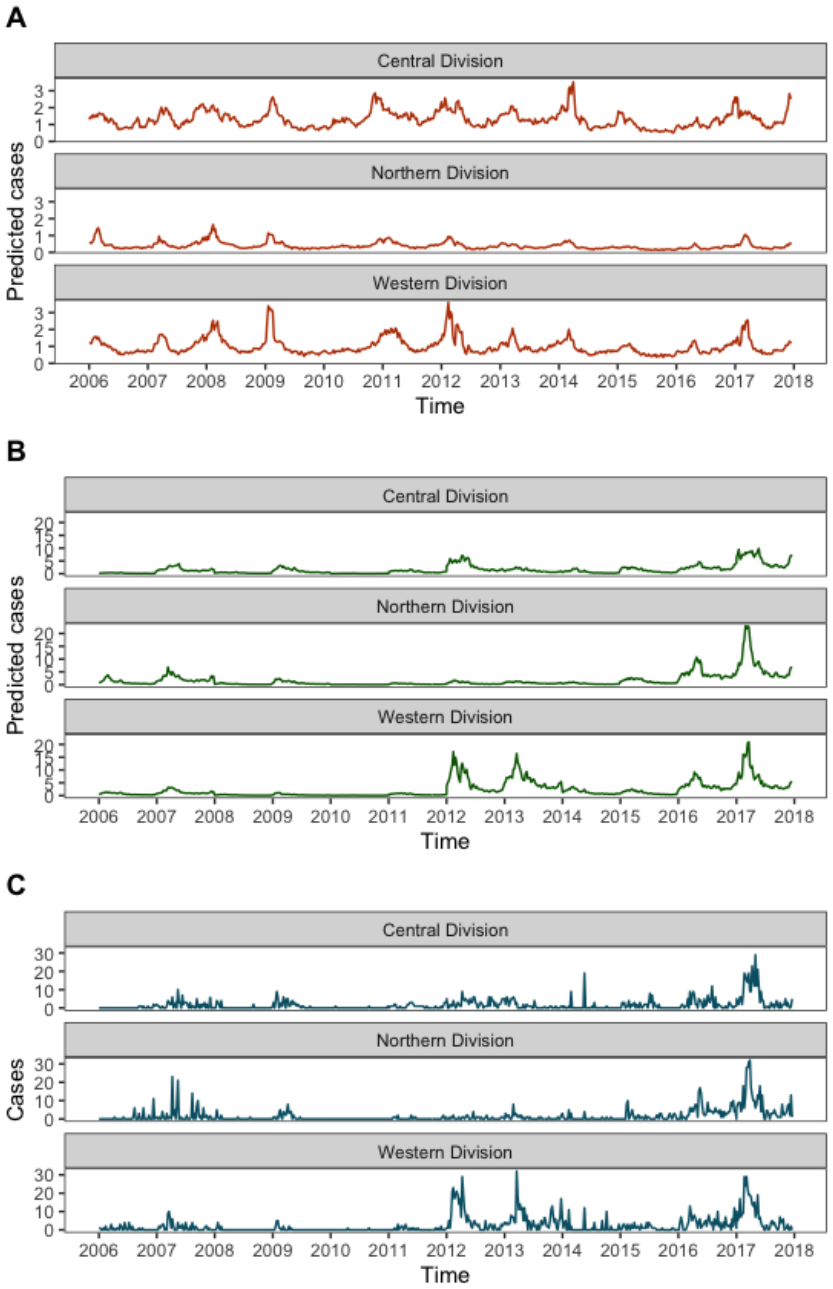
Supplementary Fig. 2. Relative improvement in model fit between the random effect only model and full model. Blue bars represent weeks when the model fit of the full model was better than the random effects only model (i.e., the difference between the observed versus model fitted cases was smaller for the full model compared with the random effects model; n=362). Red bars represent weeks when the model fit of the random effects only model was better than the full model (n=256). At zero there is no difference between the two models, and they performed equivalently (n=5).



Supplementary Fig. 3. Weekly random effects for the random effect (RE) only model, shown in orange, and the final model which included precipitation, Niño 3.4 and minimum temperature shown in blue.



Supplementary Fig. 4. Yearly random effects for the random effect (RE) only model (dashed lines) and the final model which included precipitation, Niño 3.4 and minimum temperature (solid lines), for the Central (blue), Northern (yellow) and Western (red) divisions.



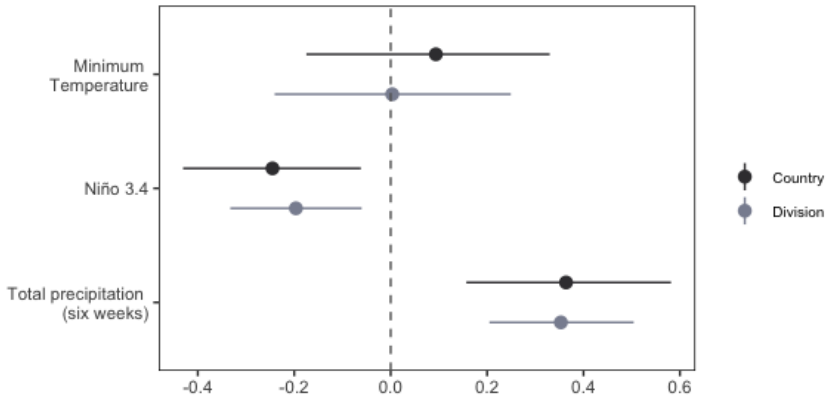
Supplementary Fig. 5. Comparison of (A) the climate variables and model parameter estimates, (B) the full model including seasonal and interannual random effects, and (C) weekly leptospirosis cases reported in Fiji between 2006 and 2017 by division. For (A), the three climate coefficients were extracted from the best performing model and then using the timeseries of total precipitation, minimum temperature and Niño 3.4 indicator, we multiplied the climate coefficients to extract the contribution of the climate covariates to the overall leptospirosis incidence rate estimates.

Supplementary Table 3. Likelihood ratio R_{LR}^2 statistics are shown for weekly and monthly division models.

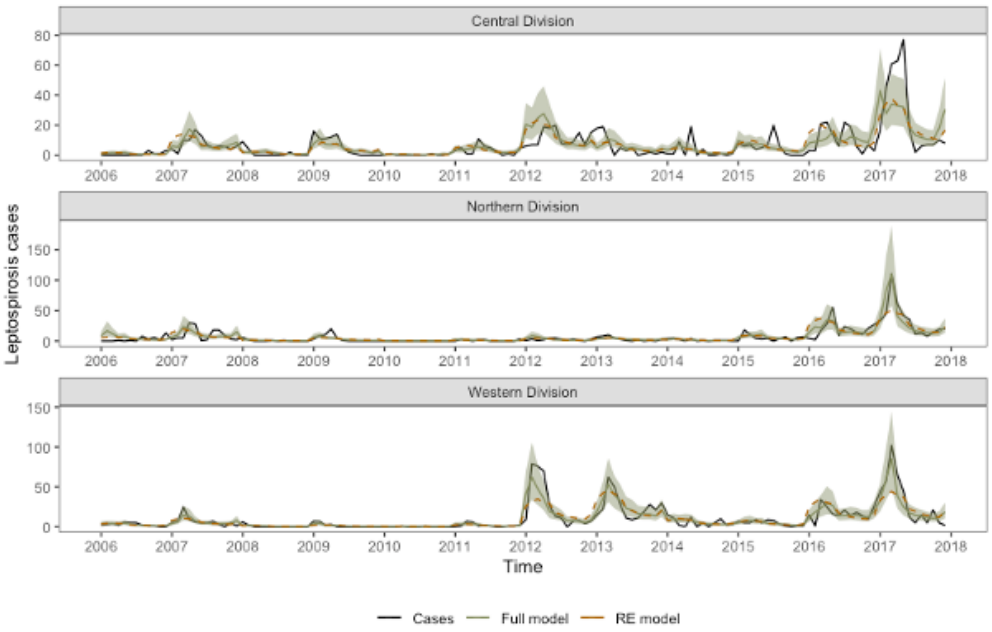
Model	**R_{LR}^2 (%) (weekly) Null**	**R_{LR}^2 (%) (weekly) RE**	**R_{LR}^2(%) (monthly) Null**	**R_{LR}^2(%) (monthly) RE**
All divisions	47.4	2.9	68.0	7.4
Central division	39.8	1.6	58.1	5.8
Western division	54.9	6.7	77.8	19.8
Northern division	40.3	-1.2	60.9	-3.0

Supplementary Table 4. Model goodness of fit results for models of ELISA-positive leptospirosis cases per month reported in Fiji from 2007 to 2017. The widely applicable information criterion (WAIC), the cross-validated (CV) mean logarithmic score, and the likelihood ratio R_{LR}^2 statistic are shown for models of increasing complexity.

	Model	**WAIC**	**CV log score**	**R_{LR}^2 RE(%)**
1	$\alpha + \delta_{t,s} + \gamma_w$ Baseline model (seasonal and inter-annual random effects)	2191	2.541	0
2	$\alpha + \delta_{t,s} + \gamma_w + x_{1tsw}$ Baseline + Tmin.1	2192	2.543	-0.2
3	$\alpha + \delta_{t,s} + \gamma_w + x_{2tsw}$ Baseline + Niño34.2	2177	2.525	3.7
4	$\alpha + \delta_{t,s} + \gamma_w + x_{3tsw}$ Baseline + TotPrcp2	2168	2.514	4.7
5	$\alpha + \delta_{t,s} + \gamma_w + x_{2tsw} + x_{3tsw}$ Baseline + Niño34.2 + TotPrcp2	2159	2.504	7.4
6	$\alpha + \delta_{t,s} + \gamma_w + x_{1tsw} + x_{2tsw} + x_{3tsw}$ Baseline + Tmin.1 + Niño34.2 + TotPrcp2	2160	2.505	7.4



Supplementary Figure 6. Parameter estimates for explanatory variables for monthly cases of leptospirosis in Fiji from 2006 to 2017 for the overall country model (black; which included monthly and yearly random effects) and for the division-level model (grey; which included monthly random effects replicated by division, and yearly random effects). Posterior mean and 95% credible intervals are shown for minimum temperature (lagged by one month), total precipitation from the previous two months, and Niño 3.4 lagged by two months.



Supplementary Fig. 7. Model posterior distributions for monthly leptospirosis cases in Fiji between 2006 and 2017 by division. Observed cases (grey line), posterior mean (green line) and 95% credible intervals (green shading) are shown for the best performing model which included total precipitation and Niño 3.4. The random effect only model is shown as an orange dashed line.

C

Supplementary Material Chapter 3

Supplementary material:

Supplementary Table 1. Summary, advantages and disadvantages of MAT and ELISA test used for the diagnosis of leptospirosis [1-5].

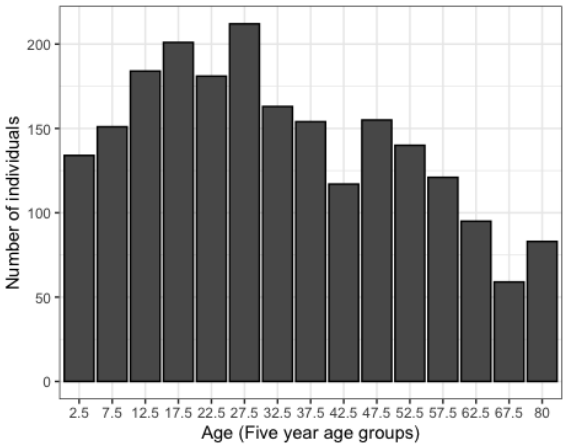
Diagnostic test	Summary	Advantage	Disadvantage
MAT	Patient serum is incubated with live antigen leptospires. Agglutination then occurs, which is detected using dark-field microscopy. Live antige leptospires are diluted sequentially, and the highest dilution in which 50% agglutination occurs is recorded. IgG and IgM antibodies can be detected using dark field microscopy.	'Gold standard' test, due to high specificity and ability to distinguish between serovars.	Requires maintenance of a panel of live leptospires, it can be time consuming and difficult to interpret the results and requires the correct selection of leptospire serovars on the panel. Cross reaction between different serogroups may occur.
ELISA	Detection of (usually) IgM antibodies in patient serum using a broad- spectrum antigen against pathogenic *Leptospira* spp.	More sensitive than MAT during the acute phase of the illness. It is easy to perform and results are rapidly available.	Not serovar-specific and detects both pathogenic and non-pathogenic *Leptospira* spp. Sensitivity and specificity variable.

MAT, microscopic agglutination test; ELISA, enzyme-linked immunosorbent assay.

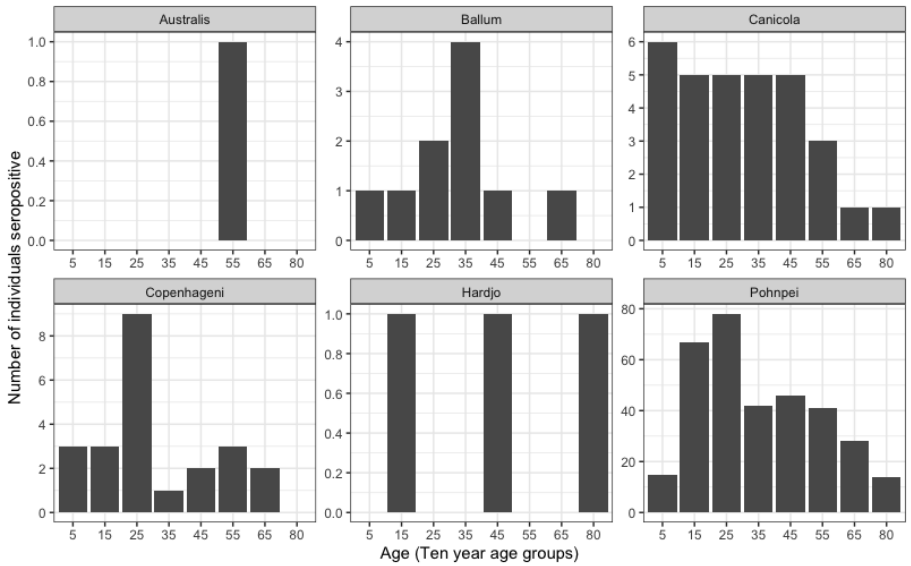
Supplementary Table 2. Description of the different models fitted and priors used.

Model	Priors	Number of parameters
Catalytic model	FOI ~ Uniform(0,0.5)	1
Reverse catalytic model	FOI ~ Uniform(0,0.5) Waning ~ Uniform(0,10)	2
Reverse catalytic model by sex	FOI ~ Uniform(0,0.5) Waning ~ Uniform(0,10)	3
Reverse catalytic model by administrative division	FOI ~ Uniform(0,0.5) Waning ~ Uniform(0,10)	4
Reverse catalytic model by serovar	FOI ~ Uniform(0,0.1) Waning ~ Uniform(0,10)	5
Constant FOI with 1 outbreak (2 years)	FOI ~ Uniform(0,0.1) Waning ~ Uniform(0,10) T1 ~ Uniform(0,2)	3
Constant FOI with 1 outbreak (5 years)	FOI ~ Uniform(0,0.1) Waning ~ Uniform(0,10) T1 ~ Uniform(0,5)	3
No constant FOI & 1 Outbreak (10 years)	FOI ~ Uniform(0,0.1) Waning ~ Uniform(0,10) T1 ~ Uniform(0,10)	3

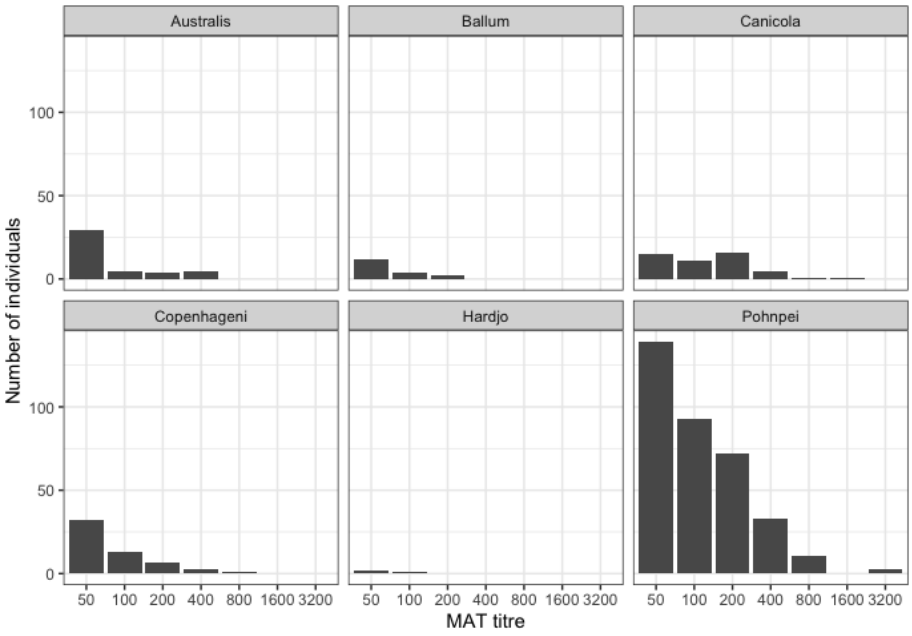
FOI, Force of infection; T1, timing of the outbreak.



Supplementary Figure 1. Number of individuals included within the 2013 leptospirosis serosurvey by five-year age groups.



Supplementary Figure 2. Number of individuals seropositive by serovar by ten-year age groups (n = 399). Individuals that had the same titre for two serovars, and therefore infecting titre could not be assumed, were excluded (n=18).

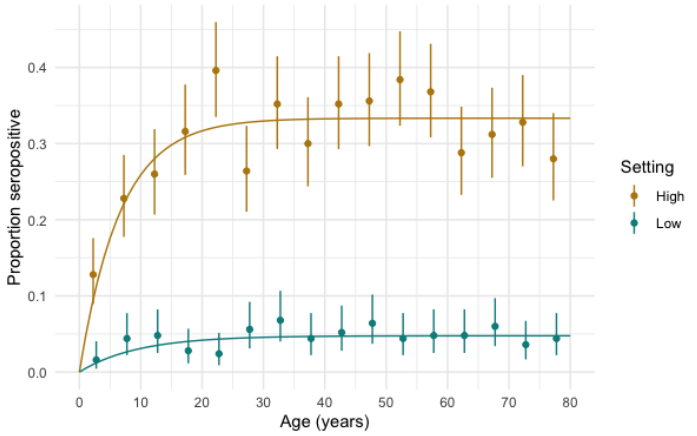


Supplementary Figure 3. Distribution of MAT titres by serovar for seropositive individuals. 89 individuals had titres for more than one serovar, and so are included more than once in this plot (n=520).

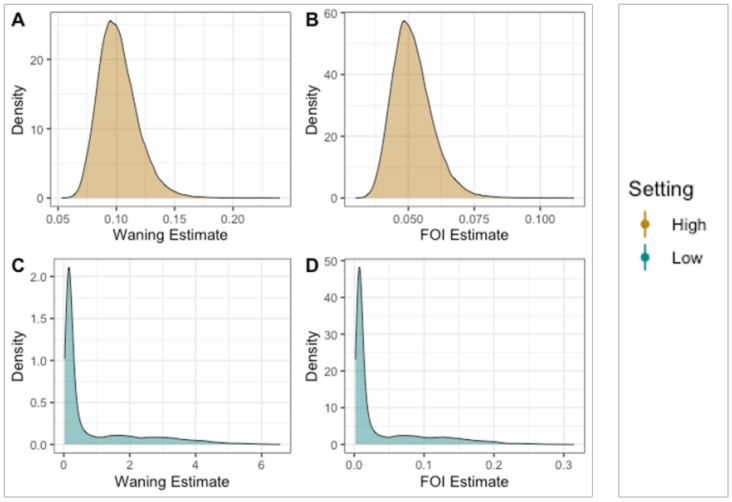
Supplementary Table 3. Simulation recovery study. Estimating the FOI and waning from a high FOI and low FOI setting.

Setting	True parameter values		Model estimates	
	FOI	Waning	FOI (95% CrI)	Waning (95% CrI)
High FOI	0.05	0.1	0.051 (0.039 - 0.068)	0.101 (0.074 - 0.138)
Low FOI	0.005	0.1	0.032 (0.004 - 0.178)	0.715 (0.072 – 4.028)

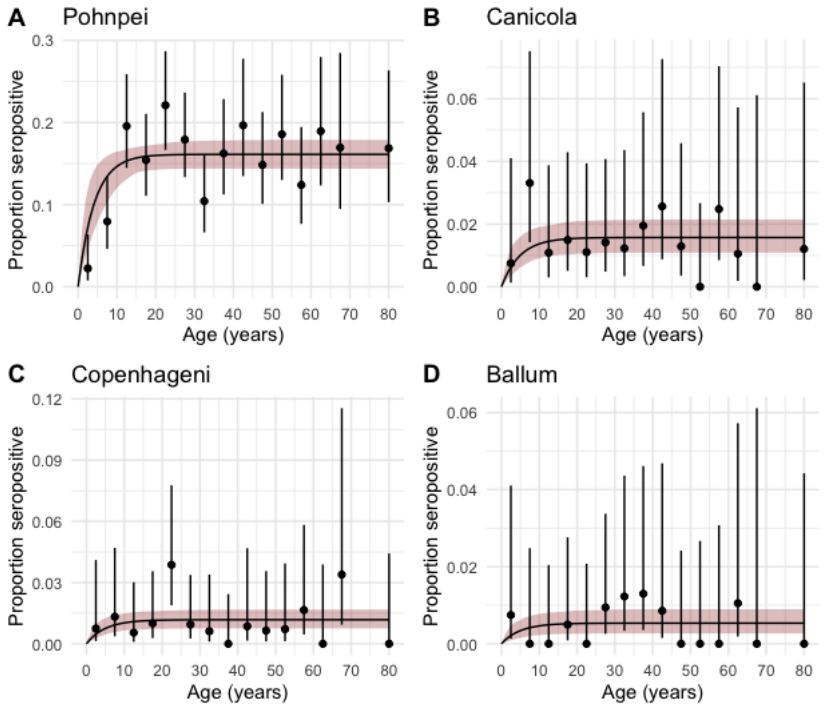
FOI, Force of infection



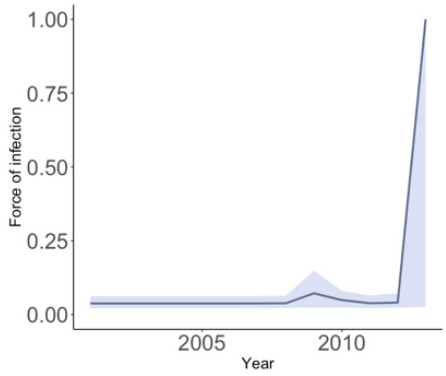
Supplementary Figure 4. Simulation recovery study. Sample estimates (mean and 95% binomial confidence interval) and model fit (solid line) for the high FOI (shown in orange) and low FOI (shown in blue) scenario. Under the high FOI scenario, the parameter estimates obtained were similar to the true parameter values. Under the low FOI scenario, the model was able to reproduce the data, but there was much greater uncertainty in the true underlying parameters.



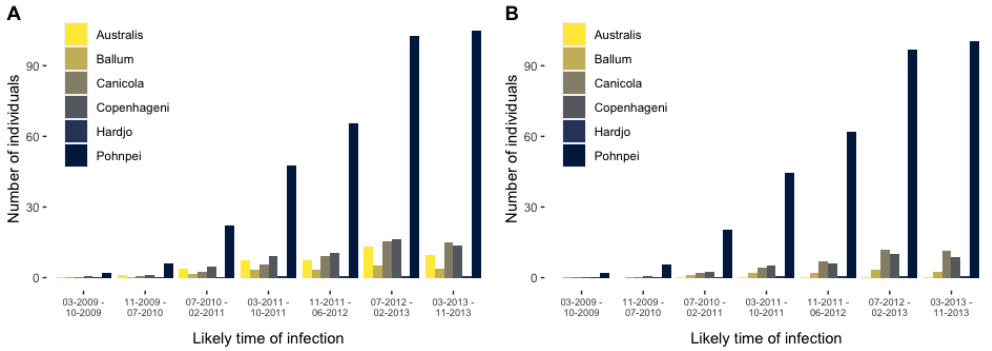
Supplementary Figure 5. Simulation recovery study. Posterior distributions for waning and force of infection (FOI) for the high FOI scenario (orange) and low FOI scenario (blue). Under the high FOI scenario, the parameter estimates obtained were similar to the true parameter values. Under the low FOI scenario, although the true parameter values were included within the 95% credible intervals, there was much greater uncertainty in the estimates.



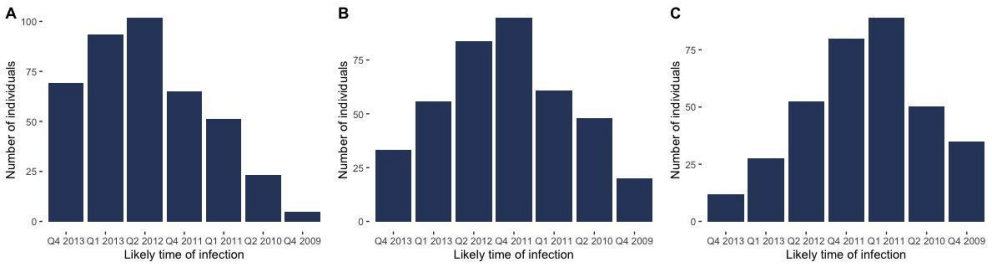
Supplementary Figure 6. Proportion of seropositive individuals by age (black points represent the mean and the error bars represent the binomial 95% confidence intervals), from national serosurvey conducted in Fiji in 2013 (n = 2,152) by serovar Pohnpei (A), Canciola (B), Copenhageni (C) and Ballum (D). The reverse catalytic model is shown for each serovar including model 95% credible intervals (red shading).



Supplementary Figure 7. Time-varying FOI from the constant FOI model with one outbreak (occurring in the preceding five years).



Supplementary Figure 8. Estimating the most likely time of infection from leptospirosis seroprevalence data from Fiji by serovar. (A) assumes that individuals can be seropositive for more than one serovar at different times (n = 520), whilst (B) using results of the serovar associated with the highest titre (n = 417).



Supplementary Figure 9. Sensitivity analysis for estimating the most likely time of infection from the seroprevalence data, using different initial titre distributions based on the geometric mean reported in Lupidi *et al*.. The initial titre distributions were shifted to correspond to a geometric mean (a) one dilution titre higher, (b) two dilutions titres higher and (c) three dilution titres higher.

Supplementary Table 4. Results from the mixed-effects linear model from the point source outbreak in Italy (Lupidi *et al.*). Antibody drop time was defined as the time taken in months for antibodies to drop one antibody titre level (e.g. from 1:100 to 1:50).

Serovar	Antibody titre drop time in months (95% CrI)	Time taken to reach undetectable levels (years)
Bratislava	6.94 (5.63 - 9.05)	6.05
Australis	9.30 (6.88 - 15.08)	6.66
Iora	7.51 (6.38- 9.12)	6.99

CrI, credible interval.

References:

1. Picardeau M. Diagnosis and epidemiology of leptospirosis. Médecine et Maladies Infectieuses 2013;43:1–9. doi:10.1016/j.medmal.2012.11.005
2. Picardeau M, Bertherat E, Jancloes M, et al. Rapid tests for diagnosis of leptospirosis Current tools and emerging technologies. Diagnostic Microbiology and Infectious Disease 2014;78:1–8. doi:10.1016/j.diagmicrobio.2013.09.012
3. Haake DA, Levett PN. Leptospirosis in humans. *Current topics in microbiology and immunology* 2015;**387**:65–97. doi:10.1007/978-3-662-45059-8_5
4. Levett PN. Leptospirosis. *Clinical Microbiology Reviews* 2001;**14**:296–326. doi:10.1128/CMR.14.2.296-326.2001
5. Musso D, La Scola B. Laboratory diagnosis of leptospirosis: A challenge. *Journal of Microbiology, Immunology and Infection* 2013;**46**:245–52. doi:10.1016/j.jmii.2013.03.001

D

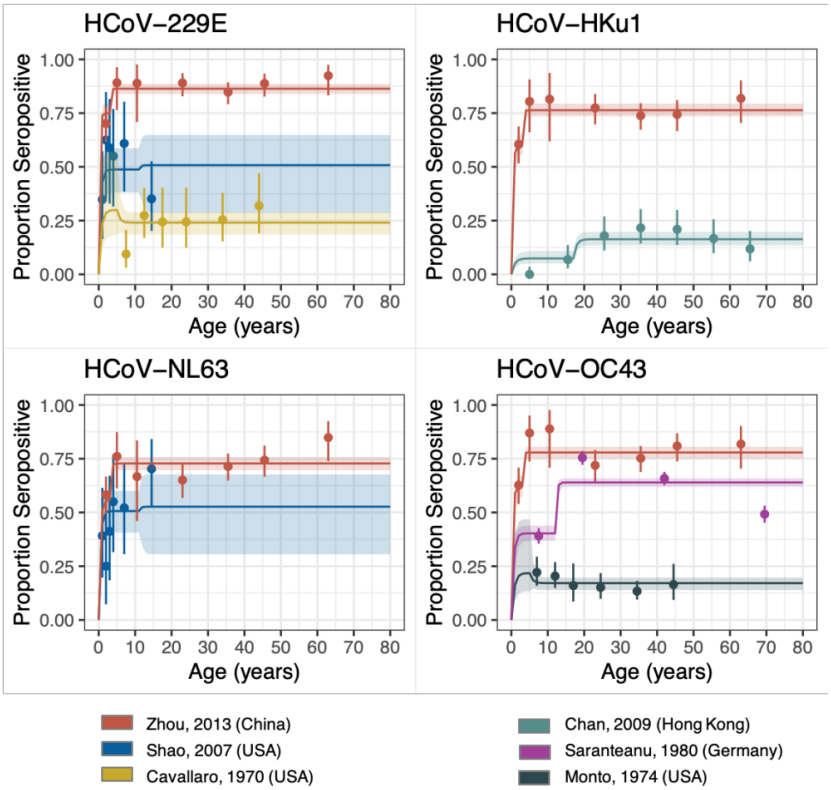
Supplementary Material Chapter 4

Supplementary material

Sensitivity analysis: Less informative priors for FOI

Supplementary Table 1. Parameter estimates from the age-varying FOI reverse catalytic model. FOI was allowed to vary by study, whilst alpha and the cut-off were allowed to vary across settings. Waning was held across all studies and strains. Less informative priors were used for FOI, Normal ~ (0.3,0.5).

Strain	First Author	FOI	Alpha	Cut-off	Waning	WAIC	LOO
HCoV-229E	Shao	1.03 (0.58 - 1.76)	1.08 (0.42 - 1.9)	11.14 (0.48 - 19.62)	1.08 (0.61 - 1.68)	536.4 (SE: 99.6)	546.0 (SE: 100.6)
	Zhou	3.22 (1.95 - 4.85)	2.12 (1.72 - 2.58)	3.17 (2.02 - 4.51)			
	Cavallaro	0.46 (0.20 - 1.49)	0.74 (0.23 - 1.32)	5.69 (0.30 - 19.2)			
HCoV-HKU1	Chan	0.09 (0.04 - 0.16)	2.44 (1.61 - 3.63)	17.38 (9.63 - 19.87)			
	Zhou	1.65 (1.00 - 2.54)	2.12 (1.72 - 2.58)	3.17 (2.02 - 4.51)			
HCoV-OC43	Zhou	1.80 (1.09 - 2.77)	2.12 (1.72 - 2.58)	3.17 (2.02 - 4.51)			
	Monto	0.30 (0.14 - 0.96)	0.74 (0.23 - 1.32)	5.69 (0.30 - 19.2)			
	Sarateanu	0.73 (0.4 - 1.17)	2.63 (2.24 - 3.10)	12.57 (7.72 - 17.71)			
HCoV-NL63	Zhou	1.36 (0.83 - 2.1)	2.12 (1.72 - 2.58)	3.17 (2.02 - 4.51)			
	Shao	1.11 (0.62 - 1.9)	1.08 (0.42 - 1.90)	11.14 (0.48 - 19.62)			



Supplementary Figure 1. Reverse catalytic model with age-varying FOI. The points are the observed proportion of seropositive individuals from each study (with confidence intervals). The lines are the seroprevalence curves from the model, with shaded 95% credible intervals. Less informative priors were used for FOI [Normal ~ (0.3,0.5)].

Sensitivity analysis: Waning estimated by strain

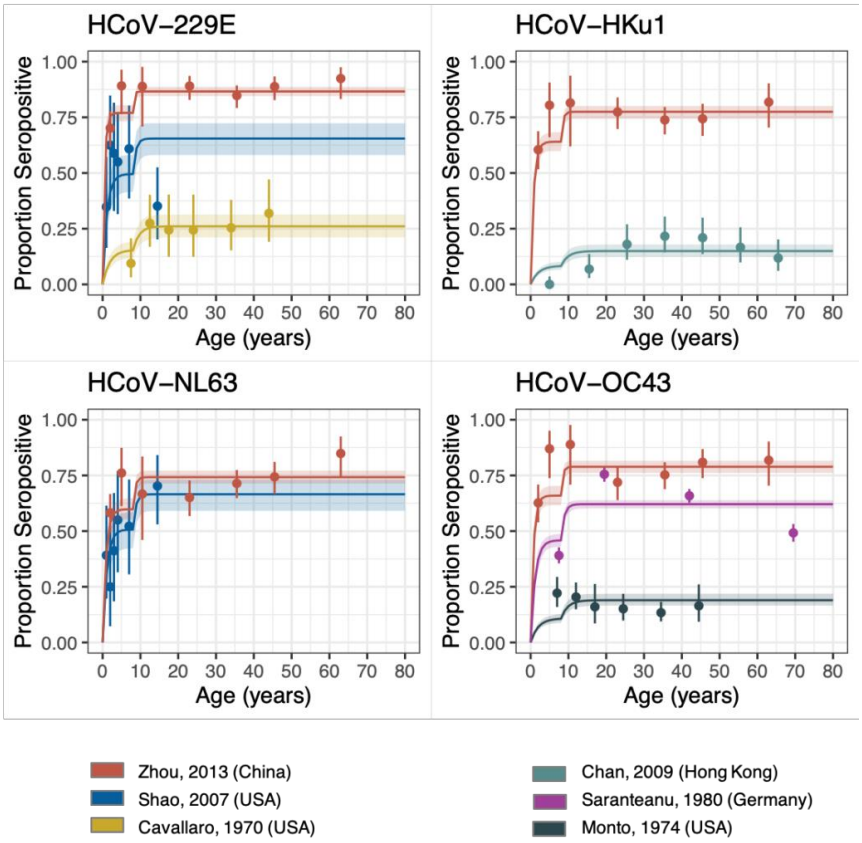
Supplementary Table 2. Parameter estimates from the age-varying FOI reverse catalytic model. FOI was allowed to vary by study, whilst alpha and the cut-off were allowed to vary across settings. Waning was allowed to vary by strain.

Strain	First Author	FOI	Alpha	Waning	Cut-off	WAIC	LOO
HCoV-229E	Shao	0.37 (0.23 - 0.63)	0.85 (0.37 - 1.76)	0.24 (0.1 - 0.52)	10.33 (0.51 - 19.57)	545.0 (SE: 99.8)	560.4 (SE 100.9)
	Zhou	0.9 (0.48 - 1.68)	1.8 (0.94 - 2.95)		2.4 (0.74 - 12.14)		
	Cavallaro	0.09 (0.04 - 0.25)	0.79 (0.41 - 1.35)		10.6 (0.41 - 19.44)		
HCoV-HKU1	Chan	0.03 (0.01 - 0.09)	2.33 (1.5 - 3.53)	0.37 (0.15 - 1.01)	16.89 (8.39 - 19.84)		
	Zhou	0.67 (0.35 - 1.56)	1.8 (0.94 - 2.95)		2.4 (0.74 - 12.14)		
HCoV-OC43	Zhou	0.85 (0.43 - 1.66)	1.8 (0.94 - 2.95)	0.44 (0.2 - 0.94)	2.4 (0.74 - 12.14)		
	Monto	0.11 (0.05 - 0.27)	0.79 (0.41 - 1.35)		10.6 (0.41 - 19.44)		
	Sarateanu	0.3 (0.15 - 0.64)	2.6 (2.17 - 3.09)		11.14 (7.56 - 16.29)		
HCoV-NL63	Zhou	0.62 (0.33 - 1.14)	1.8 (0.94 - 2.95)	0.41 (0.18 - 0.87)	2.4 (0.74 - 12.14)		
	Shao	0.53 (0.31 - 0.97)	0.85 (0.37 - 1.76)		10.33 (0.51 - 19.57)		

Sensitivity analysis: Alpha and cut-off jointly estimated by study

Supplementary Table 3. Parameter estimates from the age-varying FOI reverse catalytic model. FOI was allowed to vary by study, whilst alpha, cut-off and waning was held across all studies and strains.

Strain	First Author	FOI	Alpha	Waning	Cut-off	WAIC	LOO
HCoV-229E	Shao	0.45 (0.31 - 0.65)	1.93 (1.69 - 2.19)	0.45 (0.32 - 0.64)	8.49 (7.52 - 9.94)	622.1 (SE: 103.3)	632.5 (SE: 105.6)
	Zhou	1.52 (1.12 - 2.12)					
	Cavallaro	0.08 (0.06 - 0.12)					
HCoV-HKU1	Chan	0.04 (0.03 - 0.06)					
	Zhou	0.81 (0.61 - 1.1)					
HCoV-OC43	Zhou	0.88 (0.67 - 1.19)					
	Monto	0.06 (0.04 - 0.08)					
	Sarateanu	0.39 (0.29 - 0.52)					
HCoV-NL63	Zhou	0.68 (0.51 - 0.91)					
	Shao	0.47 (0.32 - 0.69)					

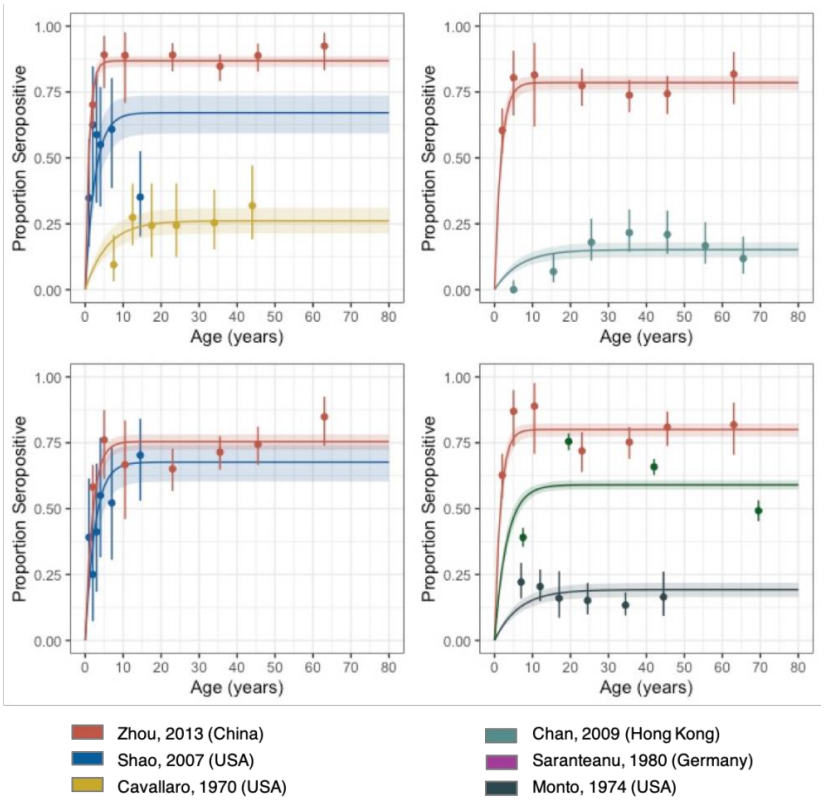


Supplementary Figure 2. Reverse catalytic model with age-varying FOI. The points are the observed proportion of seropositive individuals from each study (with confidence intervals). The lines are the seroprevalence curves from the model, with shaded 95% credible intervals. FOI was allowed to vary by study, whilst alpha, cut-off and waning was held across all studies and strains.

Reverse catalytic model

Supplementary Table 4. Parameter estimates from the reverse catalytic model. Waning was jointly estimated across all studies, but FOI was allowed to vary by study.

Strain	First Author	FOI	Waning	WAIC	LOO
HCoV-229E	Shao	0.26 (0.19 - 0.36)	0.13 (0.11 - 0.16)	717.2 (SE: 156.8)	713.8 (SE: 151.8)
	Zhou	0.85 (0.7 - 1.04)			
	Cavallaro	0.05 (0.03 - 0.06)			
HCoV-HKU1	Chan	0.02 (0.02 - 0.03)			
	Zhou	0.47 (0.39 - 0.57)			
HCoV-OC43	Zhou	0.51 (0.43 - 0.63)			
	Monto	0.03 (0.02 - 0.04)			
	Sarateanu	0.18 (0.16 - 0.22)			
HCoV-NL63	Zhou	0.39 (0.33 - 0.48)			
	Shao	0.27 (0.2 - 0.37)			

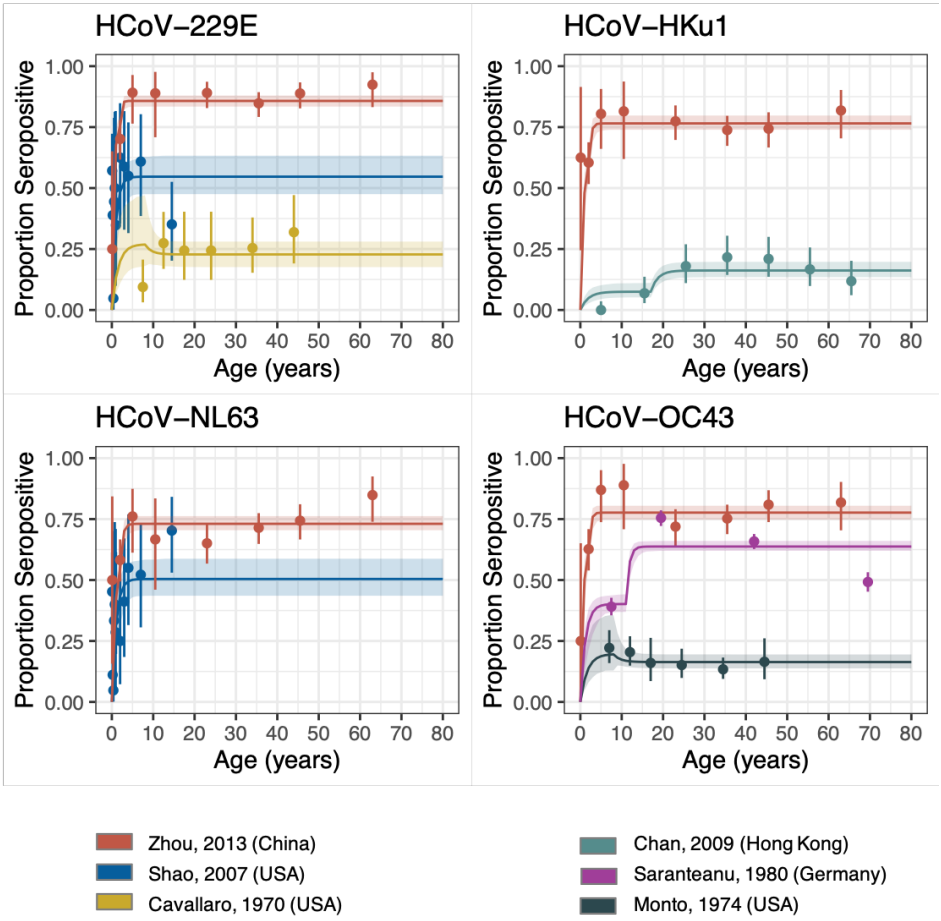


Supplementary Figure 3. Reverse catalytic model. The points are the observed proportion of seropositive individuals from each study (with confidence intervals). The lines are the seroprevalence curves from the model, with shaded 95% credible intervals.

Sensitivity analysis: Including the youngest age groups (<1 year)

Supplementary Table 5. Parameter estimates from the age-varying FOI reverse catalytic model, which includes data from the youngest age group (≤ 1 year). FOI was allowed to vary by study, whilst alpha and cut-off was allowed to vary by setting. Waning was simultaneously estimated across all studies.

Strain	First Author	FOI	Alpha	Cut-off	Waning
HCoV-229E	Shao	2.92 (2.08 - 4.01)	0.2 (0.1 - 0.35)	0.09 (0.07 - 0.14)	0.49 (0.21 - 0.78)
	Zhou	1.64 (1.04 - 2.42)	1.81 (1.06 - 2.33)	2.93 (1.85 - 7.39)	
	Cavallaro	0.18 (0.08 - 0.44)	0.8 (0.35 - 1.38)	8.43 (0.4 - 19.38)	
HCoV-HKU1	Chan	0.04 (0.02 - 0.07)	2.39 (1.56 - 3.58)	17.08 (9.14 - 19.85)	
	Zhou	0.89 (0.6 - 1.28)	1.81 (1.06 - 2.33)	2.93 (1.85 - 7.39)	
HCoV-OC43	Zhou	0.94 (0.64 - 1.37)	1.81 (1.06 - 2.33)	2.93 (1.85 - 7.39)	
	Monto	0.12 (0.05 - 0.28)	0.8 (0.35 - 1.38)	8.43 (0.4 - 19.38)	
	Sarateanu	0.33 (0.15 - 0.54)	2.62 (2.19 - 3.1)	11.36 (7.58 - 16.32)	
HCoV-NL63	Zhou	0.74 (0.5 - 1.06)	1.81 (1.06 - 2.33)	2.93 (1.85 - 7.39)	
	Shao	2.47 (1.73 - 3.41)	0.2 (0.1 - 0.35)	0.09 (0.07 - 0.14)	



Supplementary Figure 4. Reverse catalytic model with age-varying FOI, which includes data from the youngest age group (≤ 1 year). The points are the observed proportion of seropositive individuals from each study (with confidence intervals). The lines are the seroprevalence curves from the model, with shaded 95% credible intervals.

Sensitivity analysis: Refitting the model using data from only two strains

Supplementary Table 6. Parameter estimates from cross comparison models, which used half the data (only two strains included at once). Alpha, cut-off and waning were held across studies, whilst FOI was allowed to vary by study.

	Strain	First Author	FOI	Alpha	Cut-off	Waning
Model 1	HCoV-OC43	Zhou	1.02 (0.73 - 1.53)	2.01 (1.75 - 2.31)	8.61 (7.53 - 10.13)	0.56 (0.38 - 0.85)
		Monto	0.06 (0.04 - 0.1)			
		Sarateanu	0.46 (0.32 - 0.69)			
	HCoV-NL63	Zhou	0.79 (0.56 - 1.16)			
		Shao	0.54 (0.35 - 0.84)			
Model 2	HCoV-229E	Shao	0.34 (0.22 - 0.55)	1.45 (0.5 - 1.96)	16.41 (1.29 - 19.81)	0.23 (0.07 - 0.42)
		Zhou	1.03 (0.74 - 1.57)			
		Cavallaro	0.06 (0.04 - 0.1)			
	HCoV-HKU1	Chan	0.03 (0.02 - 0.05)			
		Zhou	0.57 (0.42 - 0.84)			
Model 3	HCoV-NL63	Zhou	0.52 (0.39 - 0.76)	1.05 (0.42 - 1.63)	7.86 (0.48 - 19.45)	0.19 (0.07 - 0.39)
		Shao	0.33 (0.22 - 0.52)			
	HCoV-HKU1	Chan	0.03 (0.02 - 0.05)			
		Zhou	0.61 (0.46 - 0.9)			
Model 4	HCoV-NL63	Zhou	0.54 (0.4 - 0.81)	1.28 (0.68 - 1.86)	13.01 (0.77 - 19.72)	0.24 (0.12 - 0.5)
		Shao	0.35 (0.23 - 0.55)			

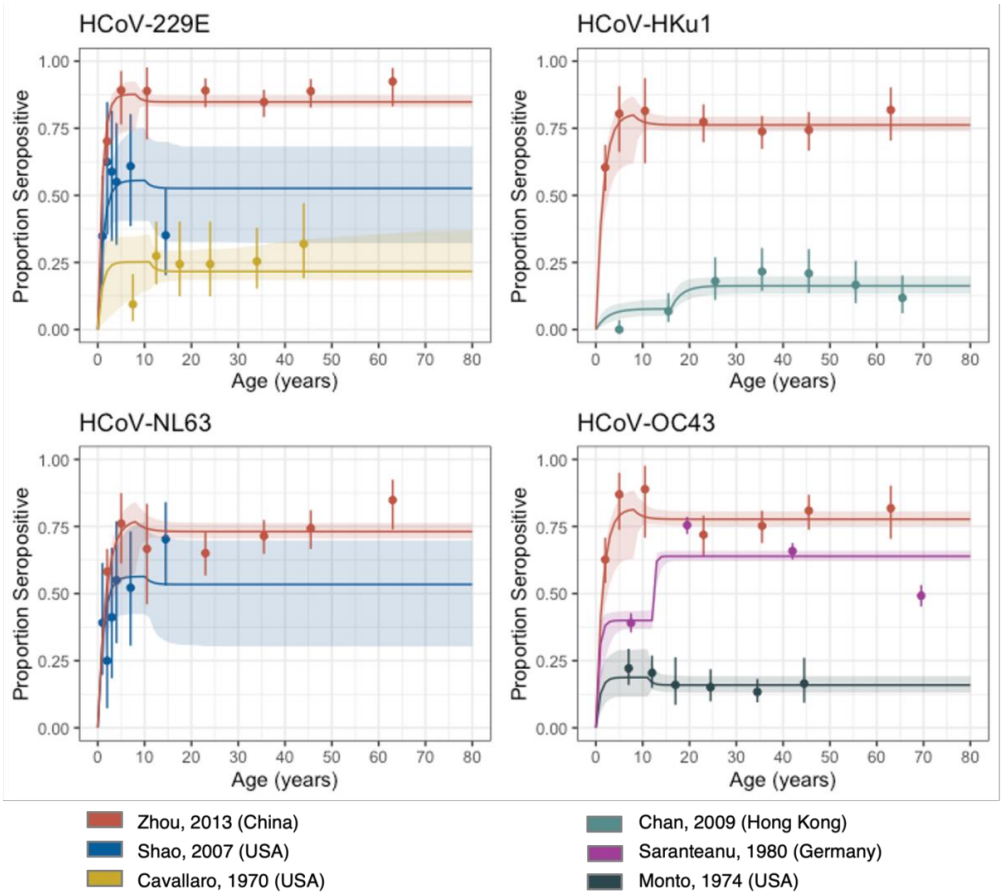
	HCoV-229E	Shao	0.35 (0.23 - 0.53)			
		Zhou	1.16 (0.82 - 1.83)			
		Cavallaro	0.07 (0.04 - 0.11)			
Model 5	HCoV-OC43	Zhou	0.97 (0.67 - 1.58)	2.1 (1.82 - 2.41)	8.5 (7.52 - 9.93)	0.54 (0.35 - 0.92)
		Monto	0.06 (0.04 - 0.1)			
		Sarateanu	0.43 (0.29 - 0.72)			
	HCoV-HKU1	Chan	0.05 (0.03 - 0.08)			
		Zhou	0.89 (0.62 - 1.45)			
Model 6	HCoV-OC43	Zhou	0.91 (0.64 - 1.35)	2.07 (1.8 - 2.37)	8.46 (7.52 - 9.95)	0.5 (0.32 - 0.76)
		Monto	0.06 (0.04 - 0.09)			
		Sarateanu	0.4 (0.27 - 0.6)			
	HCoV-229E	Shao	0.47 (0.31 - 0.72)			
		Zhou	1.58 (1.09 - 2.4)			
		Cavallaro	0.09 (0.05 - 0.14)			

Sensitivity analysis: Waning estimated by assay

Supplementary Table 7. Parameter estimates from the age-varying FOI reverse catalytic model. FOI was allowed to vary by study, whilst alpha and the cut-off were allowed to vary across settings. Waning was allowed to vary by serological assay.

Strain	First Author	Assay	FOI	Alpha	Waning	Cut-off	WAIC	LOO
HCoV-229E	Shao	ELISA (IgG)	0.47 (0.27 - 0.94)	0.89 (0.33 - 1.88)	0.38 (0.11 - 1.06)	10.2 (0.46 - 19.56)	545.1 (SE: 99.9)	560.4 (SE: 101.0)
	Zhou	IFA (IgG)	0.9 (0.66 - 1.26)	0.78 (0.45 - 2.03)	0.13 (0.07 - 0.33)	8.87 (0.42 - 18.93)		
	Cavallaro	Neutralisation	0.26 (0.02 - 1.19)	0.82 (0.47 - 1.66)	0.78 (0.02 - 3.93)	11.22 (0.49 - 19.47)		
HCoV-HKU1	Chan	ELISA (IgG)	0.03 (0.01 - 0.09)	2.33 (1.46 - 3.53)	0.38 (0.11 - 1.06)	16.86 (7.85 - 19.84)		
	Zhou	IFA (IgG)	0.52 (0.37 - 0.7)	0.78 (0.45 - 2.03)	0.13 (0.07 - 0.33)	8.87 (0.42 - 18.93)		
HCoV-OC43	Zhou	IFA (IgG)	0.57 (0.4 - 0.76)	0.78 (0.45 - 2.03)	0.13 (0.07 - 0.33)	8.87 (0.42 - 18.93)		
	Monto	CF or HI[a]	0.21 (0.07 - 0.55)	0.82 (0.47 - 1.66)	0.93 (0.3 - 2.27)	11.22 (0.49 - 19.47)		
	Sarateanu	HI	0.62 (0.2 - 1.5)	2.66 (2.25 - 3.13)	0.93 (0.3 - 2.27)	12.23 (7.68 - 17.67)		
HCoV-NL63	Zhou	IFA (IgG)	0.44 (0.31 - 0.59)	0.78 (0.45 - 2.03)	0.13 (0.07 - 0.33)	8.87 (0.42 - 18.93)		
	Shao	ELISA (IgG)	0.49 (0.27 - 1)	0.89 (0.33 - 1.88)	0.38 (0.11 - 1.06)	10.2 (0.46 - 19.56)		

Enzyme-linked immunosorbent assays (ELISA), immunofluorescence assays (IFA), complement fixation (CF), hemagglutination inhibition assays (HI). [a]For the purposes of this analysis, this was treated as HI.



Supplementary Figure 5. Reverse catalytic model with age-varying FOI. The points are the observed proportion of seropositive individuals from each study (with confidence intervals). The lines are the seroprevalence curves from the model, with shaded 95% credible intervals. FOI was allowed to vary by study, whilst alpha and cut-off were allowed to vary by setting, and waning varied by assay.

E

Supplementary Material Chapter 5

Supplementary material

Table S1. Table of all diseases listed on PHE, ECDC and WHO lists of zoonotic diseases, with reasons for exclusion if relevant.

Disease or Organism	Include	Reasons for exclusion	PHE	WHO	ECDC
Anthrax; Bacillus anthracis	**Yes**		Yes	Yes	Yes
Animal influenza; Influenza A viruses	No	Limited duration of survival in the environment. Majority of transmission to humans via direct contact with an infectious animal	Yes	Yes	Yes
Avian influenza; Influenza A viruses	No	Only included land mammals	Yes	Yes	Yes
Bovine tuberculosis; Mycobacterium bovis	No	Main routes of transmission to humans via direct contact (for the purposes of this review, contaminated meat or milk is considered to be direct contact with an infectious animal). There is limited evidence of contamination to humans via the environment, and it is not considered a primary transmission route	Yes	Yes	No
Campylobacteriosis; Campylobacter spp.	**Yes**		Yes	Yes	Yes
Cat scratch fever; Bartonella henselae	No	No evidence of environmental persistence	Yes	No	No
Cowpox; Cowpox virus	No	Transmission via direct contact, no evidence of environmental persistence	Yes	No	Yes
Cryptosporidiosis; Cryptosporidium spp	**Yes**		Yes	No	Yes
Cysticercosis / Taeniasis; Taenia spp. (Taenia solium, Taenia saginata and Taenia asiatica)	No	Humans are the definitive host. Has a very complex life-cycle, where by humans can get infected from eating raw and under-cooked pork. The environment can then be contaminated via humans. Animals are also involved in the life-cycle, but the source of cysticercosis is as a result of environmental contamination by humans. Since animal contamination does not result in this disease, this does not fit our inclusion criteria.	Yes	Yes	No
Erysipeloid; Erysipelothrix rhusiopathiae	**Yes**	E. rhusiopathiae in humans is occupationally related, principally occurring as a result of contact with contaminated animals, their products or wastes, or soil.	Yes	No	No
Fish tank / swimming pool granuloma; Mycobacterium marinum	No	Only included land mammals	Yes	No	No
Giardiasis; Giardia spp	**Yes**		Yes	No	Yes
Haemorrhagic colitis and haemolytic uraemic syndrome (HUS); Shiga toxin-producing E. coli	**Yes**		Yes	Yes	Yes
Hantavirus syndromes; Hantaviruses	**Yes**		Yes	No	No
Hepatitis E; Hepatitis E virus	**No**	The majority of Hepatitis E infections are as a result of genotypes 1 and 2, which are only found in humans. Geontypes 3 and 4 circulate in animals, but they rarely infect humans. For this reason, hepatitis was excluded, as the majority of transmission in not zoonotic.	Yes	No	No
Hydatid disease; Echinococcus granulosus	**Yes**		Yes	Yes	Yes
Leptospirosis; Leptospira spp	**Yes**		Yes	Yes	Yes
Listeriosis; Listeria spp.	No	Primarily a food borne pathogen - with very few cases of environmentally acquired transmission. Therefore exclude	Yes	No	Yes
Louping ill; Louping ill virus	No	A very rare disease in humans, therefore exclude	Yes	No	No
Lyme disease; Borrelia burgdorferi	No	Excluded vector-borne diseases	Yes	No	No
Lymphocytic choriomeningitis; Lymphocytic choriomeningitis virus (LCMV)	No	Very short-lived surival in the environment. Rare infection in humans	Yes	No	No

Orf; Orf virus	No	Transmission to humans seems to be via direct contact	Yes	No	No
Ovine chlamydiosis; Chlamydia abortus	No	Inhalation of bacteria during sheep births. Can survive in the environment for days/weeks.	Yes	No	No
Pasteurellosis; Pasteurella spp	No	Occurs via direct contact with an animal	Yes	No	No
Psittacosis; Chlamydia psittaci	No	Only included land mammals	Yes	No	No
Q fever; Coxiella burnetii	**Yes**		Yes	No	Yes
Rat bite fever; Streptobacillus moniliformis	No	Some evidence of contamination to humans via the environment. Incredibly rare diseases, and so little information is available.	Yes	No	No
Ringworm; Dermatophyte fungi	No	Excluded funguses	Yes	No	No
Salmonellosis; Salmonella spp.	**Yes**		Yes	Yes	Yes
Streptococcal sepsis; Streptococcus suis	No	Very rare in humans. Most transmission occurs via direct contact with infected animals or meat. Some evidence of ariborn transmission.	Yes	Yes	No
Streptococcal sepsis; Streptococcus zooepidemicus	No	Very rare in humans. Occurs via direct contact with animals.	Yes	No	No
Toxocariasis; Toxocara canis/catis	**Yes**		Yes	No	No
Toxoplasmosis; Toxoplasma gondii	**Yes**		Yes	No	Yes
Zoonotic diphtheria; Corynebacterium ulcerans	No	Diptheria can rarely be caused by Corynebacterium ulcerans. Occurs via direct contact with animals, or with contaminated milk	Yes	No	No
Alveolar echinococcosis; Echinococcus multilocularis	**Yes**		Yes	Yes	Yes
Brucellosis; Brucella spp.	**Yes**		Yes	Yes	Yes
Crimean-Congo haemorrhagic fever (CCHF); CCHF virus	No	Excluded vector-borne diseases	Yes	Yes	No
Ebola virus disease; Ebola virus	No	Whilst there is evidence that Ebola virus can survive in the environment, there is little evidence of humans acquiring ebola from the environment. Instead transmission to humans appears to be via direct contact with infectious animals, and direct, human to human contact	Yes	Yes	No
Glanders; Burkholderia mallei	**Yes**		Yes	No	No
Hendra virus infection; Hendra virus	No	Humans acquire infection as a result of direct infection with an infectious animal, does not appear to be much evidence of transmission via the environment	Yes	No	No
Kyasanur Forest disease; Kyasanur Forest virus	No	Transmission to humans occurs via direct contact with an infectious animal, or via an infected tick-bite	Yes	No	No
Lassa fever; Lassa virus	No	Very little evidence of the length of survival of lassa virus in the environment. Only anecdotal evidence that it survives.	Yes	Yes	Yes
Marburg virus disease; Marburg virus	No	It is unknown exactly how transmission occurs from animals to human hosts. But once in humans, it spreads via direct contact from human to human. Due to the limited information about the risk of environmental exposure this disease was not included	Yes	Yes	No
MERS; MERS Coronavirus	No	It's not exactly clear how infection passes from dromedary camels to humans, but once in humans it passes from human to human with close contact. No evidence of an environmental reservoir.	Yes	Yes	No
Monkeypox; Monkeypox virus	No	Transmission seems to mainly occur via direct contact with an infectious animal. No evidence of environmental transmission.	Yes	No	Yes
Nipah virus infection; Nipah virus	**Yes**		Yes	No	No

		Rodents are the main reservoir of infection and people are most commonly infected through rodent flea bites. People are less commonly infected by scratches or bites from infected domestic cats, by direct handling of infected animal tissues, or through laboratory exposure.			
Plague; Yersinia pestis	No	An important route of transmission is the inhalation of respiratory droplets or small particles from a patient with pneumonic plague. There is no evidence of environmental contamination	Yes	Yes	Yes
Rabies; Rabies virus and other lyssaviruses	No	Transmission occurs to humans via direct contact with an infectious animal or human. There is no evidence of environmentally-acquired infection	Yes	Yes	Yes
Rift Valley fever; Rift Valley fever virus	No	Excluded vector-borne diseases	Yes	Yes	No
Tickborne encephalitis; Tickborne encephalitis virus	No	Excluded vector-borne diseases	Yes	No	No
Trichinellosis; Trichinella spiralis	No	Transmission occurs via under-cooked meat. No evidence of environmental transmission. For the purposes of this review, animal products are considered direct transmission.	Yes	No	Yes
Tularemia; Francisella tularensis	Yes		Yes	No	Yes
West Nile virus infection; West Nile virus	No	Excluded vector-borne diseases	Yes	No	No
Yellow fever; Yellow fever virus	No	Excluded vector-borne diseases	Yes	No	No
Botulism	No	Very rare disease. Does not seem to be much evidence of the role of animals in the transmission cycle. Most cases seem to be as a result of eating contaminated food.	No	Yes	Yes
Chagas disease	No	Excluded vector-borne diseases	No	Yes	No
Chikungunya	No	Excluded vector-borne diseases	No	Yes	No
Dengue	No	Excluded vector-borne diseases	No	Yes	No
Encephalitis (including Japonese Encephalitis and tick-borne encephalitis)	No	Excluded vector-borne diseases	No	Yes	No
Crimean-Congo haemorrhagic fever (CCHF)	No	Humans can become infected via tick bites, contact with infected animal bood, and I some cases human to human contact via body fluids. Some evidence of contamination via improerly sterilised equipment. Most infection occurs via ticks.	No	Yes	No
Rift Valley fever	No	Excluded vector-borne diseases	No	Yes	No
Japanese encephalitis	No	Excluded vector-borne diseases	No	Yes	No
Leishmaniasis	No	Excluded vector-borne diseases	No	Yes	No
Zika virus	No	Excluded vector-borne diseases	No	Yes	No
Clonorchiasis	No	Infection in humans as a result of consuming contaminated fish	No	Yes	No
Paragonimiasis	No	Infection in humans as a result of consuming contaminated crustaceans	No	Yes	No
Fascioliasis	**Yes**	Infection in humans as a result of consuming contaminated aquatic plants - which is considered to be environmental contamination since the agent is on the outside of the plants. Also evidence of contamination from water directly.	No	Yes	No
Opisthorchiasis felinea	No	Infection in humans as a result of consuming contaminated fish	No	Yes	No
Opisthorchiasis viverrini	No	Infection in humans as a result of consuming contaminated fish	No	Yes	No
Schmallenberg virus	No	Excluded vector-borne diseases	No	No	Yes
Sindbis fever	No	Excluded vector-borne diseases	No	No	Yes
Babesiosis	No	Excluded vector-borne diseases	No	No	Yes
Severe Acute Respiratory Syndrome (SARS)	No	No evidence of an environmental reservoir	No	Yes	No
Variant Creutzfeldt-Jakob disease	No	Excluded prion diseases	No	Yes	Yes
Yersiniosis	**Yes**		No	No	Yes

Table S2. Individual search terms were created using disease-specific search terms shown in table 2a, and all modelling terms shown in table 2b.

Table S2a. Disease-specific search terms used in Embase, Medline and Web of Science.

Disease-specific search terms	
Anthrax	Anthrax OR Bacillus anthracis
Brucellosis	brucellos* OR brucella OR undulant fever OR Malta fever OR cyprus fever OR Mediterranean fever
Campylobacter	Campylobacter
Cryptosporidium	Cryptosporidium
E. coli	Escherichia coli OR e. coli
Echinococcosis	echinococcosis OR hydatid OR hydatidosis OR Echinococcus
Erysipeloid	Erysipeloid OR Erysipelothrix rhusiopathiae
Fascioliasis	Fascioliasis OR Fasciola hepatica OR Fasciola gigantica
Glanders	Glanders OR Burkholderia mallei
Giardia	Giardia OR Giardiasis
Hantavius	hantavirus OR hanta* virus OR puumala virus OR seoul virus OR sin nombre virus
Leptospirosis	Leptospir* OR weil disease
Meloidosis	Melioid*
Nipah Virus	Nipah Virus
Q fever	q fever* OR query fever* OR Coxiella burnetii
Salmonella	Salmonella typhimurium OR S. typhimurium OR Salmonella Dublin OR S. Dublin OR Salmonella Enteritidis OR S. Enteritidis OR Salmonella Choleraesuis OR S. choleraesuis
Toxoplasmosis	toxoplasm*
Toxocarosis	Toxocara OR Toxocarosis
Tularaemia	Tularemia* OR francisella tularensis
Yersinosis	yersiniosis OR enterocolitica OR yersinia

*Denotes truncation.

Table S2b. Modelling-specific search terms used in Embase, Medline and Web of Science

Modelling specific search terms	
Mechanistic model*[a]	Simulation model
Stochastic model*a	Mathematical model
Bayesian model*a	Analytical model
Epidemic model	SIR model
Transmission model	SEIR model
Deterministic model	Network model
Compartmental model	Epidemiological model
Theoretical model	Sensitivity analysis
Dynamic model	Population dynamics

[a]Proximity searching was used, search terms had to be within 3 words of each other. For Embase and Medline ADJ3 was used, and for Web of Science NEAR/3 was used. *Denotes truncation.

1. Leptospirosis/ or weil disease/
2. Leptospir*
3. 1 or 2
4. (mathematical adj3 model*)
5. (stochastic* adj3 model*)
6. (dynamic* adj3 model*)
7. (transmission adj3 model*)
8. (bayesian adj3 model*)
9. (mechanistic* adj3 model)
10. (epidemic adj3 model*)
11. (deterministic adj3 model*)
12. (compartmental adj3 model*)
13. (simulation adj3 model*)
14. (analytical adj3 model*)
15. (SIR adj3 model*)
16. (SEIR adj3 model*)
17. (network adj3 model*)
18. (Epidemiological adj3 model*)
19. Sensitivity analysis
20. population dynamics
21. (theoretical adj3 model*)
22. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 3 and 22

Figure S1. Example literature search for leptospirosis in Embase.

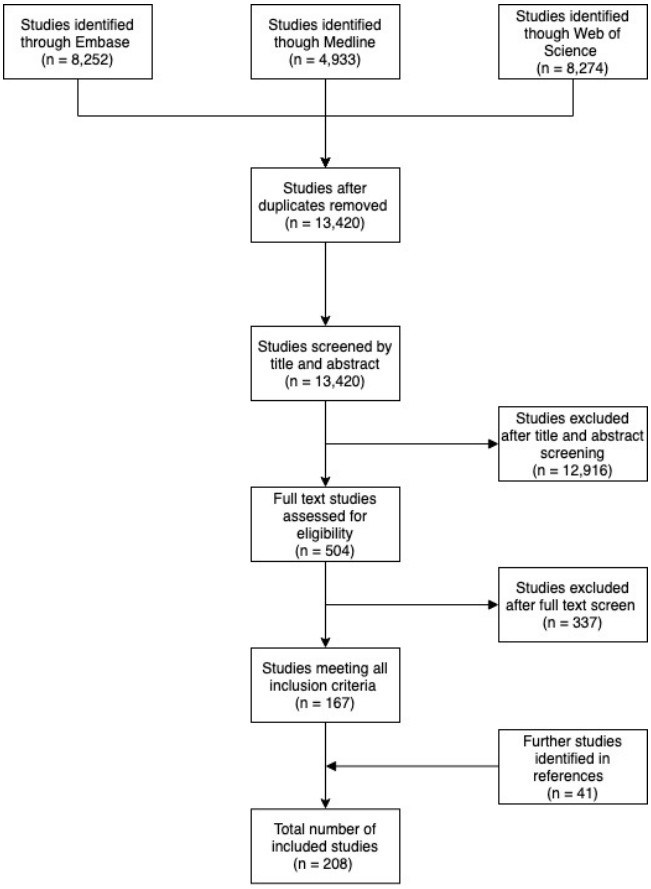


Figure S2. PRISMA flow diagram of the search and exclusion process

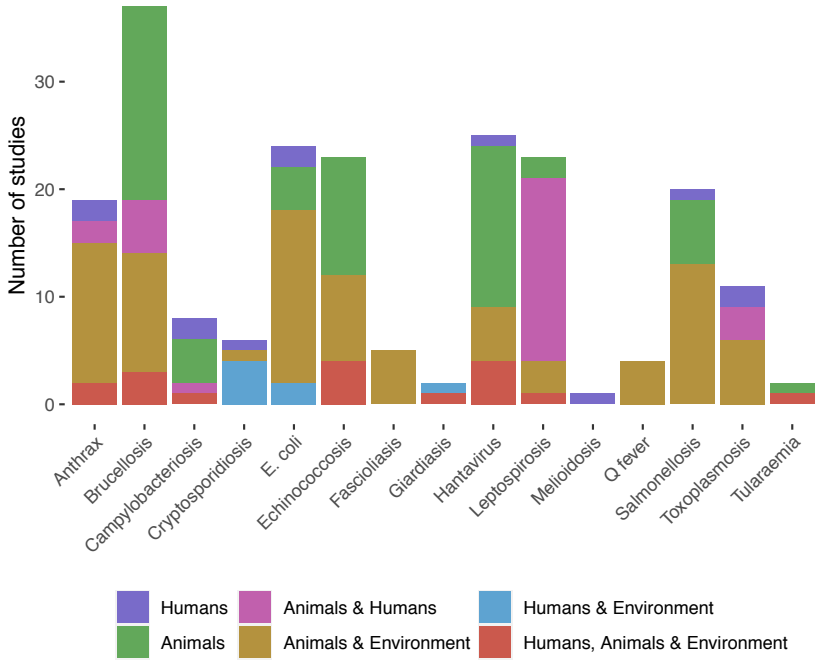


Figure S3. Number of studies by disease (n = 210). The different colours represent the different model structure by disease.

Table S3: Studies included within systematic review.

			Components			Model features						Model type	
Author	Year	Disease	Humans	Animals	Environment	Informed parameters	Model validation	Model calibration	Prediction	Animal host	Control Measures	Climate included	Det. or Stoch.	Comp. or IBM
Chen et al. [1]	2006	Anthrax	1	0	0	1	1	1	0	3	1	-	2	2
Croicu [2]	2018	Anthrax	0	1	1	1	0	0	0	3	1	-	1	1
Efraim *et al.* [3]	2018	Anthrax	1	1	1	1	1	1	0	3	0	-	1	1
Friedman and Yakubu [4]	2013	Anthrax	0	1	1	0	0	0	0	3	0	-	1	1
Furniss and Hahn [5]	1981	Anthrax	0	1	1	1	1	0	0	3	0	-	1	1
Gomez *et al.* [6]	2018	Anthrax	0	1	1	1	1	1	1	3	0	-	1	1
Hahn and Furniss [7]	1983	Anthrax	0	1	1	1	1	0	0	3	0	-	1	1
Mushayabasa [8]	2015	Anthrax	0	1	1	1	0	0	0	3	1	-	1	1
Mushayabasa [9]	2016	Anthrax	0	1	1	1	0	0	0	3	1	-	1	1
Mushayabasa *et al.* [10]	2017	Anthrax	0	1	1	1	0	0	0	3	0	-	1	1
Osman and Makinde [11]	2018	Anthrax	1	1	0	1	0	0	0	3	0	-	1	1
Osman and Makinde [12]	2018	Anthrax	1	1	0	1	0	0	0	3	1	-	1	1
Pantha *et al.* [13]	2016	Anthrax	0	1	1	1	1	1	0	3	1	-	1	1
Saad-Roy *et al.* [14]	2017	Anthrax	0	1	1	1	0	0	0	3	1	-	1	1
Sinkie and Murthy [15]	2016	Anthrax	0	1	1	1	0	0	0	3	0	-	1	1
van den Driessche [16]	2017	Anthrax	0	1	1	0	0	1	0	3	0	-	1	1
van den Driessche and Yakubu [17]	2018	Anthrax	0	1	1	0	0	0	0	3	0	-	1	1
Yakubu and Ziyadi [18]	2018	Anthrax	1	1	1	0	0	0	0	3	0	-	1	1
Zaric *et al.* [19]	2008	Anthrax	1	0	0	1	0	0	1	3	1	-	1	1
Abatih *et al.* [20]	2015	Brucellosis	0	1	0	1	0	0	0	1	1	0	1	1
Ainseba *et al.* [21]	2010	Brucellosis	0	1	1	1	0	0	1	1	1	0	1	1
Almeida *et al.* [22]	1988	Brucellosis	0	1	0	0	0	0	0	1	1	0	1	1
Beauvais *et al.* [23]	2016	Brucellosis	0	1	1	1	1	1	0	1	1	0	1	1
Cantrell *et al.* [24]	2001	Brucellosis	0	1	0	0	0	0	0	1	0	0	1	1
Darbon *et al.* [25]	2018	Brucellosis	0	1	0	1	1	1	0	1	1	0	1	1

Table S3: Studies included within systematic review.

Author	Year	Disease	Components			Model features						Model type	
			Humans	Animals	Environment	Informed parameters	Model validation	Model calibration	Prediction	Animal host	Control Measures	Climate included	Det. or Stoch.	Comp. or IBM
Dobson and Meagher [26]	1996	Brucellosis	0	1	0	1	1	0	0	1	1	0	1	1
Ebinger *et al.* [27]	2011	Brucellosis	0	1	0	1	1	1	0	1	1	0	2	2
England *et al.* [28]	2004	Brucellosis	0	1	1	1	0	0	0	1	1	0	1	1
Fournie *et al.* [29]	2017	Brucellosis	0	1	0	1	0	0	0	1	0	0	2	1
Gonzalez-Guzman and Naulin [30]	1994	Brucellosis	0	1	0	1	0	0	1	1	1	0	1	1
Havas *et al.* [31]	2014	Brucellosis	1	1	0	1	1	1	0	1	1	0	2	2
Hegazy *et al.* [32]	2009	Brucellosis	0	1	0	1	1	1	0	1	1	0	2	1
Hou and Sun [33]	2016	Brucellosis	0	1	0	1	1	1	0	1	1	0	1	1
Hou and Zhang [34]	2016	Brucellosis	0	1	1	0	0	0	0	1	0	0	1	1
Hou *et al.* [35]	2013	Brucellosis	1	1	1	1	1	1	0	1	1	0	1	1
Hou *et al.* [36]	2014	Brucellosis	0	1	1	0	0	0	0	1	0	0	1	1
Inchaisri *et al.* [37]	2016	Brucellosis	0	1	0	1	0	0	0	1	1	0	1	1
Li *et al.* [38]	2014	Brucellosis	1	1	1	1	1	1	0	1	1	0	1	1
Li *et al.* [39]	2017	Brucellosis	1	1	1	0	0	0	0	1	0	0	1	1
Li *et al.* [40]	2017	Brucellosis	0	1	1	0	0	0	0	1	0	0	1	1
Li *et al.* [41]	2014	Brucellosis	0	1	1	0	0	0	0	1	0	0	1	1
Lolika and Mushayabasa [42]	2018	Brucellosis	0	1	0	0	0	0	0	1	1	0	1	1
Lolika and Mushayabasa [43]	2018	Brucellosis	0	1	0	1	0	0	0	1	1	0	1	1
Lolika *et al.* [44]	2018	Brucellosis	0	1	0	1	0	0	0	1	1	1	1	1
Lolika *et al.* [45]	2017	Brucellosis	0	1	0	1	0	0	0	1	1	1	1	1
Lou *et al.* [46]	2016	Brucellosis	1	1	0	1	1	1	1	1	1	1	1	1
Nepomuceno [47]	2017	Brucellosis	0	1	0	1	0	0	0	1	1	0	2	2
Nie *et al.* [48]	2014	Brucellosis	0	1	1	1	1	1	0	1	1	0	1	1
Schley *et al.* [49]	2012	Brucellosis	0	1	0	1	0	0	0	1	0	0	3	3
Sun and Zhang [50]	2014	Brucellosis	0	1	1	0	0	0	0	1	1	0	1	1

Table S3: Studies included within systematic review.

			Components			Model features						Model type	
Author	Year	Disease	Humans	Animals	Environment	Informed parameters	Model validation	Model calibration	Prediction	Animal host	Control Measures	Climate included	Det. or Stoch.	Comp. or IBM
Tumwiine and Robert [51]	2017	Brucellosis	0	1	0	1	0	0	0	1	1	0	1	1
Wang *et al.* [52]	2018	Brucellosis	1	1	0	1	1	1	0	1	1	0	2	1
Yang *et al.* [53]	2017	Brucellosis	0	1	1	1	0	0	0	1	1	1	1	1
Zhang *et al.* [54]	2014	Brucellosis	0	1	1	1	1	1	0	1	1	0	3	1
Zhou *et al.* [55]	2018	Brucellosis	1	1	0	1	1	1	0	1	1	0	1	1
Zinsstag [56]	2005	Brucellosis	1	1	0	1	1	1	1	1	1	0	1	1
Bhatt and Hughes [57]	2017	Campylobacter	1	1	0	1	0	0	0	1	0	0	1	1
Cousins *et al.* [58]	2019	Campylobacter	1	1	1	1	1	1	1	1	0	1	1	1
Goddard *et al.* [59]	2014	Campylobacter	0	1	0	1	1	1	0	1	1	0	1	1
McBride *et al.* [60]	2014	Campylobacter	1	0	0	1	1	0	1	1	0	1	1	1
Neves *et al.* [61]	2019	Campylobacter	0	1	0	1	1	1	0	1	0	0	1	1
Rodriguez *et al.* [62]	2018	Campylobacter	0	1	0	1	0	0	0	1	1	0	1	1
Singer *et al.* [63]	2007	Campylobacter	1	0	0	1	1	1	0	1	0	0	1	1
Van Gerwe *et al.* [64]	2005	Campylobacter	0	1	0	1	1	1	0	1	0	0	2	1
Brookhart *et al.* [65]	2002	Cryptosporidium	1	0	1	1	1	1	0	3	0	0	1	1
Eisenberg *et al.* [66]	1998	Cryptosporidium	1	0	1	1	1	1	0	3	1	0	1	1
Eisenberg *et al.* [67]	2002	Cryptosporidium	1	0	1	1	1	1	0	3	1	0	1	1
Eisenberg *et al.* [68]	2005	Cryptosporidium	1	0	1	1	1	1	1	3	1	0	1	1
McBride *et al.* [60]	2014	Cryptosporidium	1	0	0	1	1	0	1	3	0	1	1	1
Springer *et al.* [69]	2017	Cryptosporidium	0	1	1	1	0	1	0	3	0	1	2	2
Ayscue *et al.* [70]	2009	E. coli	0	1	1	1	1	0	0	1	1	0	3	1
Brookes *et al.* [71]	2015	E. coli	1	0	1	1	1	1	0	1	1	0	2	2
Chen and Sanderson [72]	2013	E. coli	0	1	1	1	0	0	0	1	0	0	3	3
Dopfer *et al.* [73]	2006	E. coli	0	1	0	1	1	1	0	1	0	0	2	1
Gautam *et al.* [74]	2011	E. coli	0	1	1	1	1	0	0	1	0	1	1	1
Gautam *et al.* [75]	2015	E. coli	0	1	1	1	1	1	0	1	0	0	1	1

Table S3: Studies included within systematic review.

			Components			Model features						Model type	
Author	Year	Disease	Humans	Animals	Environment	Informed parameters	Model validation	Model calibration	Prediction	Animal host	Control Measures	Climate included	Det. or Stoch.	Comp. or IBM
Geenen *et al.* [76]	2004	E. coli	0	1	0	1	1	1	0	1	0	0	2	1
Geenen *et al.* [77]	2005	E. coli	0	1	0	1	1	1	0	1	0	0	2	1
Huijbers *et al.* [78]	2016	E. coli	0	1	1	1	1	1	0	1	0	0	1	1
Jose and Bobadilla [79]	1994	E. coli	1	0	0	1	0	0	0	1	0	0	1	1
Liu *et al.* [80]	2007	E. coli	0	1	1	1	1	1	0	1	0	0	2	1
Liu *et al.* [81]	2007	E. coli	0	1	0	1	1	0	0	1	0	0	1	1
Liu *et al.* [82]	2005	E. coli	0	1	1	1	1	1	0	1	0	0	2	1
Mathews *et al.* [83]	2006	E. coli	0	1	1	1	1	1	0	1	0	0	2	1
Matthews *et al.* [84]	2006	E. coli	0	1	1	1	1	1	0	1	0	0	2	2
Seto *et al.* [85]	2007	E. coli	1	0	1	1	1	1	0	1	1	0	2	1
Talaminos *et al.* [86]	2016	E. coli	1	0	0	1	1	0	0	1	1	0	1	1
Turner *et al.* [87]	2006	E. coli	0	1	1	1	1	0	0	1	1	0	2	1
Vosough *et al.* [88]	2007	E. coli	0	1	1	1	0	0	0	1	1	0	1	1
Wang *et al.* [89]	2014	E. coli	0	1	1	1	0	0	0	1	1	1	2	1
Widgren *et al.* [90]	2018	E. coli	0	1	1	1	1	1	0	1	1	1	1	1
Wood *et al.* [91]	2007	E. coli	0	1	1	1	0	0	0	1	1	0	2	2
Zhang [92]	2012	E. coli	0	1	1	1	1	1	0	1	1	0	2	2
Zhang and Woolhouse [93]	2010	E. coli	0	1	1	1	1	1	0	1	1	0	2	2
Azlaf *et al.* [94]	2007	Echinococcosis	0	1	0	1	1	1	0	1	0	0	1	1
Budgey *et al.* [95]	2017	Echinococcosis	0	1	1	1	0	0	0	1	1	0	2	2
Budke *et al.* [96]	2005	Echinococcosis	0	1	1	1	1	1	0	1	0	0	1	1
Harris *et al.* [97]	1980	Echinococcosis	0	1	0	1	0	0	0	1	1	0	1	1
Hassan *et al.* [98]	2019	Echinococcosis	0	1	1	1	0	0	0	1	1	0	1	1
Heinzmann *et al.* [99]	2011	Echinococcosis	0	1	0	1	1	1	0	1	0	0	2	2
Huang *et al.* [100]	2011	Echinococcosis	0	1	1	1	0	0	0	1	1	0	2	2
Ishikawa *et al.* [101]	2003	Echinococcosis	0	1	0	1	0	0	0	1	0	1	1	1

Table S3: Studies included within systematic review.

			Components			Model features						Model type	
Author	Year	Disease	Humans	Animals	Environment	Informed parameters	Model validation	Model calibration	Prediction	Animal host	Control Measures	Climate included	Det. or Stoch.	Comp. or IBM
Lewis *et al.* [102]	2014	Echinococcosis	0	1	0	1	1	1	0	1	0	0	1	1
Liu *et al.* [103]	2015	Echinococcosis	0	1	0	1	0	0	0	1	0	0	1	1
Nishina and Ishikawa [104]	2008	Echinococcosis	0	1	1	1	1	0	0	1	1	1	2	2
Otero-Abad *et al.* [105]	2017	Echinococcosis	0	1	0	1	1	1	0	1	0	0	1	1
Roberts *et al.* [106]	1995	Echinococcosis	0	1	0	1	0	0	0	1	1	0	1	1
Rong *et al.* [107]	2018	Echinococcosis	1	1	1	0	0	0	0	1	0	0	1	1
Takumi and Van Der Giessen [108]	2005	Echinococcosis	0	1	1	1	0	0	0	1	1	0	1	1
Torgerson [109]	2003	Echinococcosis	0	1	0	1	0	0	0	1	1	0	1	1
Wang *et al.* [110]	2017	Echinococcosis	1	1	1	1	1	1	1	1	0	0	1	1
Wang *et al.* [111]	2013	Echinococcosis	1	1	1	1	0	0	0	1	0	0	1	1
Wang *et al.* [112]	2014	Echinococcosis	0	1	1	0	0	0	0	1	0	0	1	1
Wu *et al.* [113]	2013	Echinococcosis	0	1	1	1	0	0	0	1	1	0	1	1
Xu and Ai [114]	2017	Echinococcosis	0	1	0	0	0	0	0	1	0	0	1	1
Zhang *et al.* [115]	2017	Echinococcosis	1	1	1	0	1	0	1	1	1	0	1	1
Ziadinov *et al.* [116]	2008	Echinococcosis	0	1	0	1	0	0	0	1	0	0	1	1
Meek and Morris [117]	1981	Fasciolasis	0	1	1	1	1	0	1	1	1	1	2	2
Smith [118]	1984	Fasciolasis	0	1	1	1	1	0	1	1	1	0	1	1
Smith [119]	1982	Fasciolasis	0	1	1	1	0	0	0	1	1	0	1	1
Smith [120]	1984	Fasciolasis	0	1	1	1	0	0	0	1	0	0	1	1
Turner *et al.* [121]	2016	Fasciolasis	0	1	1	1	1	0	1	1	1	1	2	2
Eisenberg *et al.* [67]	2002	Giardia	1	0	1	1	1	1	0	1	1	0	1	1
Waters *et al.* [122]	2016	Giardia	1	1	1	1	1	0	0	1	0	0	1	1
Abramson and Kenkre [123]	2002	Hantavirus	0	1	0	0	0	0	0	2	0	0	1	1
Abramson *et al.* [124]	2003	Hantavirus	0	1	0	0	0	0	0	2	0	1	1	1
Adler *et al.* [125]	2008	Hantavirus	0	1	0	1	1	1	0	2	1	0	1	1

Table S3: Studies included within systematic review.

			Components			Model features						Model type	
Author	Year	Disease	Humans	Animals	Environment	Informed parameters	Model validation	Model calibration	Prediction	Animal host	Control Measures	Climate included	Det. or Stoch.	Comp. or IBM
Aguirre *et al.* [126]	2002	Hantavirus	0	1	0	0	0	0	0	2	0	0	1	1
Allen *et al.* [127]	2006	Hantavirus	0	1	0	1	0	0	0	2	0	0	3	1
Allen *et al.* [128]	2009	Hantavirus	0	1	0	1	0	0	0	2	0	0	3	1
Buceta *et al.* [129]	2004	Hantavirus	0	1	0	1	0	0	0	2	0	1	1	1
Chen and Clemence [130]	2006	Hantavirus	0	1	0	1	0	0	0	2	0	0	1	1
Escudero *et al.* [131]	2004	Hantavirus	0	1	0	0	0	0	0	2	0	0	2	1
Guzzetta *et al.* [132]	2017	Hantavirus	0	1	0	1	1	1	1	2	1	0	2	2
Haredasht *et al.* [133]	2013	Hantavirus	1	1	1	1	1	1	0	2	0	1	2	1
Kaplan *et al.* [134]	2016	Hantavirus	1	1	1	1	1	0	0	2	0	0	3	2
Laverty and Adler [135]	2009	Hantavirus	0	1	0	1	0	0	0	2	0	0	1	1
Luis *et al.* [136]	2018	Hantavirus	1	0	0	1	1	1	0	2	0	0	1	1
Madec and Wolf [137]	2012	Hantavirus	1	1	1	1	0	0	0	2	0	0	1	1
Peixoto and Abramson [138]	2006	Hantavirus	0	1	1	0	0	0	0	2	0	0	1	1
Porcasi *et al.* [139]	2005	Hantavirus	0	1	0	1	1	0	0	2	0	0	1	1
Reinoso and de la Rubia [140]	2013	Hantavirus	0	1	0	1	0	0	0	2	0	1	1	1
Sauvage *et al.* [141]	2007	Hantavirus	1	1	1	1	0	0	0	2	0	0	1	1
Sauvage *et al.* [142]	2003	Hantavirus	0	1	1	1	0	0	0	2	0	0	1	1
Wesley *et al.* [143]	2010	Hantavirus	0	1	1	1	1	0	0	2	0	0	1	1
Wolf [144]	2004	Hantavirus	0	1	1	0	0	0	0	2	0	0	1	1
Wolf *et al.* [145]	2006	Hantavirus	0	1	1	1	0	0	0	2	0	0	1	1
Yusof *et al.* [146]	2010	Hantavirus	0	1	0	1	0	0	0	2	1	0	1	1
Yusof *et al.* [147]	2014	Hantavirus	0	1	0	1	0	0	0	2	1	0	1	1
Babylon *et al.* [148]	2018	Leptospirosis	0	1	1	1	1	0	0	3	0	0	1	1
Baca-Carrasco *et al.* [149]	2015	Leptospirosis	1	1	1	1	0	0	0	3	0	0	1	1
Bennet [150]	1993	Leptospirosis	0	1	0	1	0	0	0	3	1	0	1	1
Buhnerkempe *et al.* [151]	2017	Leptospirosis	0	1	0	1	1	1	0	3	0	0	2	1

Table S3: Studies included within systematic review.

			Components			Model features						Model type	
Author	Year	Disease	Humans	Animals	Environment	Informed parameters	Model validation	Model calibration	Prediction	Animal host	Control Measures	Climate included	Det. or Stoch.	Comp. or IBM
El-Shahed [152]	2014	Leptospirosis	1	1	0	0	0	0	0	3	0	0	1	1
Holt *et al.* [153]	2006	Leptospirosis	0	1	1	1	1	0	0	3	1	1	1	1
Ismail *et al.* [154]	2017	Leptospirosis	1	1	0	0	0	0	0	3	0	0	1	1
Khan *et al.* [155]	2013	Leptospirosis	1	1	0	0	0	0	0	3	0	0	1	1
Khan *et al.* [156]	2014	Leptospirosis	1	1	0	1	0	0	0	3	1	0	1	1
Khan *et al.* [157]	2014	Leptospirosis	1	1	0	1	0	0	0	3	0	0	1	1
Khan *et al.* [158]	2012	Leptospirosis	1	1	0	0	0	0	0	3	1	0	1	1
Khan *et al.* [159]	2016	Leptospirosis	1	1	0	1	0	0	0	3	0	0	1	1
Khan *et al.* [160]	2013	Leptospirosis	1	1	0	1	0	0	0	3	0	0	1	1
Kongnuy and Naowanich [161]	2011	Leptospirosis	1	1	0	0	0	0	0	3	0	0	1	1
Minter *et al.* [162]	2018	Leptospirosis	0	1	1	1	1	1	0	3	1	0	1	1
Okosun *et al.* [163]	2016	Leptospirosis	1	1	0	1	0	0	0	3	1	0	1	1
Pimpunchat *et al.* [164]	2013	Leptospirosis	1	1	0	0	0	0	0	3	0	0	1	1
Pongsumpun [165]	2012	Leptospirosis	1	1	0	1	0	0	0	3	0	0	1	1
Pongsumpun *et al.* [166]	2008	Leptospirosis	1	1	0	1	0	0	0	3	0	0	1	1
Rafiq *et al.* [167]	2019	Leptospirosis	1	1	0	0	0	0	0	3	0	0	1	1
Sadiq *et al.* [168]	2014	Leptospirosis	1	1	0	1	0	0	0	3	1	0	1	1
Triampo *et al.* [169]	2007	Leptospirosis	1	1	0	1	1	0	0	3	0	1	1	1
Zaman *et al.* [170]	2012	Leptospirosis	1	1	0	0	0	0	0	3	0	0	1	1
Mahikul *et al.* [171]	2019	Meloidosis	1	0	0	1	1	1	0	3	0	0	1	1
Bontje *et al.* [172]	2016	Q fever	0	1	1	1	0	0	0	1	1	0	3	1
Courcoul *et al.* [173]	2010	Q fever	0	1	1	1	1	1	0	1	0	0	2	2
Courcoul *et al.* [174]	2011	Q fever	0	1	1	1	1	1	0	1	1	0	2	2
Pandit *et al.* [175]	2016	Q fever	0	1	1	1	1	0	0	1	1	0	2	2
Correia-Gomes *et al.* [176]	2014	Salmonella	0	1	1	1	1	1	0	1	0	0	2	1
Hill *et al.* [177]	2008	Salmonella	0	1	0	1	1	0	0	1	0	0	2	1

Table S3: Studies included within systematic review.

			Components			Model features							Model type	
Author	Year	Disease	Humans	Animals	Environment	Informed parameters	Model validation	Model calibration	Prediction	Animal host	Control Measures	Climate included	Det. or Stoch.	Comp. or IBM
Ivanek and Lahodny [178]	2015	Salmonella	0	1	1	1	0	0	0	1	0	0	1	1
Ivanek *et al.* [179]	2004	Salmonella	0	1	0	1	0	0	0	1	0	0	2	1
Krieter [180]	2004	Salmonella	0	1	1	1	1	0	0	1	0	0	1	1
Lanzas *et al.* [181]	2010	Salmonella	0	1	0	1	1	0	0	1	0	0	2	1
Lanzas *et al.* [182]	2008	Salmonella	0	1	1	1	1	1	0	1	1	0	1	1
Lanzas *et al.* [183]	2008	Salmonella	0	1	0	1	1	1	0	1	0	0	1	1
Nauta *et al.* [184]	2000	Salmonella	0	1	1	1	0	0	0	1	0	0	1	1
Nielsen *et al.* [185]	2007	Salmonella	0	1	1	1	1	1	0	1	0	0	1	1
Nielsen *et al.* [186]	2012	Salmonella	0	1	1	1	1	0	0	1	1	0	2	1
Prevost *et al.* [187]	2006	Salmonella	0	1	1	1	1	0	0	1	0	0	1	1
Ranta and Maijala [188]	2002	Salmonella	0	1	0	1	1	1	0	1	0	0	2	1
Van der Gaag *et al.* [189]	2004	Salmonella	0	1	1	1	0	0	0	1	1	0	2	1
Van Schaik *et al.* [190]	2007	Salmonella	0	1	0	1	1	0	0	1	0	0	1	1
Wang and Xiao [191]	2015	Salmonella	0	1	1	0	0	0	0	1	0	0	1	1
Watier *et al.* [192]	1993	Salmonella	1	0	0	1	1	1	1	1	0	1	1	1
Xiao *et al.* [193]	2005	Salmonella	0	1	1	1	0	0	0	1	1	0	1	1
Xiao *et al.* [194]	2006	Salmonella	0	1	1	1	0	0	0	1	0	0	2	1
Xiao *et al.* [195]	2007	Salmonella	0	1	1	1	0	0	0	1	1	0	3	1
Aranda *et al.* [196]	2008	Toxoplasmosis	1	0	0	1	0	0	0	3	1	-	1	1
Arenas *et al.* [197]	2010	Toxoplasmosis	0	1	1	1	0	0	0	3	1	-	1	1
Cen *et al.* [198]	2014	Toxoplasmosis	0	1	1	1	0	0	0	3	0	-	1	1
Ferreira *et al.* [199]	2017	Toxoplasmosis	1	1	0	0	0	0	0	3	0	-	1	1
Gonzalez-Parra [200]	2009	Toxoplasmosis	1	1	0	1	0	0	0	3	1	-	1	1
Jiang *et al.* [201]	2012	Toxoplasmosis	0	1	1	1	0	0	0	3	0	-	2	2
Li *et al.* [202]	2016	Toxoplasmosis	0	1	1	0	0	0	0	3	1	-	3	1
Mateus-Pinilla *et al.* [203]	2002	Toxoplasmosis	0	1	1	1	0	0	0	3	1	-	1	1

Table S3: Studies included within systematic review.

			Components			Model features						Model type	
Author	Year	Disease	Humans	Animals	Environment	Informed parameters	Model validation	Model calibration	Prediction	Animal host	Control Measures	Climate included	Det. or Stoch.	Comp. or IBM
Rafiq *et al.* [204]	2018	Toxoplasmosis	1	0	0	0	0	0	0	3	0	-	1	1
Turner *et al.* [205]	2013	Toxoplasmosis	0	1	1	1	0	0	0	3	1	-	1	1
Yongzhen *et al.* [206]	2018	Toxoplasmosis	1	1	0	1	0	0	0	3	0	-	1	1
Dobay *et al.* [207]	2015	Tularemia	0	1	0	1	1	0	0	2	0	-	1	1
Gee *et al.* [208]	2012	Tularemia	1	1	1	1	0	0	0	2	1	-	1	1

For model components, informed parameters, model validation, model calibration, prediction, control measures and climate included, 0 and 1 refer to whether or not they were included in the study. For deterministic or stochastic, 1 corresponds to determinstic, 2 corresponds to stochastic and 3 corresponds to both. For compartmental or individual based models (IBM), 1 corresponds to compartmental, and 2 corresponds to IBM. For animal host, 1 is domestic animals, 2 is wild animals and 3 is domestic and wild animals.

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