Understanding and predicting mosquito-borne disease under current and future scenarios of global change

Lydia Holly Vita Franklinos

A thesis submitted for the degree of:

Doctor of Philosophy of University College London

March 2022

Primary supervisor:

Prof. Ibrahim Abubakar

Secondary supervisors:

Prof. Kate E. Jones

Tertiary supervisors:

Dr. David W. Redding
Dr. Rory J. Gibb

Institutions:

Institute for Global Health &
Centre for Biodiversity and Environment Research,
University College London,
London WC1E 6BT

2

I, Lydia Holly Vita Franklinos, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, these are indicated in the thesis. The contributions of co-authors to specific chapters are described in full in the thesis outline.

Abstract

There is a rapidly growing awareness of the influence of global change processes such as land-use, climate change and socioeconomic factors on the burden of mosquito-borne disease (MBD). Although individual effects of different processes on MBD risk have been studied widely, a holistic approach that considers the combined influence of different global change processes has rarely been implemented. Here, I evaluate the effects of different global change processes on MBD risk, both generally, and in a series of modelling studies using the understudied MBD, Japanese encephalitis (JE) as a case study. I integrate different data types and approaches from ecology and epidemiology, with the aim of informing public health decision-makers in the era of accelerating global change. Firstly, I synthesise current knowledge on relative and interacting effects of global change processes on MBD risk and examine how these factors have been incorporated into existing analyses, highlighting how future research could be improved. Secondly, I compile a vector surveillance database for the predominant vector of JE (*Culex tritaeniorhynchus*). I use a novel approach that leverages information from sparse vector surveillance data to predict seasonal vector abundance over large spatial scales, that has the potential to be used to provide guidance for the targeting of suitable interventions. I use this information in an epidemiological study of JE case surveillance data and show that human JE incidence is associated with climate, land-use and socioeconomic factors, and these factors can be used to predict JE outbreaks in north-eastern India. Thirdly, I examine possible trends in JE epidemiology by projecting into the future under various scenarios of global change to show divergence in JE risk and burden under different socioeconomic and environmental policy scenarios. Finally, I integrate the implications of these results into our understanding of the effects of global change processes on MBD, the epidemiology and control of JE, and a holistic approach to the understanding and prediction of MBD risk.

Impact statement

The latest Intergovernmental Panel on Climate Change (IPCC) report (IPCC, 2022) provides a stark overview of the effects of human-induced environmental change on the health of nature and humans, signalling that the "people and ecosystems least able to cope are being hardest hit". Mosquito-borne diseases (MBDs) are an example of a negative health outcome that results from changing environmental conditions that disproportionately affect economically vulnerable populations (Colón-González, *et al.*, 2021a; IPCC, 2022). Despite the growing threat MBDs pose to global public health, a lack of evidence on the drivers of these diseases has hindered our understanding of present-day burdens and how disease risk may vary under future scenarios of global change (Campbell-Lendrum *et al.*, 2015).

This thesis applies tools and concepts from ecological and epidemiological modelling to understand how socio-ecological factors affect MBD risk, both in general and for a case study of Japanese encephalitis (JE) in India. Understanding the effects of different global change processes on understudied MBDs such as JE is hindered by the lack of reliable, high quality surveillance data on mosquito vectors. In Chapter 3, I addressed gaps in vector surveillance data using a novel modelling approach to estimate seasonal vector abundance for the main vector for JE across India. This work was published in 2022 in PLOS Neglected Tropical Diseases and details a methodology that is easily adaptable for other MBDs that have limited vector surveillance data. Consequently, the findings from this Chapter will be of significant interest for academic research and policy audiences in ecology and public health sectors.

The findings from Chapters 3 to 5 will contribute significantly to public health efforts to prevent and control JE, the leading cause of viral encephalopathy in Asia. This work improves understanding of current and future potential endemic areas of JE and the important underlying drivers of this disease in India. These findings will help public health practitioners and policymakers to communicate and develop effective and efficient interventions to safeguard public health with ongoing global changes.

In Chapter 2, I reviewed MBD modelling studies and found that there has been significant research on the role of climate change. This review was published in 2019 in Lancet Infectious Diseases and concludes that MBD research should not only focus on the role of climate change but consider growing evidence for additional factors that modulate disease risk. Chapter 5 address this gap by evaluating how future climatic, agricultural, and socioeconomic change may impact JE risk in northeast India over the coming decades. This work represents a step towards incorporating MBD risk into public health and environmental policy decisions to identify trade-offs across land-use, climate, food security and human health. Consequently, the subject matter and findings will be of significant interest for academic research and policymakers across public health, agricultural and environmental sectors, as well as being of broader public interest.

Acknowledgements

To my best friend, confidante, little brother Theo, I completed this thesis for you.

To my loving partner Tom, who provided endless support, encouragement, and joy that were essential for me to continue with my thesis.

To mum, for her support and for always being willing to read countless drafts.

To my baby growing inside me, whose kicks and shoves kept me going during difficult times.

To my dad and friends for their support and encouragement.

To Rory, for all his help in shaping me from the vet I was to the scientist I now am.

To Kate, for providing me with female role model in academia and for her encouragement, support, and helping me to always see the bigger picture.

To Dave, for his inspiring outlook and infectious curiosity.

To Ibrahim, for showing me that despite academic success, you can always make time to support people.

Reproducibility and data access

Data and code (where not freely available online) used in the analysis chapters are provided in the accompanying linked repositories, and full lists of all data sources are provided in the appendices for each chapter. Repository links are included in the end notes for each chapter.

Table of contents

Thesis outline of contents and collaborators

Chapter 1

Introduction

This chapter reviews current knowledge of the effects of climate, land-use and socioeconomic change on mosquito-borne disease (MBD) risk. Some of the material from this introduction and the discussion (Chapter 6) is published in an Analysis article at BMJ under the title "Ecosystem perspectives are needed to manage zoonotic disease risks in a changing climate".

Chapter 2

The impact of global change on mosquito-borne disease

In this chapter, I review and synthesise the current state of knowledge on the impact of global change processes on MBD risk to identify knowledge and data gaps for later chapters. This work was conducted in collaboration with Ibrahim Abubakar, Kate E. Jones, and David W. Redding. I undertook the literature review and wrote the paper with feedback from all co-authors. This chapter was published in 2019 in the journal Lancet Infectious Diseases under the title 'The impact of global change on mosquito-borne disease' (Franklinos, *et al.*, 2019), and the typeset published paper is provided in Appendix 5. I have presented this chapter at the 2018 Planetary Health Meeting (Edinburgh). Additional thanks to R. Gibb, S. Daly, and F. Spooner.

Chapter 3

Joint spatiotemporal modelling reveals seasonally dynamic patterns of Japanese encephalitis vector abundance across India

In this chapter, I develop a novel modelling approach to predict seasonal vector abundance for the predominant Japanese encephalitis (JE) vector across India, as well as to examine the environmental drivers of these patterns. The work was conducted in collaboration with DWR, KEJ, IA, Rory J. Gibb, and Tim C.D. Lucas. This work was published in PLOS Neglected Tropical Diseases under the title 'Joint spatiotemporal modelling reveals seasonally dynamic patterns of Japanese

encephalitis vector abundance across India', and the typeset published paper is provided in Appendix 5. Additional thanks to L. Enright, E. Browning, and S. Daly.

Chapter 4
Climate, land-use and socioeconomic factors predict spatiotemporal dynamics of Japanese encephalitis risk

In this chapter, I conduct spatial and temporal epidemiological analyses of the socio-ecological drivers of JE in northeast India, predict endemic areas of transmission, and evaluate whether environmental factors and vaccination coverage can be used to predict temporal trends in JE incidence. The work was conducted in collaboration with RJG, TCDL, DWR and KEJ. Additional thanks to S. Daly.

Chapter 5
Predicting Japanese encephalitis risk under different scenarios of global change

In this chapter, I evaluate how future climatic, agricultural, and socioeconomic change may impact JE risk in northeast India. The work was conducted in collaboration with RJG and KEJ. Additional thanks to S. Daly.

Chapter 6
Discussion

In this chapter I review and discuss the key conclusions and contributions of the thesis, and propose recommendations for future research, with an emphasis on the importance of adopting a holistic approach to the understanding and prediction of MBD risk.

List of main text tables

List of main text figures

Chapter 1:
Introduction

1.1   Understanding the effects of global change on human health

There is a rapidly growing awareness of the connection between human health and the state of natural systems on which societies depend (Whitmee *et al.*, 2015). Humans rely on nature to provide essential services such as food, water, shelter, medicine, and to mitigate climatic extremes and emerging diseases (IPBES, 2019). However, human exploitation of the environment has resulted in natural systems being degraded to an unprecedented extent (Whitmee *et al.*, 2015), leading to dramatic environmental changes that include deforestation, agricultural and urban expansion, and climate change. Indeed, it is suggested that the planetary boundaries within which humans can thrive have already been transgressed (Steffen *et al.*, 2015). Human health is an increasingly apparent outcome of environmental degradation, characterised by wide-ranging changes in food and water security, climate regulation, and dynamics of emerging and endemic diseases (Hassell *et al.*, 2021a). Several holistic approaches have emerged to identify and address ways in which anthropogenic impacts on natural systems are adversely affecting human and animal health (Lerner and Berg, 2017). Whereas One Health advocates an interdisciplinary health sciences approach to safeguard health at the interface between humans, animals, and their environment, the EcoHealth concept focuses on the relationship between health, ecosystems, and sustainable development (Lerner and Berg, 2017). Planetary Health has been put forward as an alternative to these approaches which have suffered from siloed thinking (Manlove *et al.*, 2016), and instead promotes a systems approach to understanding how human health outcomes are influenced by complex interactions between social and natural systems (Pongsiri *et al.*, 2017).

Infectious diseases are emerging at an increasing rate globally (Smith *et al.*, 2014). Importantly, approximately two thirds of emerging infectious diseases are zoonoses, diseases of animals that can be transmitted to humans (CDC, 2017), and the majority (72%) of these have a wildlife origin (Jones *et al.*, 2008; Allen *et al.*, 2017). As

illustrated with the emergence of SARS-CoV-2 virus, zoonotic emerging infectious diseases pose a significant threat to global health, global economy and global security (Grace *et al.*, 2012a; Morens and Fauci, 2012; Heymann *et al.*, 2015). Given that the increased incidence of outbreaks has occurred in tandem with habitat degradation, environmental change is suggested to impact human health (Gibb, Moses, Redding and Jones, 2017; Hassell *et al.*, 2017; MacDonald and Mordecai, 2019; Plowright *et al.*, 2021). Indeed, many drivers of the global infectious disease emergence have been linked to the increasing rate of human impact on the environment and ecosystems (Whitmee *et al.*, 2015; Hassell *et al.*, 2021a). For example, land-use change, such as deforestation, urbanisation, agricultural land conversion and intensification, increases the risk of zoonotic disease emergence by altering species composition in ecological communities to favour wildlife hosts and increasing contact between people, vectors (e.g., mosquitoes, ticks), domestic animals and wildlife (Romanelli *et al.*, 2015; Hassell *et al.*, 2017; Gibb *et al.*, 2020a; Plowright *et al.*, 2021). In addition, climate change further impacts infectious disease emergence either directly by promoting climate-sensitive diseases such as those transmitted by vectors, or indirectly via effects on human vulnerability to disease (e.g., nutrition, poverty) (Watts *et al.*, 2021) and biodiversity (Romanelli *et al.*, 2015).

Viewing infectious disease systems from an ecological perspective whereby the diseases are situated at the nexus between environmental change, ecosystems, and health, could significantly improve understanding of how global change impacts human health (Gibb *et al.*, 2020b). For instance, ecological theories and perspectives have already been embedded in public health management of many zoonoses, and have been influential in existing disease control programmes such as the eradication of rabies in wildlife in Western Europe (Smith *et al.*, 2008) and management of leptospirosis and dengue in urban centers (Reis *et al.*, 2008; Seidahmed *et al.*, 2018). In particular, knowledge of the strong influence of environmental conditions on vector life histories (Patz *et al.*, 2000; Ciota *et al.*, 2014; Verhoef, Venter and Weldon, 2014; Ladeau *et al.*, 2015; Paul *et al.*, 2016; Mordecai *et al.*, 2019) has enabled the prediction of climatic and land-use-associated geographic and seasonal trends in estimates of vector-borne disease (VBD) risk (Baeza, *et al.*, 2011; Baeza *et al.*, 2017; Leta *et al.*, 2019; Purse *et al.*, 2020; Colón-González *et al.*, 2021a; Diuk-Wasser, VanAcker and Fernandez, 2021; Lowe *et al.*,

2021; Peralbo-Moreno *et al.*, 2022). Modelling approaches that incorporate ecological processes are gaining traction in VBD research (Sokolow *et al.*, 2015, 2017; Childs *et al.*, 2019; Ryan *et al.*, 2019), for example, seasonal climatic variations have been used to predict outbreaks of Rift Valley fever in East Africa (Anyamba, Chretien, Small and Tucker, 2009), dengue in South America (Lowe *et al.*, 2017a) and cutaneous leishmaniasis in South America (Lewnard *et al.*, 2014), helping to inform mitigation actions.

In order to fully understand the impact of environmental processes, it is also critical to account for other influences such as the socioeconomic factors that drive human exposure and vulnerability to infection (Parham *et al.*, 2015). For instance, climate-based predictions of dengue outbreaks are improved when information on population immunity is included in the models (McGough *et al.*, 2021). In the future, changing climates, widespread anthropogenic transformations of natural landscapes (e.g., urbanization, agricultural expansion and intensification) and socioeconomic change will lead to shifts in the way reservoir hosts, vectors and humans interact, and impact disease systems (Lafferty, 2009; Dahlgren *et al.*, 2016; Ryan *et al.*, 2019; Gibb *et al.*, 2020a). Recent modeling advances that incorporate ecology and epidemiology show great potential for predicting future disease risk and for testing the effects of interventions within projected scenarios of global change (Iacono *et al.*, 2018; Li *et al.*, 2019; Childs *et al.*, 2019; Redding *et al.*, 2019; Lund *et al.*, 2021).

Although the link between human health and natural and anthropological systems is becoming clearer (Whitmee *et al.*, 2015), major gaps in knowledge remain in the underlying mechanisms by which environmental degradation endangers human health (Hassell *et al.*, 2021a; Plowright *et al.*, 2021). Therefore, it has been difficult to clearly communicate the importance and impact of environmental change on human health to policymakers. As a result, current global health policy often does not adequately consider the importance of natural systems in promoting health, and the negative impact their disruption can have (Waugh, Lam and Sonne, 2020; Hassell *et al.*, 2021a). The One Health concept, has attempted to strengthen the links between human, animal and ecosystem health (Lerner and Berg, 2015; One Health Commission, 2021) and to guide research and policy in the field of emerging infectious diseases (Galaz *et al.*, 2015). Although this approach has been widely

embraced by public health communities and policymakers (WHO, FAO and OIE, 2019), in practice it has tended to focus mainly on human-livestock interactions on a relatively local scale (Falzon *et al.*, 2018). It has been concluded that safeguarding human health in the era of dramatic global change requires a considerable framework shift together with the integration of the broader Planetary Health concept across scientific fields and policy (Waugh, Lam and Sonne, 2020).

1.2   Understanding mosquito-borne disease through a socio-ecological lens

More than 17% of the global burden of infectious disease is attributable to VBDs and over 80% of the global population is at risk of one of more vector-borne pathogens (WHO, 2017). Researchers have concluded that diseases transmitted by arthropod vectors such as mosquitoes, ticks and midges pose an increasing threat to human health (National Academies of Sciences, Engineering and Medicine, 2016; James *et al.*, 2018). In particular, diseases transmitted by mosquito vectors account for the highest number of reported VBD-associated cases, deaths, and disability-adjusted life years worldwide (WHO, 2017). This is partly due to the wide variety of pathogens that they can transmit, ranging from parasites such as malaria and lymphatic filariasis to multiple viruses, including West Nile, yellow fever, dengue, chikungunya and Zika (Reiter, 2001; Tolle, 2009). Many mosquito-borne diseases (MBDs) are zoonotic and exist within sylvatic cycles that perpetuate new outbreaks through spillover from animal host populations into humans (Gould and Solomon, 2008; Fornace *et al.*, 2016; Ali *et al.*, 2017; Pandit *et al.*, 2018).

Globally, MBDs have been reported to be increasing in incidence and have expanded their geographic distribution emerging in new areas (Stanaway *et al.*, 2016; Ali *et al.*, 2017; Paixão, Teixeira and Rodrigues, 2017) and re-emerging in non-endemic regions (Buonsenso *et al.*, 2014; Grobbelaar *et al.*, 2016). This is exemplified by the dramatic geographic expansion of Zika virus in the Americas since 2015 (Ali *et al.*, 2017) and the global emergence and resurgence of dengue virus that has resulted in a 30-fold increase in disease incidence since the 1980s (Gubler, 2011; Bhatt *et al.*, 2013; Stanaway *et al.*, 2016). Climate change, land-use change and socioeconomic factors (e.g., poverty, trade and travel) have all been implicated

in the increasing threat of MBDs on global health (Jones *et al.*, 2008; Kilpatrick and Randolph, 2012; Roche *et al.*, 2013; Parham *et al.*, 2015). Although the impact of global change processes on MBD transmission is undoubtedly important, it is also highly uncertain due to limitations in knowledge, data and methodological approaches that can integrate the diverse epidemiological, ecological and socioeconomic factors driving disease risk (Parham *et al.*, 2015).

The changing pattern of MBD risk is substantially determined by the relationship between mosquito vectors and their environment which may vary spatially and temporally (Ladeau *et al.*, 2015; Tjaden *et al.*, 2018). Since mosquitoes are ectothermic, ambient temperatures influence epidemiologically significant life history traits, such as survival, dispersion, feeding, reproduction and development (Mordecai *et al.*, 2019). Precipitation can positively impact mosquito populations by creating aquatic habitats for their breeding (Morin, Comrie and Ernst, 2013). However, excess rainfall can result in larval habitats being destroyed (Stewart Ibarra *et al.*, 2013). Mosquito breeding habitat availability also depends on species-specific preferences and other factors that influence the development of water bodies, such as land-use type and intensity (Erlanger *et al.*, 2005; Keiser *et al.*, 2005a; Day and Shaman, 2008; Baeza *et al.*, 2011).

Interactions between land-use and climate can also influence MBD risk (Lowe *et al.*, 2021). Since mosquito ecology is dependent on the environment, any change in habitat due to land-use conversion will have a significant effect on populations (Ladeau *et al.*, 2015). For instance, deforestation is reported to influence mosquito populations by providing ideal vector breeding habitats (Vittor *et al.*, 2009), reducing competition and predation (Burkett-Cadena and Vittor, 2017) and increasing interactions between vectors and hosts (Despommier, Ellis and Wilcox, 2006; Gibb *et al.*, 2020a). This has been demonstrated by the strong association between MBD incidence and practices associated with deforestation, such as mining, logging and road construction (Vasconcelos *et al.*, 2001; Hahn *et al.*, 2014; Fornace *et al.*, 2016; Chaves *et al.*, 2018; Brock *et al.*, 2019; Fletcher *et al.*, 2019). Increasing urbanisation has promoted the emergence and spread of MBDs such as dengue, Zika virus disease and chikungunya due to the proliferation of urban-adapted *Aedes* mosquitoes (Gubler, 2011; Li *et al.*, 2014; Baker *et al.*, 2021). Furthermore, water

19

management practices such as irrigated agriculture have been reported to promote MBD risk globally (Ijumba and Lindsay, 2001; Erlanger *et al.*, 2005; Keiser *et al.*, 2005b; Baeza *et al.*, 2011; Kibret *et al.*, 2016).

Land-use change may also interact with socioeconomic factors which can further influence MBD dynamics. For example, it has been observed that the introduction of irrigation systems into an area leads to an initial increase in MBD risk followed by a decline. This phenomenon known as the 'paddies paradox', has been reported for malaria in Africa (Ijumba and Lindsay, 2001) and Asia (Mukhtar *et al.*, 2003; Baeza *et al.*, 2011). The effect is thought to reflect the increasing socioeconomic status of people who live near irrigation schemes as they can afford improved education, housing conditions, or other types of protection from mosquitoes (Ijumba and Lindsay, 2001). Bidirectional feedback between land-use conversion and MBD incidence has also been reported in the Amazon, where deforestation was found to significantly increase malaria transmission and high malaria burdens reduced deforestation, likely mediated by human behaviour or economic development (MacDonald and Mordecai, 2019).

Socioeconomic factors such as poverty, public infrastructure, human behaviour, trade and travel are recognised as important drivers of MBD risk (Reiter *et al.*, 2003; Ali *et al.*, 2017; Oviedo-Pastrana *et al.*, 2017; WHO, 2020a; Athni *et al.*, 2021; Baker *et al.*, 2021). Poverty can increases the risk of MBDs since it determines the quality and accessibility of health care, affects education, access to running water and reduces ameliorative measures such as limiting outdoor activities, vector protection and vaccination (Reiter *et al.*, 2003; Lambin *et al.*, 2010; Oviedo-Pastrana *et al.*, 2017). In addition, poverty greatly impacts the lifestyle and regional environment of populations, which have been reported as important drivers of morbidity and mortality (Ye *et al.*, 2023). For example, housing conditions which are an indicator of poverty (UNDP and OPHI, 2021), can influence the number of infected vectors via sanitation conditions that promote mosquito breeding sites (e.g., inadequate water supply leading to water storage and refuse collection services) (Russell *et al.*, 2009; Lowe *et al.*, 2021) and can influence exposure to pathogens via protective measures such as mosquito screens (Reiter *et al.*, 2003). In addition, poverty influences exposure to pathogens since the capital of impoverished people is often biological (e.g., crops,

livestock, forests, wildlife) and this capital is embedded within systems of ecological interactions that include human pathogens (Godfrey and Randolph, 2011; Ngonghala *et al.*, 2014, 2017). Accordingly, a strong association between poverty and MBD risk has been reported for neglected tropical diseases (NTDs) such as Zika (Hotez, 2016; Ali *et al.*, 2017; WHO, 2020a). Vector-borne NTDs disproportionately affect economically deprived populations and can lead to 'poverty traps'; a self-reinforcing mechanism enabling poverty and diseases to persist (Bowles, Durlauf and Hoff, 2006; Hotez *et al.*, 2009). In affected countries, MBDs impose a great burden on maternal and child health, population growth, investment, productivity, and labour and impede socioeconomic development (Sachs and Malaney, 2002; Hotez *et al.*, 2009; Sarma *et al.*, 2019). However, some studies have suggested that since evidence linking poverty and MBD risk is mainly observational and does not account for co-morbidities or inequalities in care-seeking behaviour, it is too weak to support causal relationships (Utzinger and Tanner, 2013; Mulligan *et al.*, 2015). Advances in the modelling of coupled economic–epidemiological systems have improved understanding of the structural relationship between disease risk and economic growth (Ngonghala *et al.*, 2014, 2017; Baeza *et al.*, 2017; Sokolow *et al.*, 2022). A study investigated how socioeconomic processes that occur during land-change affect malaria epidemiology and included poverty in their model by having poverty influenced by capital (e.g. products) which affects access to disease protection and treatment (Baeza *et al.*, 2017). Therefore, in this model economic prosperity reduces the vulnerability of populations to malaria by reducing the possibility that exposure to infected vectors will result in disease. Studies on other VBDs have described mechanisms by which poverty influences disease vulnerability via reduced resistance to infection associated with stress and limited access to vaccination (Godfrey and Randolph, 2011). Furthermore, VBDs may influence the dynamics of poverty via their effect on labour, leading to shocks in agricultural yield (Rinaldo *et al.*, 2021). The geographic spread of MBDs may also be related to increasing wealth associated with globalisation (IOM, 2008) which has resulted in an expansion of movement of people, animals and commodities, together with pathogens and vectors (Githeko *et al.*, 2000; Gubler, 2011; Nunes *et al.*, 2014; Kampen *et al.*, 2016; Baker *et al.*, 2021). Indeed, human factors such as behaviour, population immunity, and age distribution are critical in shaping patterns of disease risk (Funk, Salathé and Jansen, 2010). Behavioural risk factors for VBDs include protective practices (Dutta *et al.*, 2011;

Aerts *et al.*, 2020; Bron *et al.*, 2020), human movement (Stoddard *et al.*, 2009), recreational behaviour (Trienekens *et al.*, 2022), housing conditions (Seidahmed *et al.*, 2018; Chastonay and Chastonay, 2022), and scepticism surrounding immunisation (Saikia, 2017; Sakamoto *et al.*, 2019). The age distribution of the population, age-related behaviours and the associated seroprevalence in different age groups also has a major impact on the spatiotemporal distribution of VBD risk (Li *et al.*, 2016; Kwak, Hong and Kim, 2021; Kugeler *et al.*, 2022; Trienekens *et al.*, 2022). Additionally, socioeconomic factors may influence MBD risk in a way that complicates understanding of environmental drivers (Béguin *et al.*, 2011; Parham *et al.*, 2015). For example, following natural disasters changes in public infrastructure, healthcare access, water storage and housing quality can expose people to a high density of infected mosquitoes (Ali *et al.*, 2017). Furthermore, the international export of commodities such as timber, tobacco, cocoa, coffee and cotton has been estimated to drive approximately 20% of the risk of malaria in deforestation hotspots (Chaves *et al.*, 2020).

Identifying hotspots of MBD risk is critical for informing effective interventions and safeguarding public health (Smith, Dushoff and McKenzie, 2004). However, definitions of risk remain inconsistent (Johnson, Escobar and Zambrana-Torrelio, 2019). This can confound the different processes contributing to risk and hinder accurate quantification and comparisons between studies (Hosseini *et al.*, 2017). The field of quantitative risk analysis can be used to understand risk by breaking down the different processes into hazard, exposure and vulnerability of the risk (Stamatis, 2014). Using this framework, 'hazard' is the relative number of available pathogens acting as potential sources of risk to a target population; 'exposure' is the likelihood of contact between a target population and the hazards; 'vulnerability' is the possibility of a given exposure to a hazard that results in harm (Hosseini *et al.*, 2017; Johnson, Escobar and Zambrana-Torrelio, 2019) (Figure 1.1). Exposure factors may include labour (e.g., agricultural work) or cultural (e.g., behavioural practices) factors that influence physical exposure to the hazard. Vulnerability factors may include socioeconomic (e.g., poverty, age, inequality, immunocompromised people, displaced people) or infrastructure (e.g., healthcare access, road density) factors influencing the possibility that a given exposure to a hazard results in harm. For example, populations that live in areas of economic insecurity and/or political

instability will be more vulnerable to disease outbreaks since they may have reduced access to healthcare infrastructure and less trust of public health resources (Hosseini *et al.*, 2017). Other infectious disease risk frameworks combine hazard and exposure and separate vulnerability which includes socioeconomic factors (e.g., inequality, poverty) and vulnerable groups (e.g., children, displaced people, food insecurity, health conditions), from coping capacity which considers the availability of resources such as physical infrastructure (e.g., road density, sanitation), governance, communication (e.g., internet use, adult literacy rates) and healthcare access (Marin-Ferrer, Vernaccini and Poljansek, 2017; Wong *et al.*, 2020). A recent study on tick-borne disease risk included coping capacity in simulation models via effects of tick removal due to public awareness and found that awareness in high hazard areas had a strong impact on tick bite incidence (Vanwambeke and Schimit, 2021). However, awareness also modified the areas and populations at the highest risk, revealing the dynamic nature of coping capacity. Overall, separating the different components of risk will help to determine how global change drivers may act differently on each (Hosseini *et al.*, 2017). Indeed, environmental changes such as agricultural expansion, rapid urbanisation and increases in extreme weather can both exacerbate the hazards (e.g., presence and abundance of mosquito vectors and hosts which comprise MBD hazard (Kilpatrick and Pape, 2013)), and amplify existing vulnerabilities (e.g., food and water insecurity, social inequalities) (Cardona *et al.*, 2012; Hosseini *et al.*, 2017). Considering the different component of risk in model-based analyses could also help to disentangle the consensus and discord between different future climate, land-use and disease models (Caminade *et al.*, 2014), supporting long-term strategic planning in both health and environmental sectors.
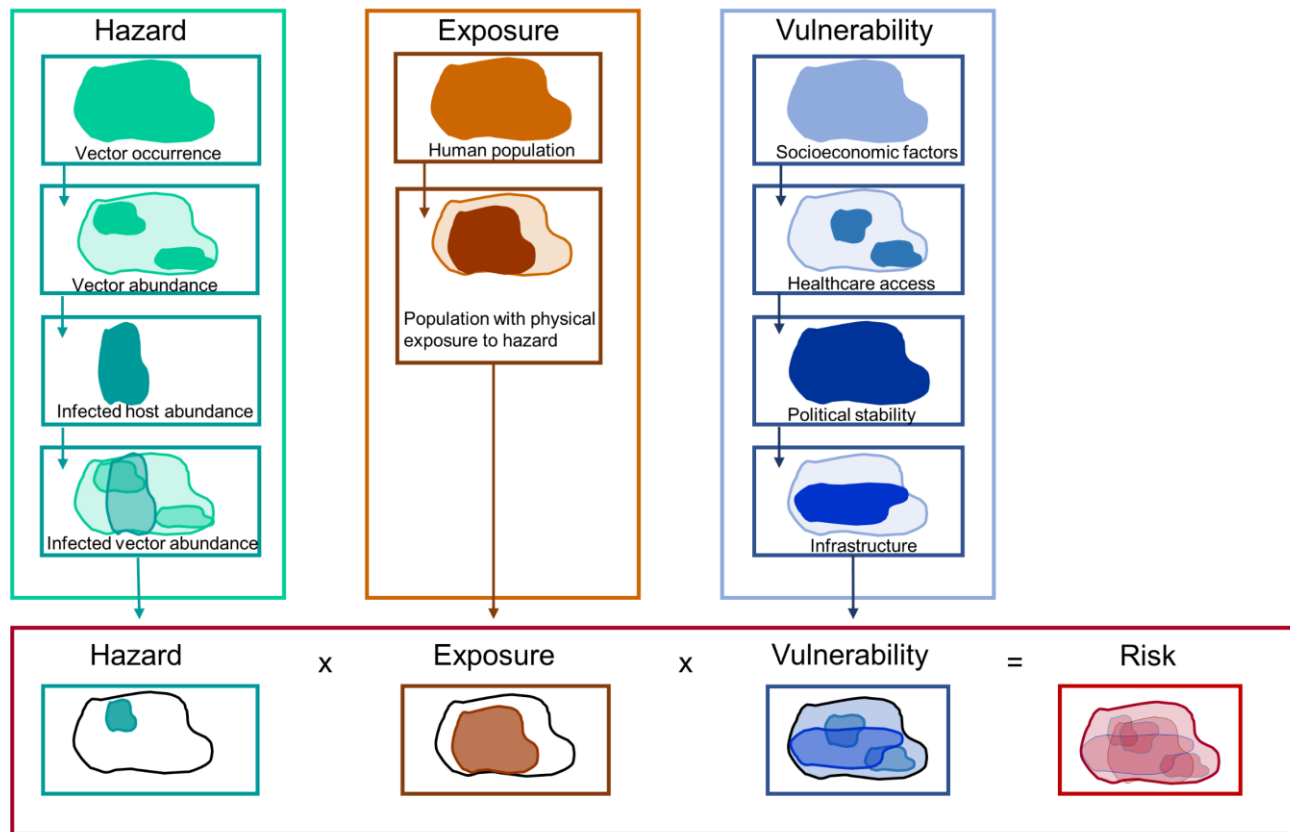
Figure 1.1. Mosquito-borne disease risk conceptual model.

MBD risk can be broken down into 'hazard' which is the available infected vectors acting as potential sources of risk to a target population; 'exposure' which is the likelihood of contact between a target population and the hazards and 'vulnerability' which is the possibility of a given exposure to a hazard that results in harm. Coping capacity (i.e., resources available to alleviate the impact of disease outbreaks) is included within the vulnerability component of this framework.

24

1.3 Challenges in the understanding and prediction of the effects of global change on mosquito-borne disease risk

Considering the complexities of how different global change processes act and interact to influence MBD risk highlights the limitations of previous approaches to understanding disease systems which have concentrated on epidemiology and public health perspectives (Bedford *et al.*, 2019). MBD research conducted through an epidemiological or public health lens primarily focuses on transmission dynamics of the infection in host and vector populations (Mandal, Sarkar and Sinha, 2011; Amaku *et al.*, 2016) and rarely integrates ecological understanding (Gibb *et al.*, 2020b). Moreover, when ecological information is incorporated into the studies, the focus is often on the role of climate in shaping the geographic range of potential MBD transmission related to climate-sensitive traits of the mosquitoes (Caminade *et al.*, 2014; Parham *et al.*, 2015; Tjaden *et al.*, 2018; Rocklöv and Dubrow, 2020). This is also true for other VBDs such as those transmitted by ticks and biting midges (González *et al.*, 2010; Moo-Llanes *et al.*, 2013; Ogden *et al.*, 2014a; Parham *et al.*, 2015; Williams *et al.*, 2015; Alkishe, Peterson and Samy, 2017; McPherson *et al.*, 2017). Although research on the impact of climate change on the risk and distribution of MBDs has been recognised and has informed many policy briefs worldwide (IPCC, 2014a; Watts *et al.*, 2021) sole focus on the effects of climate have reinforced knowledge gaps on the impact of different global change drivers and how they might interact to influence MBD risk (Campbell-Lendrum et al., 2015).

Quantifying and predicting the effects of different global change processes on MBD risk is hindered by the complexity of how these relationships and interactions may vary across different disease systems, landscapes, and timeframes (Campbell-Lendrum *et al.*, 2015). For example, while climate change is implicated in driving the geographic distribution and increasing burdens of many MBDs and their vectors (Caminade *et al.*, 2014; Feachem *et al.*, 2019; Ryan *et al.*, 2019; Iwamura, Guzman-Holst and Murray, 2020; Colón-González *et al.*, 2021a), it is unclear whether this trend is consistent when the effects of non-climatic global change processes such as environmental, social, economic and demographic factors are also considered (Parham *et al.*, 2015). Knowledge of MBD drivers also varies depending on the

disease, with underlying drivers remaining poorly defined for many diseases (Gibb *et al.*, 2020b; Swei *et al.*, 2020), especially for understudied MBDs (e.g., NTDs) that often do not have sufficient resources or available long-term systematic surveillance data (Malecela, 2019; WHO, 2020a).

There is a paucity of reliable, high quality surveillance data on vectors (ECDC and EFSA, 2018; Rund *et al.*, 2019), reservoir host populations (Britch *et al.*, 2013; Lord, Gurley and Pulliam, 2015; DeCarlo *et al.*, 2017; Pandit *et al.*, 2018) and human incidence, especially for marginalised communities (Lowe *et al.*, 2020) and NTDs (WHO, 2020a). This has led to the popularity of correlative models such as ecological niche models (ENMs; otherwise known as species distribution models) in MBD research to predict vector, pathogen and MBD risk distributions (Kraemer *et al.*, 2016; Tjaden *et al.*, 2018; Johnson, Escobar and Zambrana-Torrelio, 2019). Although useful in instances of incomplete data or undefined environmental associations (Phillips, Anderson and Schapire, 2006; Redding *et al.*, 2016), these correlative models do not enable the identification of underlying causal relationships (Kraemer, Reiner and Bhatt, 2019) and tend to assume linear and non-hierarchical relationships for covariates, reducing their applicability to novel settings (Washburne *et al.*, 2019). Furthermore, ubiquitous sampling biases in surveillance data and a lack of ecological information on the vector, pathogen and reservoir hosts within a disease system may impede the ability of models to predict distributions correctly (Johnson, Escobar and Zambrana-Torrelio, 2019). In addition, surveillance data are often aggregated at coarse spatial scales which results in a loss of local socio-ecological information associated with the outbreak (Allen *et al.*, 2017). These issues confound interpretation of spatial patterns and trends, and impede the ability of these models to predict current and future scenarios of MBD risk and the opportunity to inform public health interventions (Campbell-Lendrum *et al.*, 2015; Parham *et al.*, 2015).

Gaps in data and knowledge of underlying drivers hinders understanding of present-day MBD burdens and how disease risk may vary under future scenarios of global change (Campbell-Lendrum *et al.*, 2015). Furthermore, reliance on simple correlative models such as ENMs to define risk without considering the complexity of disease systems may compound this lack of understanding (Johnson, Escobar and Zambrana-Torrelio, 2019). Instead, separating the different components of MBD risk

and considering how global change processes may act on each separately, may provide a solution in the study of complex MBD systems and inform which interventions to use and crucially, where, when, and how to implement them (Hosseini *et al.*, 2017). A recent study on VBD schistosomiasis in Senegal used this approach to disentangle and identify the impacts of social (i.e., exposure and vulnerability) and environmental (i.e., hazard) processes on disease risk, and highlighted the importance of including both social and environmental interventions in the model (Lund *et al.*, 2021). This methodology is complemented by conceptual developments that have distilled the complex mechanisms underpinning zoonotic pathogen spillover (Plowright *et al.*, 2017). The conceptual framework proposed by Plowright *et al.*, (2017) provides a clear structure with which to model and interpret the effect of different drivers on the separate components of risk for diverse disease systems. Recent VBD studies have used this framework to show the importance of ecological interactions between environment, vectors and hosts in determining disease risk (Childs *et al.*, 2019; Burthe *et al.*, 2021). Such approaches emphasise the connection between natural and social systems and provide insights into opportunities to safeguard human and environmental health simultaneously.

1.4 Opportunities for a socio-ecological/holistic approach in the understanding and prediction of mosquito-borne disease risk

In this thesis, I use a socio-ecological systems-based approach to assess and predict the effects of global change on MBD. While, climate, land-use and socioeconomic factors are key drivers of MBD, the relative and combined effect of these processes is unclear (Sutherst, 2004; Tabachnick, 2010; Parham *et al.*, 2015). By adopting an integrative approach and considering the influence of different global change processes, I aim to challenge previous siloed-thinking and help to inform best policy practices for public health, land planning and environmental policy decision-makers.

I use Japanese encephalitis (JE) in India as a case study since it is a relatively understudied MBD (LaBeaud, 2008) despite it being a leading cause of viral encephalopathy in Asia (Campbell *et al.*, 2011; Quan *et al.*, 2020). The causative pathogen, Japanese encephalitis virus (JEV), is maintained in an enzootic

transmission cycle between *Culex* mosquitoes (van den Hurk, Ritchie and Mackenzie, 2009; Pearce *et al.*, 2018) and vertebrate hosts including domestic pigs and ardeid wading birds (e.g. herons and egrets) (Buescher *et al.*, 1959; van den Hurk, Ritchie and Mackenzie, 2009; Le Flohic *et al.*, 2013) (Figure 1.2). Although susceptible to the virus, humans, and other mammals such as cattle and horses are considered 'dead-end' hosts because they do not mount sufficient viraemia to infect mosquitoes. Since first described in Japan in 1935, JEV has spread across the region (Mackenzie, Gubler, and Petersen 2004) and now is endemic in 24 Asian and Western Pacific countries (Erlanger et al. 2009; Campbell et al. 2011). Since JE is not notifiable in most Asian countries, the true burden of the disease remains unknown and instead has been estimated by systematic reviews (Campbell *et al.*, 2011; Quan *et al.*, 2020). A 2020 systematic review of JE disease burden estimated that approximately 100,000 cases and 25,000 deaths occur globally each year, primarily affecting children and those living in rural, agricultural areas (Baig *et al.*, 2013; Quan *et al.*, 2020). However, 87% of JE cases in Asia come from just four countries; India, Nepal, China, and Vietnam (Heffelfinger *et al.*, 2017; Lindquist, 2018).
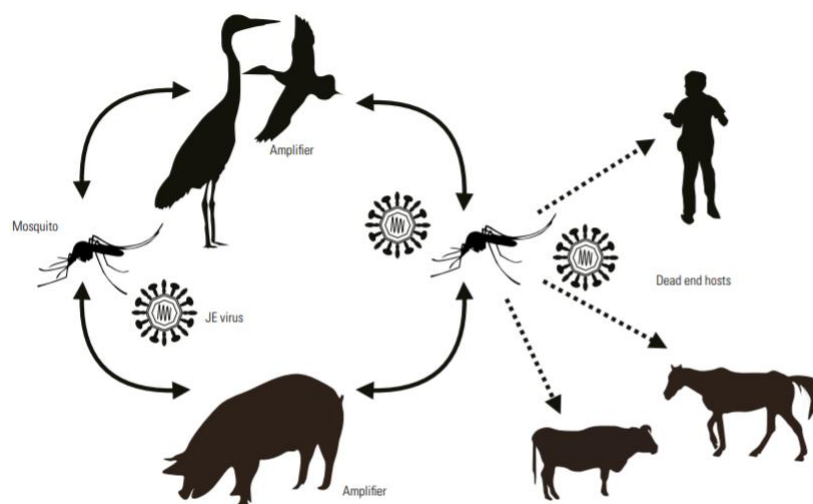
Figure 1.2. Graphical representation of the Japanese encephalitis virus transmission cycle.

The virus is maintained in an enzootic cycle between amplifiers (pigs and wild birds) and mosquito vectors and may spill-over to dead-end hosts which include humans, horses and cattle [taken from (Morita, Nabeshima and Buerano, 2015)].

In endemic areas, JE primarily affects children under 15 years of age, while most adults have protective immunity after natural exposure to the virus (Potula, Badrinath and Srinivasan, 2003; Bista and Shrestha, 2005; Kari *et al.*, 2006; Yen *et al.*, 2010; Li *et al.*, 2016). Conversely, in regions with childhood JE vaccination programmes, most cases occur among unvaccinated adults (Hombach *et al.*, 2005; Arai *et al.*, 2008; Lee *et al.*, 2012; Gurav *et al.*, 2016; Li *et al.*, 2016; Sunwoo *et al.*, 2016). The duration of protection provided by both natural immunity and vaccines remains uncertain and requires further research with improved surveillance (SAGE Working Group on Japanese encephalitis vaccines, 2014). While most JEV infections are asymptomatic, clinical disease occurs in approximately 1 in 250 infections (Fischer *et al.*, 2008; SAGE Working Group on Japanese encephalitis vaccines, 2014). Symptoms are non-specific and may include headache, fever, vomiting, myalgia, mental confusion and seizures (Solomon and Vaughn, 2002). For symptomatic cases, the mortality rate can be as high as 30% and 20-30% of survivors experience permanent neurologic and psychiatric sequelae such as paralysis, recurrent seizures, or inability to speak (Fischer *et al.*, 2008). There is no specific treatment for JE however, supportive care can improve health outcomes.

Japanese encephalitis is an important paediatric health issue in India. Since the first case was recorded in 1955 in Tamil Nadu, JE outbreaks have been reported in most states (Government of India, 2014; Kulkarni *et al.*, 2018). A major JE outbreak in Uttar Pradesh in 2005 lead to approximately 6000 cases and 1400 deaths (Parida *et al.*, 2006) and resulted in the Indian Government introducing a vaccination programme targeting districts with high numbers of reported cases (Government of India, 2014). More recently, there have been large outbreaks reported in the state of Odisha in 2012, Bihar in 2014 and in Manipur in 2016 (Bagcchi, 2014; Kulkarni *et al.*, 2018). National surveillance case data collected from endemic states during 2008 to 2013 revealed that children under the age of 15 years were most vulnerable and cases general occur from July with a peak in September to October (Government of India, 2014). Whereas in Assam state, cases occur from February and peak in July.

The estimated population seroprevalence for JEV across Asia remains uncertain due to the lack of seroepidemiological studies (Ramli *et al.*, 2022) which have been hindered by serological assays that are unable to account for cross-reactivity with

other flaviviruses (Nealon *et al.*, 2019). Of the few seroprevalence studies in Asia, most have detected high seropositivity in adolescents (range: 61% - >75%), relatively low seropositivity in adults (range: <25% - 43%) and high seropositivity in older adults/elderly (range: 52% - 86%) (Arai *et al.*, 2008; Hsu *et al.*, 2014; Sudjaritruk *et al.*, 2022). This trend may be attributable to childhood vaccination in adolescents and historical natural infection in older adults/elderly. However in India, a population-based cross-sectional serosurvey conducted in the district of Alappuzha in Kerala state in 2012 reported JE seropositivity rates of 15.6%, 15.4%, 18.1% and 12.9% for children, adults, older adults, and elderly, respectively (Balakrishnan *et al.*, 2017). This low estimated seroprevalence may have resulted from the exclusion of vaccinated children from the study and the fact that Alappuzha is a non-endemic region (Government of India, 2014). Nonetheless, if the estimated population seroprevalence is representative of regions nationally, this would mean a high proportion of the population remain susceptible to JEV infection.

India first introduced a JE vaccination campaign in 2006 using a single dose of the SA 14-14-2 live attenuated JE vaccine, targeting children aged 1–15 years (Government of India, 2014). A two-dose vaccine regime was introduced in 2013 with the first administered in children aged nine months and the second in children aged 16-24 months (Government of India, 2014). Though the vaccine efficacy is reported to be 97.5% for a two-dose regimen (Hennessy *et al.*, 1996), studies have reported vaccine efficacy of 30% - 40% in India (Vashishtha and Ramachandran, 2015; Tandale *et al.*, 2018). Possible explanations for this may include challenges with cold chain transport (Saikia, 2017), differences in circulating JEV genotypes in India (Schuh *et al.*, 2013) or cross-reactive immunity to other flaviviruses. In addition, India's vaccination programme is only reported to occur in 40–50% of JE-endemic districts (Vannice *et al.*, 2021) and studies have shown vaccination coverage is lower than reported (Murhekar *et al.*, 2017). Poor JE surveillance data and a lack of trust in the Indian public health system are substantial challenges to the success of the national vaccination strategy (Government of India, 2014; Singh *et al.*, 2015; Saikia, 2017).

Limited surveillance data have also hindered the understanding of JE incidence, its potential geographic distribution, and important drivers of disease risk (Lord, Gurley

and Pulliam, 2015; Longbottom *et al.*, 2017). Although climate and land-use have been cited as major drivers of JE risk due to their impact on the dynamics of mosquito populations (Figure 1.3) (Keiser *et al.*, 2005b; Le Flohic *et al.*, 2013), the relative importance of different socio-ecological factors and their potential interactions remains uncertain (Lord, Gurley and Pulliam, 2015). Indeed, climate change is predicted to influence JE risk (Pearce *et al.*, 2018) but the impact of projected irrigated agricultural expansion (IRRI, 1988; Alexandratos and Bruinsma, 2012) and potential future socioeconomic scenarios (Riahi *et al.*, 2017) has not been explored. JE risk in India serves as an excellent case study because of the high burden of disease as a consequence of large outbreaks over recent years (Heffelfinger *et al.*, 2017; Kulkarni *et al.*, 2018; Lindquist, 2018), and India's biologically diverse landscapes (MOEF, 2019), high proportion of irrigated agriculture (Alexandratos and Bruinsma, 2012) and its recognition as a global infectious disease hotspot (Gupta and Guin, 2010; Grace *et al.*, 2012b). An improved understanding of the distribution, drivers, and dynamics of JE in India is needed to formulate public health measures that will minimise risk by preventing or mitigating conditions that drive JE outbreaks.
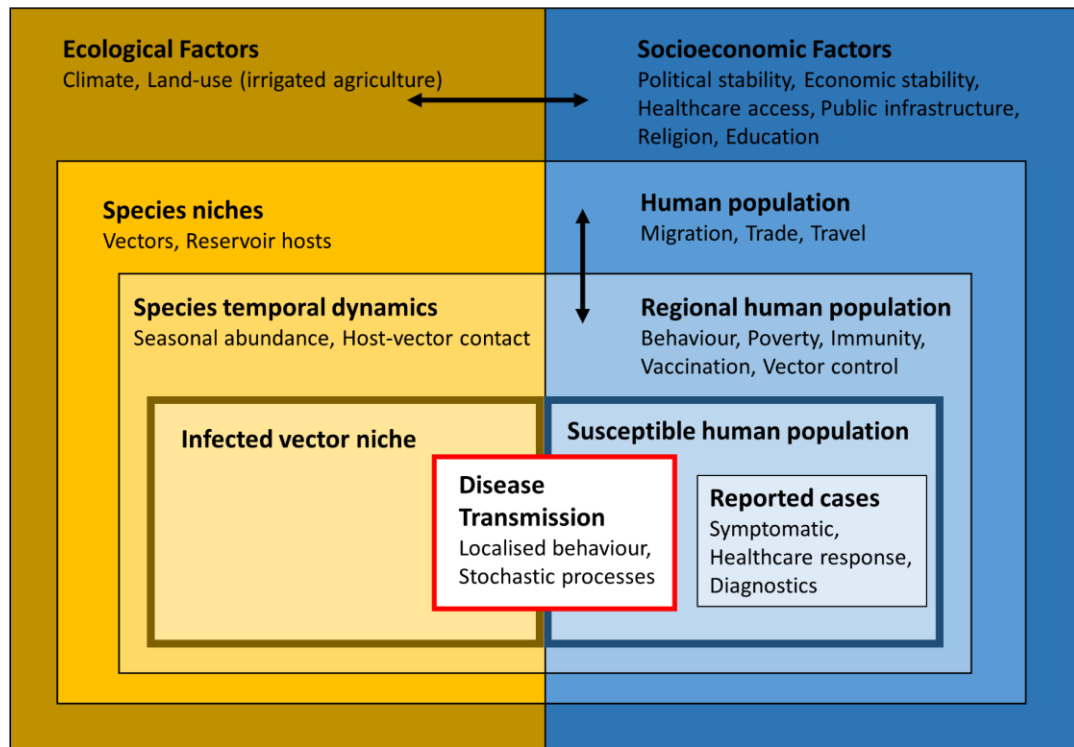
Figure 1.3. Conceptual framework underpinning approach to modelling Japanese encephalitis transmission.

The blocks indicate major system components, the arrows show links, and key subcomponents are in smaller font. Ecological factors (indicated by yellow blocks) such as climate and land-use determine the host and vector niches, their temporal dynamics and contact, resulting in the infected vector niche. Socioeconomic factors (indicated by blue blocks) determine the susceptible human population, and disease transmission occurs when infected vectors (hazard), susceptible people (vulnerability) and spill-over factors (exposure) overlap, resulting in infected human populations (risk). Of these, only a proportion will be reported cases. The diagram provides a conceptual framework for how different socio-ecological factors interact to promote disease risk however, the relative importance of these components and their potential interactions remains uncertain for JE (Lord, Gurley and Pulliam, 2015).

In Chapter 2, I review current knowledge on the relative effect of global change processes on MBD risk in general and investigate how these processes have been previously incorporated into existing analyses. I consider whether the focus on the effects of climate change in MBD research without accounting for the effects of other drivers is justified, and how the ability to predict and forecast risk might be improved in the future. I then apply this understanding in the following chapters which focus on quantitative modelling approaches to capture JE risk in India.

Previously, process-based mechanistic models have been used to reproduce complex interactions and predict pathogen spillover for multiple MBDs (Tompkins and Ermert, 2013; Laneri *et al.*, 2015; Iacono *et al.*, 2018; Tennant *et al.*, 2021). However, these models are often difficult to parameterise due to the vast amount of data they require (Tjaden *et al.*, 2018). At the other end of the spectrum, correlative models such as ENMs require less information to predict the geographic distributions of pathogens, vectors or MBD risk (Tjaden *et al.*, 2018; Johnson, Escobar and Zambrana-Torrelio, 2019) but they often fail to consider ecological interactions (Johnson, Escobar and Zambrana-Torrelio, 2019), socioeconomic, and land-use factors (Tjaden *et al.*, 2018). By contrast, Bayesian hierarchical modelling approaches have a superior ability to model complex interactions (McElreath, 2020c) and compensate for data biases (Redding *et al.*, 2017a). This has led to their increasing use in defining the relationship between socio-ecological drivers and disease risk (Redding *et al.*, 2017b; Childs *et al.*, 2019; Lowe *et al.*, 2021) and in assessing potential disease spread with future global change (Redding *et al.*, 2019; Ryan *et al.*, 2019).

In Chapter 3, I use a novel modelling approach to address data and knowledge gaps in the spatiotemporal patterns and drivers of JE vector abundance - a key component of JE hazard. To do this, I assemble a database of JE vector occurrence and abundance records from India (340 unique records from 24 published studies) and use a joint-likelihood modelling technique that leverages information from sparse vector surveillance data. I aim to determine which environmental factors drive seasonal JE vector abundance and highlight areas to target future surveillance effort to reduce sampling bias and improve surveillance data. I also consider whether vector abundance alone may be used as a proxy for JE hazard.
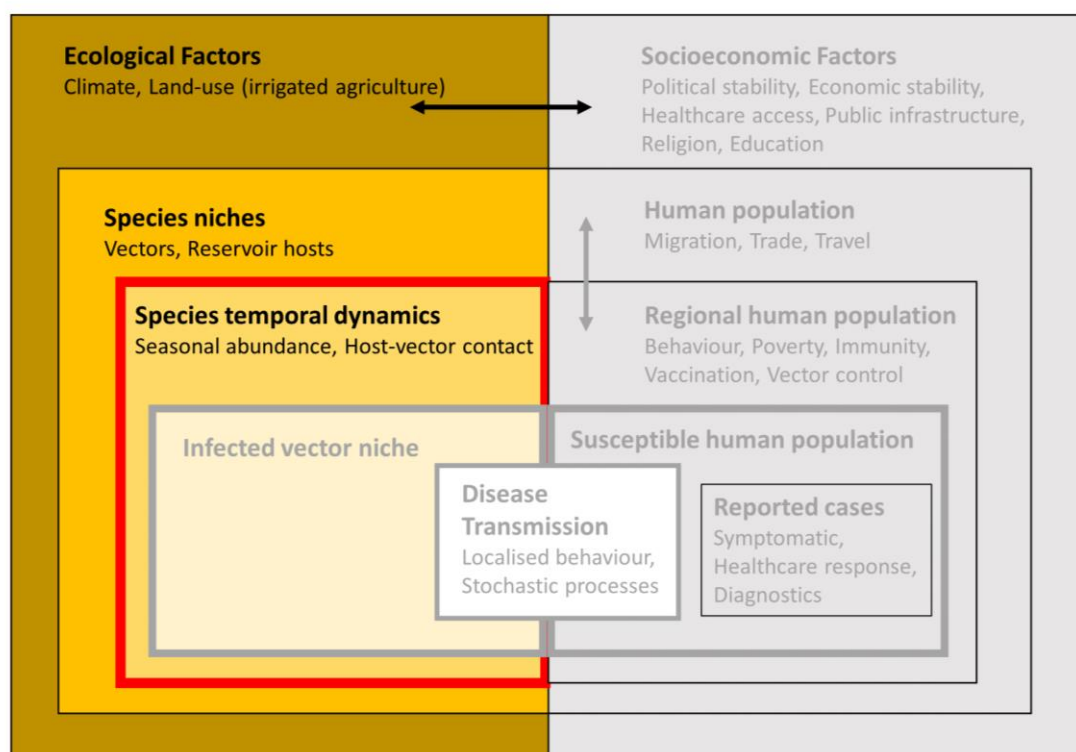
Figure 1.4. Conceptual framework underpinning approach to Chapter 3

In Chapter 3, I aim to predict seasonal JE vector abundance (i.e., vector species temporal dynamics) using ecological factors. I also consider whether seasonal vector abundance may be used as a proxy for JE hazard (i.e., infected vector niche). However, my correlative analysis will be limited by a lack of mechanistic understanding behind the effects of climate and land use factors on the occurrence and abundance of JE vectors. Furthermore, I will not include reservoir host-vector contact or infection data in my analysis and so seasonal vector abundance will be considered as a proxy for JE hazard (i.e., infected vector abundance).

In Chapter 4 I perform a spatiotemporal epidemiological analysis of passive JE human case surveillance data from 2009-2019 to analyse the impact of socio-ecological drivers in shaping the spatial and seasonal dynamics of JE risk. I investigate the relative importance of different environmental and socioeconomic factors in driving spatial patterns of JE risk and determine if these factors can be used to predict endemic areas of JE transmission and seasonal patterns in JE cases. I aim to improving understanding of this understudied disease and define potential areas of underreporting with a view to informing future surveillance efforts and public health interventions.
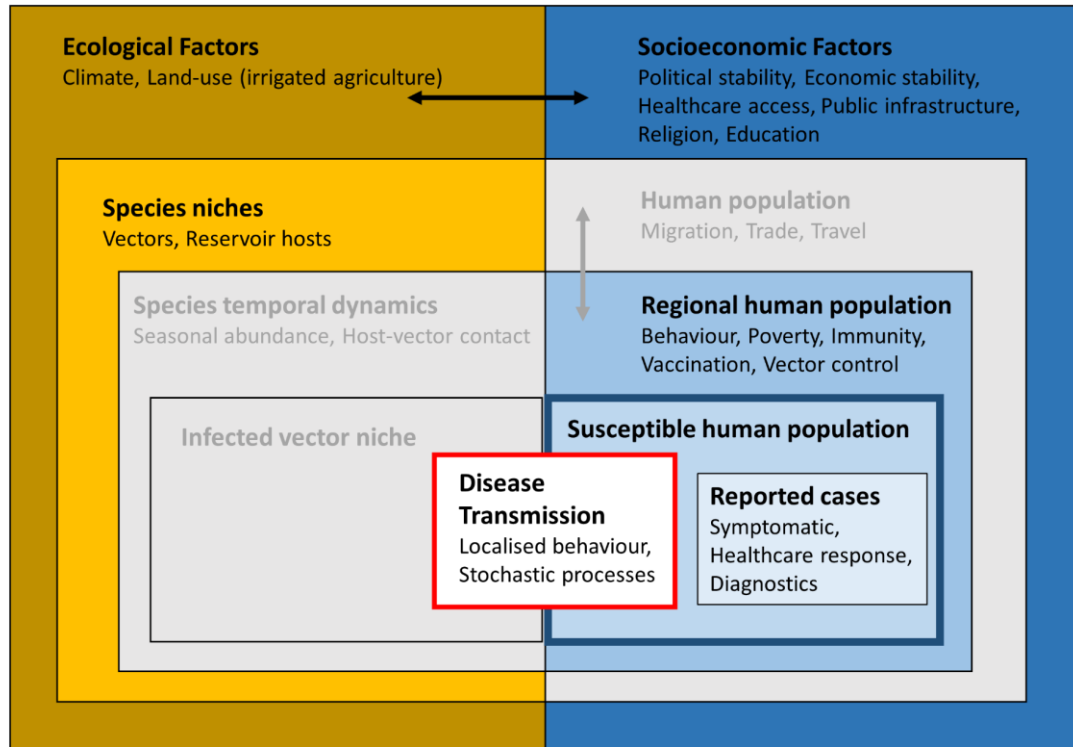
Figure 1.5. Conceptual framework underpinning approach to Chapter 4

In Chapter 4, I investigate the relative importance of different ecological and socioeconomic factors in driving spatial and temporal patterns of JE risk. Owing to data paucity, I do not consider the components of human population movement, temporal dynamics of host and vector species or the infected vector niche in my models. Instead, I use ecological factors to define the vector and host species niches and socioeconomic factors to determine the susceptible human population. This correlative approach is limited by a lack of mechanistic understanding behind the effects of ecological and socioeconomic factors on JE disease risk.

In Chapter 5, I extend the JE risk model developed in Chapter 4 to test scenarios of global change on JE risk. I explore how different climatic, agricultural, and socioeconomic change scenarios might influence JE risk in north-east India over the coming decades. My goal in this chapter is a first step towards incorporating MBD risk into not only public health but also environmental policy decisions to identify trade-offs across land-use, climate, food security and human health. Finally, in Chapter 6, I review and discuss my key conclusions, evaluate any limitations, and provide insights from the thesis. In addition, I propose recommendations for future research and highlight possible global health and environmental policy relevance.

Chapter 2:

The impact of global change on mosquito-borne disease

In this chapter, I review and synthesise the current state of knowledge on the impact of global change on mosquito-borne disease risk, to ask: is current research focus on the effects of climate change justified, and what are the key knowledge gaps from the perspective of improving our ability to project disease risk and target interventions?

2.1 Abstract

Over 80% of the global population is at risk of a vector-borne disease, with mosquito-borne diseases (MBDs) being the largest contributor to human disease burden. Although many global processes such as land-use and socioeconomic change are thought to influence MBD dynamics, research to-date has strongly focused on the role of climate change. I show, through a review of contemporary modelling studies, that there is no clear consensus on how future changes in climatic conditions will impact MBDs, possibly because of the interacting effects of other global change processes which are often excluded from the analyses. I conclude that research should not only focus on the role of climate change but consider growing evidence for additional factors that modulate disease risk. Furthermore, future research should adopt new technologies, including developments in remote sensing and system dynamics modelling techniques, enabling a better understanding and mitigation of MBDs in a changing world.

2.2 Introduction

Diseases transmitted by arthropod vectors such as mosquitoes and ticks are major contributors to the global burden of infectious disease (WHO, 2017), with nearly half the world's human population being infected with a vector-borne pathogen at any moment (WHO, 2014). In particular, MBDs are a key group of concern, as they include both very high burden and important emerging diseases such as: Human malaria (~212 million cases per year), Dengue (~96 million cases per year),

Chikungunya (~693 000 cases per year) and Zika virus disease (~500,000 cases per year) (Table 2.1) (Kilpatrick and Randolph, 2012).

Table 2.1. Number of cases per annum for the major mosquito-borne diseases of global health significance and the genera of associated mosquito vectors.
Adapted from WHO 'A global brief on vector-borne diseases',(WHO, 2014) and 'Global vector control response 2017–2030' (WHO, 2017).

Disease	Mosquito vectors	Estimated or reported number of cases per annum
Malaria	*Anopheles*	212 million (148–304 million)
Dengue	*Aedes*	96 million (67–136 million)
Lymphatic filariasis	*Aedes, Anopheles, Culex*	38.5 million (31.3–46.7 million)
Chikungunya	*Aedes, Anopheles, Culex, Mansonia*	693 000 *(Americas)*
Zika virus disease	*Aedes*	500 000 *(Americas)*
Yellow fever	*Aedes, Haemagogus*	130 000 (84 000–170 000) *(Africa)*
Japanese encephalitis	*Culex*	42 500 (35 000–50 000)
West Nile fever	*Culex*	2 588

Globally, many MBDs are thought to be increasing in incidence and geographic distribution, both emerging in new areas (Stanaway *et al.*, 2016; Paixão, Teixeira and Rodrigues, 2017), and re-emerging in previously eradicated regions (Grobbelaar *et al.*, 2016; WHO, 2017). For example, there has been a 30-fold increase in the global incidence of dengue over the past 50 years, following its expansion into many new countries (Gubler, 2011; Bhatt *et al.*, 2013; Stanaway *et al.*, 2016), while yellow fever cases are reported to be increasing again in many endemic countries after previous dramatic declines (Grobbelaar *et al.*, 2016). These diseases, with their corresponding high levels of morbidity and mortality, have the potential to exert significant negative financial and societal effects and can dramatically inhibit the development and structure of economies, societies and politics (WHO, 2017). As a consequence, much research has been targeted at understanding the current and future geographic distributions of disease risk, in the context of on-going global

change, to help guide interventions and safeguard public health (Campbell *et al.*, 2015; Kraemer *et al.*, 2015; Longbottom *et al.*, 2017).

In this context, there has previously been a strong research focus on modelling the direct effects of climate change on spatial and temporal disease risk (Brady *et al.*, 2014; Christiansen-Jucht *et al.*, 2014; Mordecai *et al.*, 2017), paying less attention to other factors that are already known to interact with both climate change and vector-borne diseases, such as land-use and socioeconomics (e.g. poverty, trade and travel) (Kilpatrick and Randolph, 2012; Gottdenker *et al.*, 2014; Parham *et al.*, 2015). Indeed, these additional global processes, and the interactions between them, may reasonably be shown to have a stronger immediate impact on future MBD burden than climate change effects (Newbold, 2018). This would mean a more complete understanding of the role of global change in modulating the spatial and temporal distributions of MBDs will be essential for the successful prediction and management of disease risk in the future (Whitmee *et al.*, 2015). In this review, I synthesise current knowledge on the relative impact of global change processes on MBD risk and critically examine how these have been incorporated into existing analyses. I argue that the current focus on the effects of climate change is insufficient, considering growing evidence for the key role of other global change processes in modulating MBD risk. I suggest an alternative approach to modelling MBD risk and recommend future directions for research.

2.3 Climate change as a driver of mosquito-borne disease

2.3.1 Review of current literature

I reviewed the scope and outcome of climate-based MBD modelling studies, structuring the search to explore two main axes. Firstly, I considered different mechanisms examined by each study as climate and climate change may affect MBD epidemiology via different pathways, such as influencing pathogen development within the mosquito, and vector population dynamics (Ladeau *et al.*, 2015; Lounibos and Juliano, 2018). Secondly, I examined how different modelling approaches, such as mechanistic and correlation-based methods, have been used to

predict the effect of climate on the risk of multiple MBDs over different geographic and temporal scales (Tjaden *et al.*, 2018).

Owing to time limitations, I conducted a rapid review in which components of the systematic review process are simplified or omitted (Tricco *et al.*, 2015). This included limiting the search to literature published in English within two databases, PubMed and Web of Science, between 1st January 2014 to 28th March 2018 inclusive. This time period was selected to reflect the field since the publication in 2014 of the WHO document, 'A global brief on vector-borne diseases' which called for further research on this topic (WHO 2014). In addition, only one person screened the literature search results and quality appraisal of the studies was not conducted. Search terms were related to models of human MBDs and climate change: ("mosquito*" or "mosquito-borne disease*" or "mosquito borne disease*") AND ("climate chang*" or "climat* change*" or "climat* warm*" or "chang* climat*") AND ("model*" or "modelling"). I excluded treatment papers, reviews, case studies and surveillance reports and focused on modelling studies that evaluated the effect of climate change on MBDs and their vectors. Climate change was defined as an alteration (either observed or projected) in climatic parameters over several decades, with changes in MBD risk being inferred from variations in disease incidence or vector populations.

Of the 234 papers identified, 46 met the inclusion criteria (Appendix 1 Table S2.1). Overall, 54% of studies demonstrated a positive relationship between climate change and MBD risk, with increased variations in meteorological values associated with increased vector abundance or disease incidence. However, the proportion of studies showing this positive relationship varied depending on the geographic scale of the study (Figure 2.1A). Of those studies that predicted increased disease risk with climate change, less than half included key biological information, such as vector critical climatic thresholds and 28% considered other global processes (Figure 2.1B). Global change processes examined in the 46 studies included land-use in 17%, human population density in 11%, of which less than half considered future human density projections, and socioeconomics in 7%.

Temperature, precipitation and humidity were the main parameters used to model climate change (Appendix 1 Table S2.1). Over 97% of studies included the effect of temperature change in their analyses, whereas 78% included precipitation and 22% considered humidity. Temperature has been a predominant research focus since mosquitoes are ectothermic and so ambient temperature strongly influences important epidemiological processes including vector development, biting rates and pathogen development rate within the vector (Reiter 2001; Mordecai et al. 2017). Precipitation is regularly included as parameters in models of MBD risk as water pools are required for mosquito development and associated humidity levels influence mosquito survival and flight (Bates, 1949; Iacono *et al.*, 2018).

Changes in these meteorological variables were determined from recorded climatic data or from projected climatic values using different scenarios of climate change (e.g. IPCC emissions) (IPCC, 2014b). Regarding modelling approaches, over 50% of the studies used correlative models to investigate statistical associations between MBD risk and explanatory variables (Tjaden *et al.*, 2018). Other studies used mechanistic models which incorporated biological or environmental mechanisms assumed to drive disease dynamics (e.g., increased rainfall providing water pools for vector development). In addition, a few studies combined correlative and mechanistic approaches in hybrid correlative models. Mechanistic models were used more commonly for small geographic area analyses such as zonal and national, compared with correlative methods which tended to be used for large-scale regional or global analyses. Most studies were prospective (i.e., predicting to into future) but a few were retrospective or theoretical.
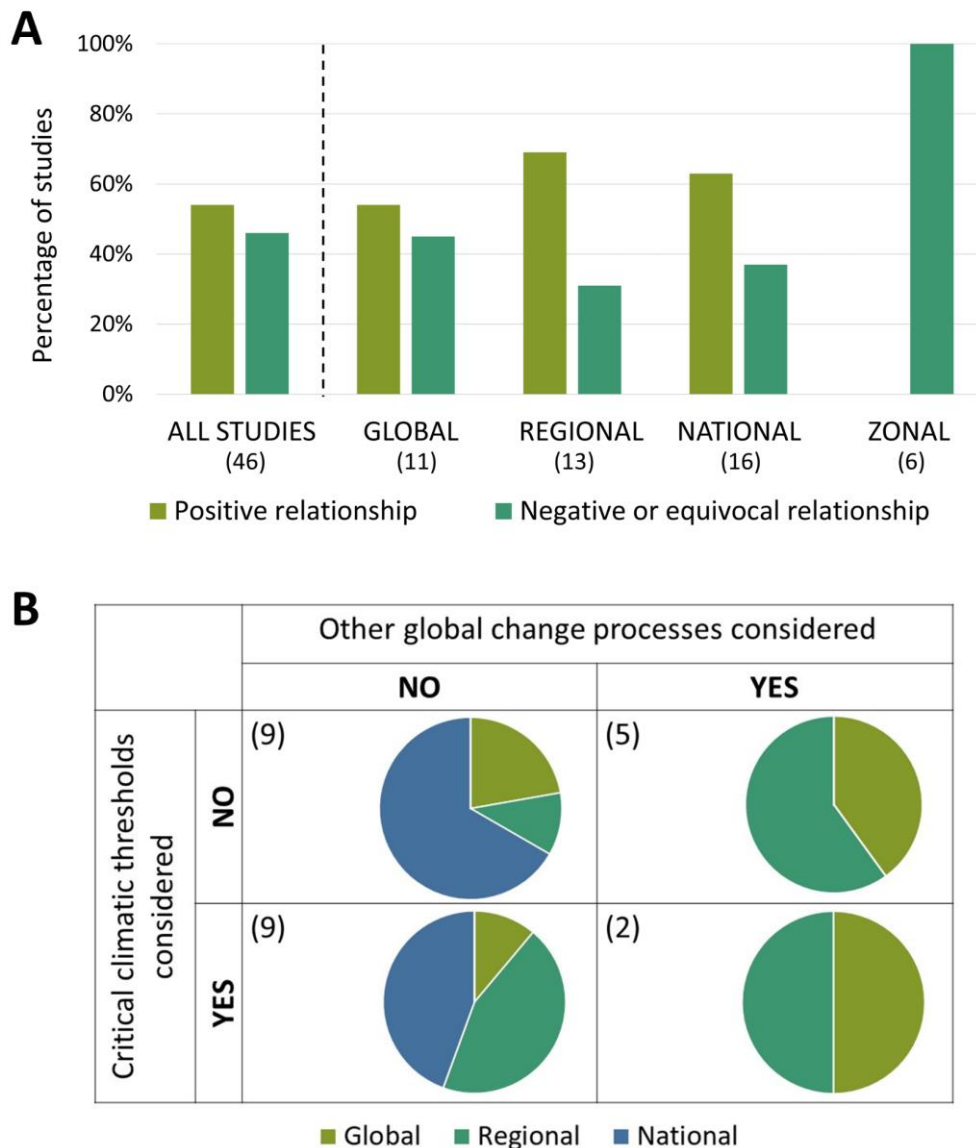
Figure 2.1. Rapid review of the impact of climate change on MBD risk.

(A) Percentage of studies predicting a positive (light green), negative or equivocal (dark green) relationship between climate change and MBD risk per geographic region; number of studies reviewed per region are indicated in parenthesis. (B) Number of positive studies that consider the influence of other global change drivers in their models and/or critical climatic thresholds affecting the vector competence of mosquitos, per by geographic region.

The overall results indicate that there is no clear consensus on how changes in climatic conditions impact MBD risk. This equivocal conclusion may reflect the choice of modelling parameters (i.e., selected climatic variables), the use of spatial or temporal scales in the analyses, the modelling approach and/or, exclusion of important factors or biological processes from the analyses.

41

2.3.2 Narrative review of current literature

The strong focus on the effects of temperature change in the field of MBD research (Caminade *et al.*, 2014; Campbell *et al.*, 2015; Paz, 2015; Tjaden *et al.*, 2017) appears to have led to a body of international scientific reports that conclude that MBD expansion will likely occur in parallel with climate change (IPCC, 2014b; Watts *et al.*, 2017). However, these conclusions are based on the assumption that temperature is a robust predictor of mosquito population dynamics, despite many temperature-dependent relationships and interactions remaining poorly defined (Paaijmans *et al.*, 2012; Christiansen-Jucht *et al.*, 2014; Ewing *et al.*, 2016). For example, the effect of increasing temperature on physiological traits in ectotherms has been shown to be generally non-linear (Paaijmans *et al.*, 2013; Mordecai *et al.*, 2017), and can result in negative outcomes such as reduced survivorship (Christiansen-Jucht *et al.*, 2014), and fast larval development, resulting in small adult mosquitoes (Westbrook *et al.*, 2010). Small mosquito body size has been associated with reductions in fecundity, bloodmeal size and immunocompetence (Murdock *et al.*, 2012). Therefore, paradoxically, climate change may actually reduce the risk of transmission in certain regions via the negative effects of increasing temperatures on vector competence (i.e., the ability of vectors to become infectious).

Temperature also influences the time taken for pathogen development within the mosquito (i.e., extrinsic incubation period [EIP]) (Paaijmans *et al.*, 2012; Mordecai, *et al.*, 2017). The EIP has a major impact on disease transmission because small changes in this parameter can greatly affect the number of mosquitoes that live long enough to become infectious. However, most climate-based MBD models do not include this parameter and when it is included, it is often based on out-dated, temperature-dependent models developed from a single mosquito species that do not consider the influence of other abiotic (e.g., larval habitat quality) or biotic (e.g., parasite competition within the mosquito) factors (Ohm *et al.*, 2018). Studies have typically demonstrated EIP to be shortened with increasing temperatures, and suggested related high infection and transmission rates (Reisen, Fang and Martinez, 2006; Barbazan *et al.*, 2010; Tjaden *et al.*, 2013). However, this effect may vary considerably depending on the specific vector and pathogen (Ohm *et al.*, 2018). For example, in *Aedes* vectors, low temperatures have been shown to shorten EIPs and

cause high viral infection rates by suppressing mosquito antiviral immunity (Westbrook *et al.*, 2010). Other studies have found large temperature fluctuations at low mean temperatures cause shorter EIPs and higher infection in vectors of dengue virus (Lambrechts *et al.*, 2011; Carrington *et al.*, 2013) and malaria (Paaijmans *et al.*, 2010), when compared with more consistent conditions. The lack of clarity about the relationship between EIP and temperature is a critical knowledge gap that requires further empirical research to inform accurate forecasting of MBD risk.

There is considerable debate about how future climate change will impact precipitation trends (IPCC, 2013; Harris *et al.*, 2014), but the consensus is that an increasing frequency of extreme precipitation levels is likely (Booth, 2018). With regard to MBDs, increased variation in precipitation may either augment vector breeding habitat formation or reduce it via detrimental periods of drought and extreme flooding. Similar to the effects of temperature, the relationship between precipitation and MBD risk is non-linear (Paz, 2015; Davis *et al.*, 2017). Several lagged effects (i.e., time-lags between water pooling and adult mosquito emergence) need to be considered in any analysis (Stewart Ibarra *et al.*, 2013). Furthermore, precipitation alone does not account for the presence of vector breeding habitat; this will also depend on species-specific preferences (i.e., water depth) and hydrological factors (e.g., as soil type, vegetation) that control temporary water body development (Day and Shaman, 2008; Davis *et al.*, 2017). A few studies have incorporated hydrological processes into their regional disease risk models (Day and Shaman, 2008; Soti *et al.*, 2012; Asare, Tompkins and Bomblies, 2016), but the practice has not been widely adopted possibly because of the increased complexity needed to model these processes or lack of collaboration between disease researchers and hydrological experts.

Although climate-based models have proved useful in understanding MBD risk at local scales (Siraj *et al.*, 2014) and short timescales (Lowe *et al.*, 2017b), models based solely on approximating the impacts of climatic factors are unlikely to be as effective over large spatial and temporal scales. Other important mechanisms that influence the geographic distributions of vector populations, such as dispersal (e.g., via host movement, wind and trade routes), and biotic interactions (e.g., competition and predation) (Peterson, 2008; Dobson, 2009; Lounibos and Juliano, 2018) are

already known. For instance, although West Nile Virus was theoretically able to exist in the Americas due to climatic suitability, it was not until 1999 that it spread from its original range in Africa, southern Europe, and Southwest Asia, to the whole of North America, likely due to dispersal by migratory birds (Peterson, 2008). Likewise, *Aedes aegypti* was expected to occupy rural habitats of southern USA due to climatic suitability, but these predictions proved inaccurate when competitor, *Aedes albopictus* was present (Lounibos and Juliano, 2018).

Therefore, the burden of disease from MBDs felt by human populations is probably an emergent property from a set of interacting processes which vary at different spatiotemporal scales. For instance, although climate change is likely to cause some predictable range shifts in vector species (Warren *et al.*, 2018), the precise impact of these changes can only be understood in the wider context of a set of non-biological factors, such as land-use change and socioeconomic development (Dobson, 2009). Such interactions may be additive as demonstrated by the synergistic effects of climate change, urbanisation, international trade and travel that have promoted the global expansion in dengue transmission risk (Campbell-Lendrum *et al.*, 2015). Alternatively, they may be subtractive as seen with the global malaria recession which has occurred in parallel with increasing urbanisation (Tatem *et al.*, 2013) and economic development (Sachs and Malaney, 2002). However, the usefulness of climate-based models of MBD risk should not be underestimated. There is a need for more complex models that consider multiple global change processes to predict distributions of MBD risk in the context of on-going global change (Caminade *et al.*, 2014).

2.4   The impact of land-use changes on mosquito-borne disease

Land-use change, from natural to human-dominated landscapes, is a key signature of the Anthropocene (Steffen *et al.*, 2011) and can alter disease risk by influencing the interactions between people, pathogens, vectors and vertebrate hosts (Lambin *et al.*, 2010; Kilpatrick and Randolph, 2012; Gottdenker *et al.*, 2014; Johnson, de Roode and Fenton, 2015; Gibb, Moses, Redding and Kate E. Jones, 2017; Hassell *et al.*, 2017). The immediacy and strength of land-use change impacts on local ecology

(Hudson *et al.*, 2014) supports the argument that it may prove to be the most important driver of recent disease emergence and global spread (Jones *et al.*, 2008; Lambin *et al.*, 2010; Kilpatrick and Randolph, 2012). However, the impact of land-use change on MBD risk will depend on several factors such as its geographic region and mode of the change (i.e., whether it was due to deforestation, agriculture, irrigation, and/or urbanisation). Each of these types of change are discussed below.

2.4.1 Deforestation

Deforestation has been associated with increased human exposure to MBDs (Fornace *et al.*, 2016; Chaves *et al.*, 2018) via its effect on the ecology of vertebrate hosts of zoonotic pathogens, vectors, and vector-host interactions. For example, biodiversity declines are associated with primary forest clearance (Newbold *et al.*, 2015) and may result in shifts in the community composition of wildlife hosts (Kilpatrick and Randolph, 2012; Roche *et al.*, 2013; Hassell *et al.*, 2017) and emergence of infectious diseases (Jones *et al.*, 2008). It is postulated that in biodiverse regions, multi-host community structures may be able to buffer against disease outbreaks since pathogen transmission may be diluted (Ostfeld and Keesing, 2000; Wilcox and Gubler, 2005; Civitello *et al.*, 2015). Despite the theoretical and empirical evidence for this 'dilution effect' being strongest for vector-borne pathogen transmission (Ostfeld and Keesing, 2000; Faust *et al.*, 2017), the generality of this theory remains disputed (Randolph and Dobson, 2012; Faust *et al.*, 2017; Luis, Kuenzi and Mills, 2018).

Since mosquito ecology is dependent on abiotic and biotic environmental conditions, land-use changes will have a significant effect on populations (Ladeau *et al.*, 2015) via altering microclimates, biotic interactions (e.g., predation and competition), and nutrient availability (Burkett-Cadena and Vittor, 2017). Deforestation promotes the growth of certain mosquito populations due to changes in sunlight and pH of water pools in cleared areas (Patz *et al.*, 2000). For instance, increased sunlight has been shown to assist mosquito survival by providing nutrients for larvae (Brouard *et al.*, 2011), and limiting entomophagic fungi growth (Rueda Páramo, López Lastra and García, 2015). Nevertheless, the effect of these changes on mosquito populations will vary depending on the specific microclimate created and the species' ecology

(Ladeau *et al.*, 2015). Frequently, deforestation has been associated with an increased abundance of mosquitoes that act as vectors of disease, with non-vector species favouring undisturbed forest (Burkett-Cadena and Vittor, 2017; Loaiza *et al.*, 2017). The mechanisms behind this remain unclear, but may reflect evolutionary processes that, due to a history of human-mosquito co-occurrence, have enabled pathogens carried by disturbance-specialist mosquito species to adapt to infect humans and proliferate in anthropogenic landscapes (Loaiza *et al.*, 2017).

2.4.2 Agriculture

Agricultural land including cropland, livestock production and irrigated land, accounts for more than 30% of the world's land-use cover (Hurtt *et al.*, 2011). Although agricultural land conversion has led to enhanced global food production and economic development, there has been an associated increase in MBD risk (WHO in collaboration with FAO, UNEP, 1996; Lindblade *et al.*, 2000; Ijumba and Lindsay, 2001; Erlanger *et al.*, 2005; Keiser *et al.*, 2005a; Baeza *et al.*, 2011; Jaleta *et al.*, 2013; WHO, 2014). Agricultural land has specific localised impacts on important MBD correlates such as livestock numbers and water management practices (Hurtt *et al.*, 2011). In particular, livestock production, may modify MBD dynamics by increasing blood meal availability for the vectors (Service, 1991) and provide competent reservoir hosts to maintain (Patz *et al.*, 2000; Le Flohic *et al.*, 2013) and even amplify (Patz *et al.*, 2000) zoonotic pathogens. For instance, domestic pigs are 'amplification' hosts for Japanese encephalitis virus (JEV) since they mount high levels of the virus in their blood which augments the proportion of infected vectors (Scherer and Buescher, 1959; Le Flohic *et al.*, 2013). Indeed, pig farming is reported to be a key correlate in the prevalence of JEV in Asia (Erlanger *et al.*, 2009). Furthermore, livestock production may influence MBD risk via its interaction with climate change since it significantly contributes to global greenhouse gas emissions; conversely, climate change may influence disease transmission in domestic animal populations (Booth, 2018).

Irrigation and dam creation have led to marked changes in the risk of global MBDs such as JE, lymphatic filariasis (LF) and malaria (Ijumba and Lindsay, 2001; Erlanger *et al.*, 2005; Keiser *et al.*, 2005b; Baeza *et al.*, 2011; Kibret *et al.*, 2016). These

practices lead to a dramatic expansion in vector breeding habitat (Patz *et al.*, 2004) and may extend disease transmission seasons (Ijumba and Lindsay, 2001), alter seasonal transmission dynamics in endemic areas (Baeza *et al.*, 2011) and enable pathogen spread into non-endemic areas (Erlanger *et al.*, 2009; van den Hurk, Ritchie and Mackenzie, 2009; Fuller *et al.*, 2012). However, the effects of these schemes on vector populations are complex and will also depend on vector species-specific life-history traits (Ladeau *et al.*, 2015). For example, *Culex quinquefasciatus*, a major vector of LF in Asia, prefers to breed in clean water whereas conspecific, *Culex tritaeniorhynchus*, principal vector of JEV, favours stagnant water (Bashar *et al.*, 2016).

Importantly, irrigation practices may also affect the socioeconomic status of a region which can influence MBD dynamics. The 'paddies paradox', whereby land conversion for irrigation leads to an initial increase and then decrease in MBD risk, has been reported for malaria in Africa (Ijumba and Lindsay, 2001) and Asia (Baeza *et al.*, 2011). This phenomenon is postulated to reflect increasing socioeconomic status in the region associated with improved crop production. Other possible mechanisms include changes in ecology which limit vector abundance (Chase and Knight, 2003) and reduce pathogen spread over time (Moore, Borer and Hosseini, 2010). With future expansion of irrigation practices and dam construction expected (Alexandratos and Bruinsma, 2012; Kibret *et al.*, 2016; Anderson *et al.*, 2018), their influence on disease risk requires consideration.

2.4.3 Urbanisation

The majority of recent urbanisation has occurred in developing countries, where rapid and unregulated urban settlements have caused a huge strain on public health programmes. In 2016, 54% of the global population was reported to reside in urban areas; a significant increase from 34% in 1960. This trend looks set to continue (The World Bank, 2016) with 2.5 billion people predicted to augment the world's urban population by 2050, predominantly in Asia and Africa (United Nations, Department of Economic and Social Affairs, 2014). Increasing numbers of people living in high densities may lead to higher overall pathogen transmission risk for some MBDs (Weaver and Reisen, 2010), while high levels of travel and trade in urban hubs can

enable the spread of vectors and pathogens between population centres (Saker *et al.*, 2004; Weaver and Reisen, 2010; Gubler, 2011; Weaver, 2013). Nevertheless, the impact of urbanisation on MBD risk is complex since evidence suggests both an expansion of some diseases and contraction of others.

For instance, urban expansion has promoted the emergence of arboviruses transmitted by *Ae. aegypti*, such as dengue, chikungunya and zika (Kwa, 2008; Gubler, 2011; Weaver, 2013; Hotez, 2017) (Table 2.1), by influencing resource availability and climatic factors that alter mosquito community ecology (Ladeau *et al.*, 2015). The phenomenon known as the urban heat island (UHI), whereby urban areas experience warmer temperatures than surrounding rural areas (Imhoff *et al.*, 2010), may increase the speed of vector development (Ladeau *et al.*, 2015). In addition, the interplay between the structural complexity of urban landscapes and precipitation has been associated with greater vector numbers and several dengue outbreaks in Asia (Booth, 2018). Vectors such as *Ae. aegypti* and *Ae. albopictus,* are well-adapted to urban areas (Brown *et al.*, 2011), and breed in water containers, drains and gutters, with limited competition or predation (Ladeau *et al.*, 2015). However, the relative impact of urbanisation on vector populations is unlikely to be geographically uniform since urban environments represent a diverse spectrum of habitat mosaics which vary in microclimatic features (Murdock *et al.*, 2017) and socioeconomic status (Ladeau *et al.*, 2015).

In contrast, increased urban development has also been associated with the global decrease in malaria over the past century (Qi *et al.*, 2012; Tatem *et al.*, 2013). However, the underlying mechanisms remains unclear. Urbanisation has been shown to reduce infectious disease burdens, likely via improved health care, education and employment when compared with rural areas (Wood *et al.*, 2017). Nevertheless, reductions in disease risk may mask strong inequalities that exist within urban populations, especially in low and middle-income countries where urban communities with high levels of poverty show higher disease transmission than nearby rural communities (Saker *et al.*, 2004).

2.5   Socioeconomics and mosquito-borne disease risk

Socioeconomic factors, are increasingly recognised as further important drivers of MBD risk (Gallup and Sachs, 2001; Mulligan *et al.*, 2015; Oviedo-Pastrana *et al.*, 2017). For malaria, there is a strong negative association between reported disease risk and national gross domestic product per capita (GDPpc) (Gallup and Sachs, 2001). This association may reflect either high rates of malaria transmission in impoverished settings or the development of poverty due to the burden of malaria on economic growth, or a combination of the two processes (Gallup and Sachs, 2001; Sachs and Malaney, 2002). Although poverty has been cited as an important factor in the spread of several arboviruses (WHO, 2010; Oviedo-Pastrana *et al.*, 2017), there is a paucity of literature on this topic to support this hypothesis (Mulligan *et al.*, 2015). The economic burden associated with MBDs includes direct costs of health provision and control programmes (i.e., vaccination and vector control), and indirect costs (i.e., impacts on education, demographics and human movement) (Gallup and Sachs, 2001; Sachs and Malaney, 2002). Furthermore, macroeconomic costs may occur due to the influence of disease on foreign investment, trade and tourism (Sachs and Malaney, 2002).

Sometimes these factors combine to impede economic development and strengthen the relationship between poverty and disease (Sachs and Malaney, 2002; Alsan *et al.*, 2012; Ngonghala *et al.*, 2017) leading to 'poverty traps'; a self-reinforcing mechanism enabling poverty and diseases to persist (Bowles, Durlauf and Hoff, 2006). This may be accelerated by the development of synergistic diseases referred to as syndemics, as seen with LF and HIV in East Africa (Singer and Bulled, 2013). Escaping from these traps is particularly difficult for underprivileged rural populations who generally rely on subsistence agriculture, have poor access to healthcare and suffer high rates of infectious diseases. A further complexity arises when disease risk is a function of underlying production systems, e.g., livestock are a major feeding resource for Rift Valley Fever vectors and rice paddies are a major habitat component for JEV vectors. Since the currency of the rural poor is often biological (i.e., crops and livestock, human health and nutrition) and the dynamics of this currency can exist within ecological systems, economic development may be tied to ecological processes (Ngonghala *et al.*, 2017). Models representing this relationship

show that 'poverty traps' are features of coupled ecological–economic systems and within these systems, infectious diseases can limit economic growth (Ngonghala *et al.*, 2017).

External intervention (e.g., use of federal funds or international aid) can allow areas with high endemic disease burden to escape disease-poverty feedbacks (Bloom, Canning and Sevilla, 2004). This economic development may then act to reduce contact between people and mosquitoes via vector protection, improved housing and environmental management (e.g., larvicide treatment, vector habitat destruction) (Tolle, 2009; Kilpatrick and Randolph, 2012). Moreover, there is often a reduction in hazardous behaviours such as accessing high risk areas for resource exploitation or settlement (Lambin *et al.*, 2010). While the weight of evidence suggests economic growth reduces MBD risk, it also results in increased movement of people, animals and commodities, with accompanying pathogens and vectors via travel and trade (Patz *et al.*, 2000; Gubler, 2011; Nunes *et al.*, 2014; Kampen *et al.*, 2016).

2.6   The interplay between global change processes

Despite growing convergence in the field of MBD research that considers interactions between global change processes (Campbell-Lendrum *et al.*, 2015), these dynamics and potential resulting trade-offs that either positively or negatively impact global health (Whitmee *et al.*, 2015), are often not represented in models. Below, I outline the impact of these interactions on the global distribution of dengue which has dramatically expanded over the last 30 years and malaria which has contracted in the same period (Figure 2.2). This comparison helps to illustrate the fact that climate is just one part of an overall mechanism that is changing the epidemiology of MBDs.
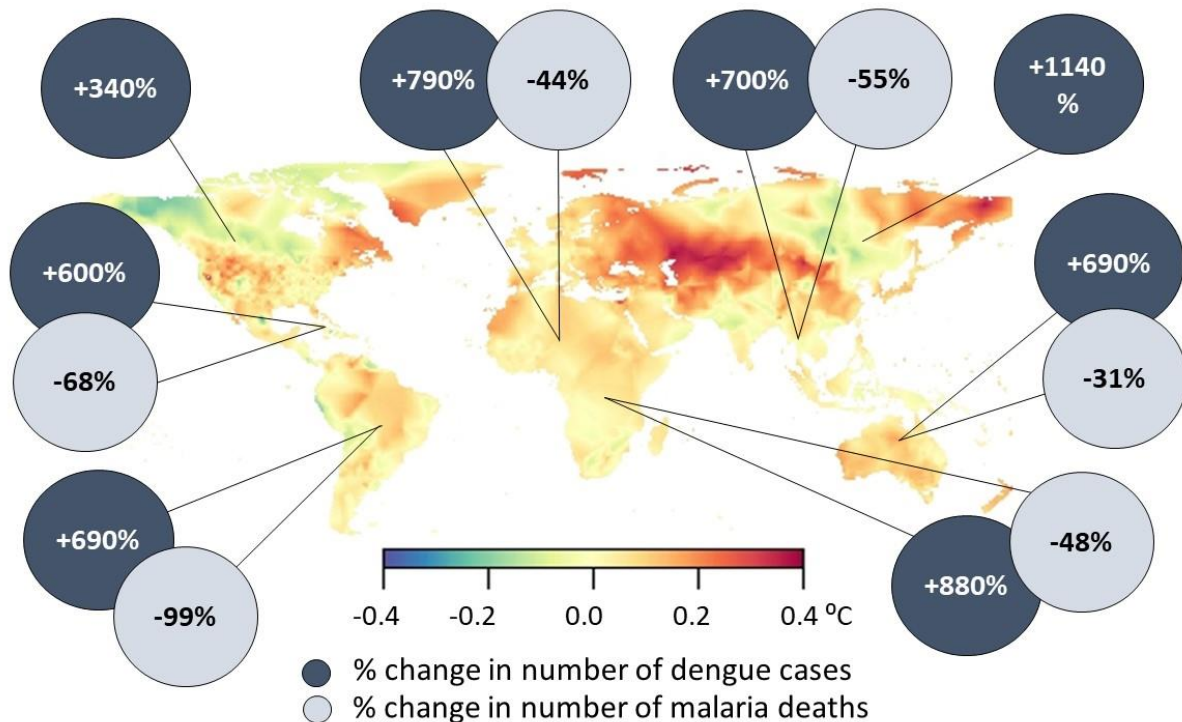
Figure 2.2. Percentage change in dengue cases and malaria deaths between 1993 and 2013 per WHO region overlaying annual mean land temperature (°C) change within the same period.

The figure demonstrates that despite changes in temperature over the period 1993-2013, disease risk for two mosquito-borne diseases diverged. This simple graphical interpretation emphasises that climate is not the only factor driving mosquito-borne disease risk however, the metrics of disease risk (i.e., cases versus deaths) used are different and differences in disease system ecology (e.g., ecology of pathogens and vectors) are not considered. WHO regions include Latin America, Caribbean, North America, North Africa and Middle East, South and Southeast Asia, Central and East Asia, Oceania, Sub-Saharan Africa. Climatic data was accessed via the Climatic Research Unit and case data retrieved from the Global Burden of Disease Survey 2013 (Stanaway *et al.*, 2016; Abajobir *et al.*, 2017).

2.6.1 Dengue

Although climate change is known to directly influence dengue transmission, Messina et al. (2015) suggested that other global change processes and their interactions with climate are likely to have a greater effect in the more immediate future. The rapid global emergence of dengue within the past 50 years (WHO, 2012) is related to interacting drivers including urbanisation, socioeconomics, climate change, travel and

trade (Guzman and Harris, 2015; Ebi and Nealon, 2016). For instance, the significant expansion of urban areas after World War II, especially in Asia, meant large numbers of people migrated into cities, often residing in housing with no sanitation or running water (Gubler, 2011). These factors, combined with poor health-care infrastructure meant that by the 1980s, dengue virus had escalated from causing sporadic epidemics to being a leading cause of morbidity and mortality in Southeast Asia (Gubler, 2011). However, the expansion of dengue was preceded by the spread of its principal vectors, *Ae. aegypti* and *Ae. albopictus*. Originally zoophilic and sylvatic, these mosquitoes became domesticated and were introduced to global urban hubs via travel and trade (Brown *et al.*, 2011; Kraemer *et al.*, 2015). Local populations of dengue vectors then increased in urban landscapes due to the higher numbers of human hosts and the abundance of suitable breeding habitats (Kraemer *et al.*, 2015; Ladeau *et al.*, 2015). Furthermore, complex interplay between UHI, pesticide use and vector competition have been reported to impact vector competence and influence dengue transmission (Ladeau *et al.*, 2015).

2.6.2 Malaria

Much research has pointed to interactions between malaria transmission, land conversion, socioeconomics and human movement (Stratton *et al.*, 2008; Baeza *et al.*, 2011; Baeza *et al.*, 2017). For instance, a recent study coupled MBD dynamics with socioeconomic outcomes that occurred during land transitions (Baeza *et al.*, 2017) and found it was common for an initial increase in malaria transmission to occur after land-use change, followed by either a further rise or a decline in transmission. This is postulated to arise due to ecological changes that promote transmission (e.g., altered breeding sites and human-vector contact rates) occurring at a much faster rate than economic changes which can reduce transmission risk (e.g., improved housing and public health infrastructure). This analysis provided a theoretical explanation for empirical observations of higher malaria risk during the early stages of irrigation schemes compared with well-established irrigated land (Lindblade *et al.*, 2000; Baeza *et al.*, 2011) and highlighted the need to consider both wide-ranging sets of underlying drivers and appropriate timescales on which each driver acts on a system.

The interacting effects of climate change and socioeconomic factors are also predicted to dramatically influence malaria risk over longer timescales. A study found that the projected population at risk in 2050 was estimated to be 5.2 billion when only climatic effects were considered, 1.74 billion when only GDP effects were considered and 1.95 billion when both factors were considered (Béguin *et al.*, 2011). This indicates that climate change may act to negate the continued contraction in malaria expected with economic development. However, feedback loops between climate change and economic development need to be better understood to improve predictions.

2.7   Recommendations for future research

Although the effects of climate change on MBD risk are significant, the influence of other global change processes and their interactions occur over shorter timescales and therefore are likely to have greater impact in the immediate future (Millennium Ecosystem Assessment, 2005). Considering the effect of climate change in isolation may result in inaccurate predictions of MBD risk which may influence the formulation of robust policy recommendations for these emerging diseases. This is compounded by the fact that many studies do not account for the multiple sources of uncertainty in their predictions (Caminade *et al.*, 2014; Harris *et al.*, 2014) including the data (e.g., health, environmental and socioeconomic), future global change scenarios (e.g., climate emission scenarios), and the structure of models and their outputs.
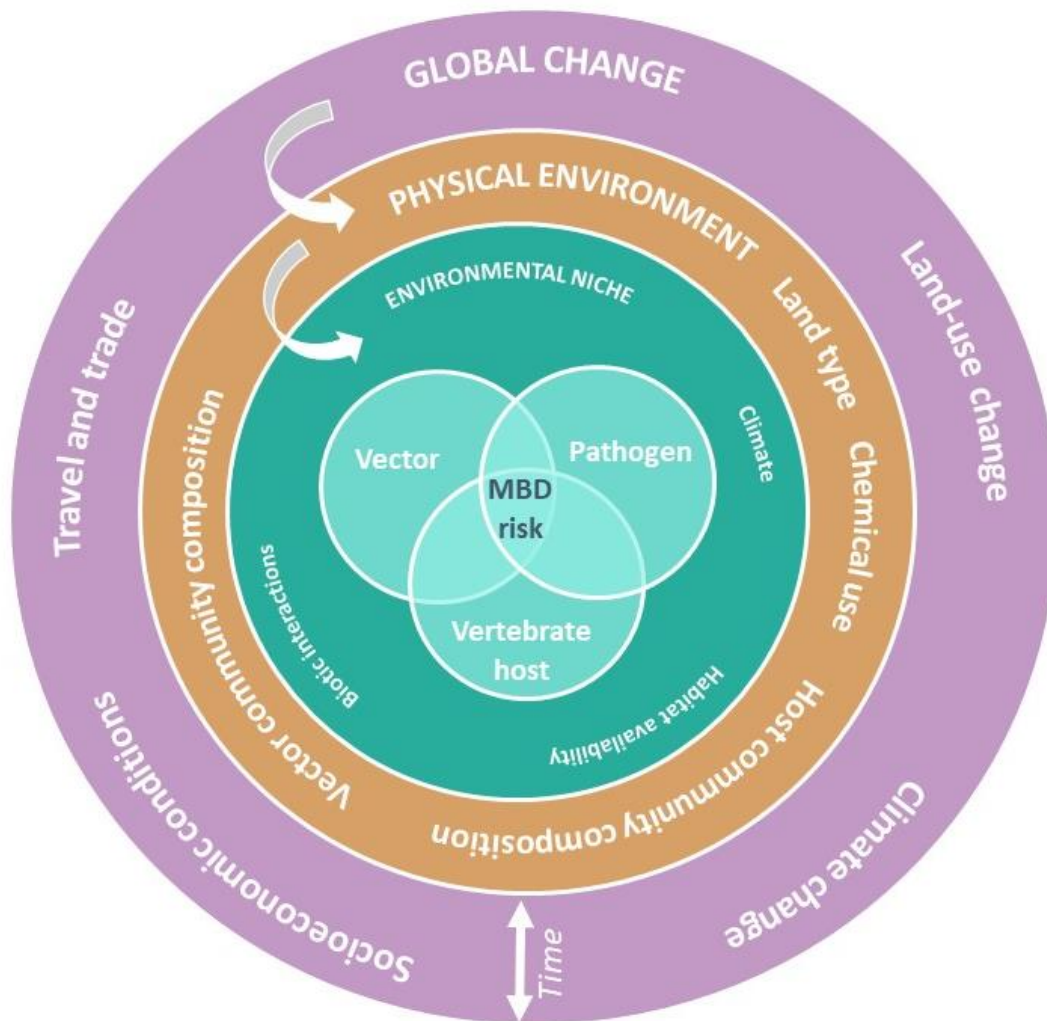
Figure 2.3. A system dynamics approach to understanding MBD risk.

A conceptual model to show a system approach to understanding MBD risk whereby public health outcomes are influenced by complex interactions between environmental and socioeconomic systems. For disease transmission to occur requires the environmental niche of the pathogen, vector and vertebrate host to overlap. The environmental niches of these groups are influenced by the wider physical environment which varies in habitat quality and composition of vector and host (animal and human) communities. Acting on these environmental systems are major global change drivers such as land-use type, climate change, socioeconomic conditions, travel, and trade that interact to influence MBD risk.

I advocate future research to adopt a holistic system dynamics approach (Figure 2.3) whereby the relationships and the feedbacks between socioeconomic and environmental systems are considered (Pongsiri *et al.*, 2017). However, to achieve this, several research gaps need to be addressed: Firstly, enhanced surveillance and evaluation of public health measures is needed to improve health data and define the

factors that promote disease risk. Secondly, empirical research is required to describe the relationships between vectors, pathogens and global change processes to improve parameterisation of MBD risk models. Thirdly, more high resolution, large-scale datasets for other global change processes are needed to match the quantity of climatic data available. Further, research is required to understand the scale at which different global change processes influence MBD risk, and how to incorporate multiple scales into MBD transmission models (Caminade *et al.*, 2014; Parham *et al.*, 2015; Booth, 2018). Addressing these gaps requires improved funding for empirical research and long-term surveillance at varying geographic scales, and enhanced collaboration between researchers working within different disciplines of MBD research. In addition, greater funding for transdisciplinary studies is required to overcome unilateral modelling approaches and improve our understanding of disease risk. The ever-increasing availability of 'big data', sensor technology and innovative software, means researchers have the ability to understand environmental heterogeneity and global change over multiple spatial and temporal scales, including from real-time perspectives (Hay *et al.*, 2013; Kraemer *et al.*, 2016; Fleming *et al.*, 2017). High-resolution satellite remote sensing (RS) data are available for variables including land-use, climate and human populations at a global scale over large time periods. For example, current Sentinel satellite RS data products are available weekly at 10 metre resolution and can be produced into environmental datasets such as land cover products via machine learning approaches (Chen *et al.*, 2020; European Space Agency, 2022). Mobile phone data has also been used to map patterns and processes in human populations (Deville *et al.*, 2014; Lai *et al.*, 2019), and to examine the effect of human movement on disease transmission data (Wesolowski *et al.*, 2015; Engebretsen *et al.*, 2020). For example, human mobility estimates generated from mobile phone data can accurately predict the distribution and timing of dengue epidemics in Pakistan (Wesolowski *et al.*, 2015). In addition, citizen science projects are engaging members of the public to record data such as mosquito occurrence via applications on their mobile phones (Mukundarajan *et al.*, 2017; Vasconcelos *et al.*, 2019; Sinka *et al.*, 2021).

2.8   Conclusion

Previous MBD research has tended to focus on unilateral climate change analyses despite the growing evidence that other global change processes are important determinants of disease risk. Adopting a system dynamics approach, whereby relationships between socioeconomic and environmental drivers are considered, may improve future MBD projections and facilitate stakeholder engagement by demonstrating the effectiveness of common goals in a changing world. Enhanced funding for transdisciplinary research and new opportunities in data availability and analyses will enable a better understanding of the interacting mechanisms that drive disease transmission which will help to guide interventions and safeguard global health (Pongsiri *et al.*, 2017).

Chapter 3:

Joint spatiotemporal modelling reveals seasonally dynamic patterns of Japanese encephalitis vector abundance across India

The rest of the thesis focuses on a case study disease, Japanese encephalitis (JE), an important mosquito-borne disease which is a leading cause of viral encephalopathy in Asia. In this chapter I develop a novel modelling approach to predict seasonal vector abundance for the predominant JE vector across India, as well as to examine the environmental drivers of these patterns.

3.1 Abstract

Predicting vector abundance and seasonality, key components of mosquito-borne disease (MBD) hazard, is essential in the identification of the hotspots of MBD risk and the effective implementation of targeted interventions. Japanese encephalitis (JE), an important MBD, is a leading cause of viral encephalopathy in Asia with 100,000 cases estimated annually, but data on the principal vector *Culex tritaeniorhynchus* is lacking. I developed a Bayesian joint-likelihood model that combined information from available vector occurrence and abundance data to predict seasonal vector abundance for *C. tritaeniorhynchus* (a constituent of JE hazard) across India, as well as to examine the environmental drivers of these patterns. Using data collated from 57 locations from 24 studies, I find distinct seasonal and spatial patterns of JE vector abundance are influenced by climatic and land-use factors. Lagged precipitation, temperature and land-use intensity metrics for rice crop cultivation were the main drivers of vector abundance, independent of seasonal, or spatial variation. The inclusion of environmental factors and a seasonal term improved model prediction accuracy (mean absolute error [MAE] for random cross validation = 0.42) compared to a baseline model representative of static hazard predictions (MAE = 0.51), signalling the importance of seasonal environmental conditions in predicting JE vector abundance. Vector abundance varied widely across India with high abundance predicted in northern, north-eastern, eastern, and southern regions, although this ranged from seasonal (e.g., Uttar Pradesh, West Bengal) to perennial (e.g., Assam, Tamil Nadu). One-month lagged predicted vector

abundance was a significant predictor of JE outbreaks (odds ratio 2.45, 95% confidence interval: 1.52-4.08), highlighting the possible development of vector abundance as a proxy for JE hazard. I demonstrate a novel approach that leverages information from sparse vector surveillance data to predict seasonal vector abundance (a key component of JE hazard) over large spatial scales, and thereby provided decision-makers with improved guidance for targeting vector surveillance and control efforts.

3.2   Introduction

Mosquito-borne diseases (MBDs) pose a substantial global health concern due to their ongoing geographic expansion and increasing incidence (WHO, 2017; Franklinos *et al.*, 2019). Identifying hotspots of MBD risk is critical in informing effective interventions and safeguarding public health (Smith, Dushoff and McKenzie, 2004). This is particularly important for understudied diseases, such as neglected tropical diseases, because resources for disease surveillance and control are often limited (World Health Organization and Department of Control of Neglected Tropical Diseases, 2017). MBD risk can be understood as the likelihood of an outbreak due to exposure of a susceptible population to an infected mosquito vector (hazard) (Hosseini *et al.*, 2017). Defining areas of MBD hazard requires knowledge of pathogen prevalence in reservoir host and vector populations but these data are often not available. Therefore, models that predict how vector populations may vary over space and time, thereby estimating a key component of hazard, have become vital tools in MBD epidemiology (Kraemer *et al.*, 2016; Tjaden *et al.*, 2018). Nevertheless, considerable costs associated with vector sampling (ECDC and EFSA, 2018) have resulted in the limited availability of long-term vector surveillance datasets over large spatial scales, hindering the ability to predict vector abundance accurately and inform interventions.

Vector abundance (i.e., the number of individuals in a site at a given time) and seasonality (i.e., intra-annual change in abundance) are important contributors to pathogen establishment, persistence and transmission (ECDC and EFSA, 2018; Tjaden *et al.*, 2018; Liu-Helmersson *et al.*, 2019). For example, regions with high

vector abundance and a low seasonality (i.e., long periods when adult vectors are active) will lead to increased likelihood of pathogen establishment and persistence (ECDC and EFSA, 2018). Long periods of high vector abundance may also increase the likelihood of pathogen transmission between vectors and hosts due to increased contact rates that could lead to pathogen exposure (e.g., via vector feeding) (White *et al.*, 2017; ECDC and EFSA, 2018). Despite the epidemiological importance of vector abundance, most commonly available vector surveillance data consist of categorical information on occurrence (i.e., presence/absence) and rarely provide quantitative information on abundance (Rund *et al.*, 2019).

The relative availability of vector occurrence data has contributed to the popularity of species distribution models (SDMs) in MBD research (Kraemer *et al.*, 2016; Tjaden *et al.*, 2018; Johnson, Escobar and Zambrana-Torrelio, 2019). These statistical models typically correlate the presence of a species at multiple locations with environmental covariates to predict species distributions (Elith and Leathwick, 2009). Although they provide valuable information on potential vector geographic distributions, knowledge of where vectors can occur is insufficient to provide an accurate estimation of MBD hazard (ECDC and EFSA, 2018) particularly because these models do not consider spatial and temporal dynamics (Becker *et al.*, 2010). In addition, for widely-used SDM approaches such as boosted regression tree (BRT) models and MaxEnt, uncertainty estimates are produced by bootstrapping data which can be computationally prohibitive (Elith, Burgman and Regan, 2002; Golding and Purse, 2016). Without predictive uncertainty metrics, results may be misleading for decision-makers since it may be difficult to distinguish between regions with accurate predictions and those that have a high degree of uncertainty (Messina *et al.*, 2019). Alternatively, seasonal vector abundance has been estimated using mechanistic models of vector populations based on a system of differential equations depicting each life stage (White *et al.*, 2017; Ewing *et al.*, 2019). However, these models rely on large amounts of experimental or empirical data (Tjaden *et al.*, 2018) which can be expensive to obtain and are often sparse for many vector species (Mordecai *et al.*, 2019). The lack of long-term abundance data (WHO, 2017; Liu-Helmersson *et al.*, 2019) has also meant that statistical models of seasonal vector abundance often exist for local (Walsh *et al.*, 2008; Chaves *et al.*, 2012; Jian *et al.*, 2014) rather than for national or regional geographic scales. Overall, there is a need for improved

59

estimates of components of MBD hazard which also account for uncertainty to enable a better understanding of seasonal patterns in the risk of disease transmission.

One of the most important yet relatively understudied MBDs is Japanese encephalitis (JE), the leading cause of viral encephalopathy in Asia (LaBeaud, 2008; G. L. Campbell *et al.*, 2011; Quan *et al.*, 2020). JE accounts for over 100,000 human cases and 25,000 deaths annually, primarily affecting children and those living in rural, agricultural areas (Baig *et al.*, 2013; Quan *et al.*, 2020). Although the disease is endemic in 24 countries (Quan *et al.*, 2020), the majority (87%) of cases in Asia are reported from India, Nepal, China and Vietnam (Heffelfinger *et al.*, 2017; Lindquist, 2018). The causative pathogen, Japanese encephalitis virus (JEV) is maintained in an enzootic transmission cycle between mosquitoes and a range of amplifying hosts including domestic pigs and ardeid wading birds (e.g., herons and egrets) (Le Flohic *et al.*, 2013). Agricultural practices such as rice cultivation and pig breeding provide an ideal environment for human exposure to JEV, but other factors such as population immunity due to vaccination will also influence the risk of disease outbreaks (Tian *et al.*, 2015). The virus is predominantly transmitted by the mosquito vector *Culex tritaeniorhynchus* Giles, 1901 (Diptera: *Culicidae*) (Pearce *et al.*, 2018) and JE outbreaks are reported to be strongly associated with vector abundance (Wada *et al.*, 1975; Matsuzaki, 1990; Kim *et al.*, 2014). Despite *C. tritaeniorhynchus* being a major threat to human health and wellbeing, there are limited surveillance data for this species (Longbottom *et al.*, 2017) which has impeded knowledge on spatiotemporal trends in vector abundance, a constituent of JE hazard.

C. tritaeniorhynchus population dynamics are strongly linked to climatic conditions, such as temperature and rainfall (Suryanarayana Murty *et al.*, 2002; Suryanarayana Murty, Srinivasa Rao and Arunachalam, 2010), and to anthropogenic activities that increase standing water, such as irrigated agriculture (Keiser *et al.*, 2005b; Sabesan, Raju Konuganti and Perumal, 2008; Raju *et al.*, 2016, 2018). Experimental studies on other *Culex* species have found important life history traits such as development rate and survival generally peak at 15.7–38.0°C (mean thermal optimum = 28.4°C) and then decline to zero for thermal minima (mean = 9.5°C) and maxima (mean = 39.5°C) (Mordecai *et al.*, 2019). Rainfall can both positively influence *C. tritaeniorhynchus*

abundance via the creation of standing water for vector breeding (Reisen, Aslamkhan and Basia, 1976; Vythilingam *et al.*, 1997; Suryanarayana Murty, Srinivasa Rao and Arunachalam, 2010) and negatively impact abundance during the monsoon (Balasubramanian and Nikhil, 2015) via the destruction of breeding sites (ICMR, 2001). Irrigated agriculture provides suitable habitat for vector development and *C. tritaeniorhynchus* is reported to breed preferentially in rice paddy fields (Keiser et al., 2005b; Sabesan, Raju Konuganti and Perumal, 2008). Indeed, previous studies have shown that vector abundance is positively associated with rice field density (Richards *et al.*, 2010), rice crop growth stage (Raju *et al.*, 2016, 2018) and standing water availability (Rajagopalan and Panicker, 1978; Keiser et al., 2005b). Interestingly, the availability of standing water due to irrigation practices may lead to a reduction in vector seasonality (i.e., by extending vector breeding seasons), especially in arid regions which would otherwise be unable to sustain vector development during summer months (Mukhtar *et al.*, 2003; Baeza *et al.*, 2011; Bashar *et al.*, 2016; Raju *et al.*, 2016, 2018). Although environmental conditions are known to underpin the seasonal dynamics of many vector populations (Lord, 2004; Ewing *et al.*, 2019), the importance of these factors in driving broad-scale spatial and temporal patterns of JE vector populations remains poorly defined.

Previous studies have investigated the spatial distribution of *C. tritaeniorhynchus* occurrence using SDMs (Masuoka *et al.*, 2010; Miller *et al.*, 2012; Longbottom *et al.*, 2017; Samy *et al.*, 2018) but, there is a paucity of data on seasonal vector abundance. Bayesian hierarchical modelling approaches have been used widely for other animal species to estimate biodiversity trends by integrating multiple data types in a single estimator (Pagel *et al.*, 2014; Humphreys *et al.*, 2019). This joint-likelihood approach has also been used in MBD research to explicitly account for differences in data quality and structure (i.e., different probability distributions) and can handle and quantify sources of uncertainty associated with each data type (Amoah, Diggle and Giorgi, 2020; Lucas *et al.*, 2021). Here, I use this approach to develop a joint-likelihood Bayesian hierarchical model that leverages spatial information from vector occurrence probability to estimate seasonal vector abundance for principal JE vector, *C. tritaeniorhynchus* across India. Firstly, my study aims to quantify the importance of different environmental drivers of *C. tritaeniorhynchus* abundance – a key component of JE hazard. I hypothesise that a critical driver of vector abundance is standing

water provided by rice crop irrigation practices and periods of heavy rainfall during the winter and monsoon seasons. Secondly, I aim to construct seasonal vector abundance maps for India that account for uncertainty in predictions. Thirdly, I use logistic regression to test whether there is a relationship between mosquito abundance estimates and JE cases and discuss the potential for vector abundance to be used as a proxy for JE hazard. The purpose of this research is to provide decision-makers with useful information that will assist in their resource allocation for intervention strategies and highlight areas to target for future vector surveillance. India is used as a case study since it has one of the highest JE burdens in Asia (Baig *et al.*, 2013; Heffelfinger *et al.*, 2017; Lindquist, 2018) and reports both endemic and epidemic epidemiological patterns (Vaughn and Hoke, 1992; Misra and Kalita, 2010).

3.3 Materials and methods

3.3.1 Datasets

3.3.1.1 Vector data

I assembled a database of geo-referenced, spatially, and temporally unique *C. tritaeniorhynchus* vector occurrence and abundance records in India from published literature. A systematic literature search was conducted in PubMed and Web of Science using the search terms "*Culex tritaeniorhynchus*" and "India". The search was limited to articles published in English between 1st January 1990 and 31st December 2017 and returned 101 unique citations. Article abstracts were screened to meet the following criteria for inclusion; (i) the reported study was undertaken after 1990, (ii) surveys provided species-level information at the studied location, and (iii) the surveys were conducted in the mainland of India. The full text articles were then reviewed and excluded if they pooled observations for more than one month since this would increase uncertainty in the associations between vector occurrence and abundance and predictor variables. The resulting 24 studies that met the inclusion criteria were used to build the dataset. The database included 340 unique records of adult vectors which ranged from 1990-2012 from 57 sampling locations resulting in data from 352 location-months (see Appendix 2 Table S3.1). Of the 340 unique records, 73 were occurrence-only records and 267 included occurrence and abundance data (Figure 3.1). Records that included occurrence and abundance data

were used twice in the analysis; once as occurrence data and once as abundance data (total occurrence data n= 340, total abundance data n= 267) (see Appendix 2 Table S3.1). The study period was chosen to maximise the number of vector surveillance records whilst enabling the use of high-resolution land cover datasets that were available from 1990s. I built on previous *C. tritaeniorhynchus* occurrence datasets developed by Miller *et al.*, (2012) and Longbottom *et al.*, (Longbottom *et al.*, 2017) to include information on mosquito presence, absence, and abundance, collection method, collection year and month, and habitat descriptions. Mosquito sampling locations in each study were identified as point locations. I calculated effort-corrected abundance values of *C. tritaeniorhynchus* from the raw measurement values by aggregating monthly counts and standardising them to survey effort (one survey hour) abundance measure for each month. Most abundance data (86%; n=228) were recorded from the state of Tamil Nadu (Figure 3.1A) and only four studies performed continuous abundance measurements over consecutive months (see Appendix 2 Table S3.1). Survey effort (one survey hour) vector abundance measures were transformed to logscale to conform to normality and ranged from 0 to 6.49 (0 to 655 true scale) with a mean of 3.61. The occurrence and abundance data used in the models were evenly distributed across all study months (Figure 3.1B). However, there is a lack of vector data from 1992 to 1998 and most abundance data were recorded from 2006 to 2012 (Figure 3.1C).

3.3.1.2 Additional inferred absence vector data

I randomly generated additional absence data for regions above 3500m since to my knowledge, this is above the altitude that *C. tritaeniorhynchus* mosquitoes have been recorded (Devi and Jauhari, 2004). To limit artefactual spatial and temporal autocorrelation in model residuals, I limited these data to a total of 20 records from 12 locations which were randomly selected from high altitude regions in the states of Arunachal Pradesh, Himachal Pradesh, Jammu and Kashmir, and Sikkim (Figure 3.1A) and randomly assigned a date from the study period.
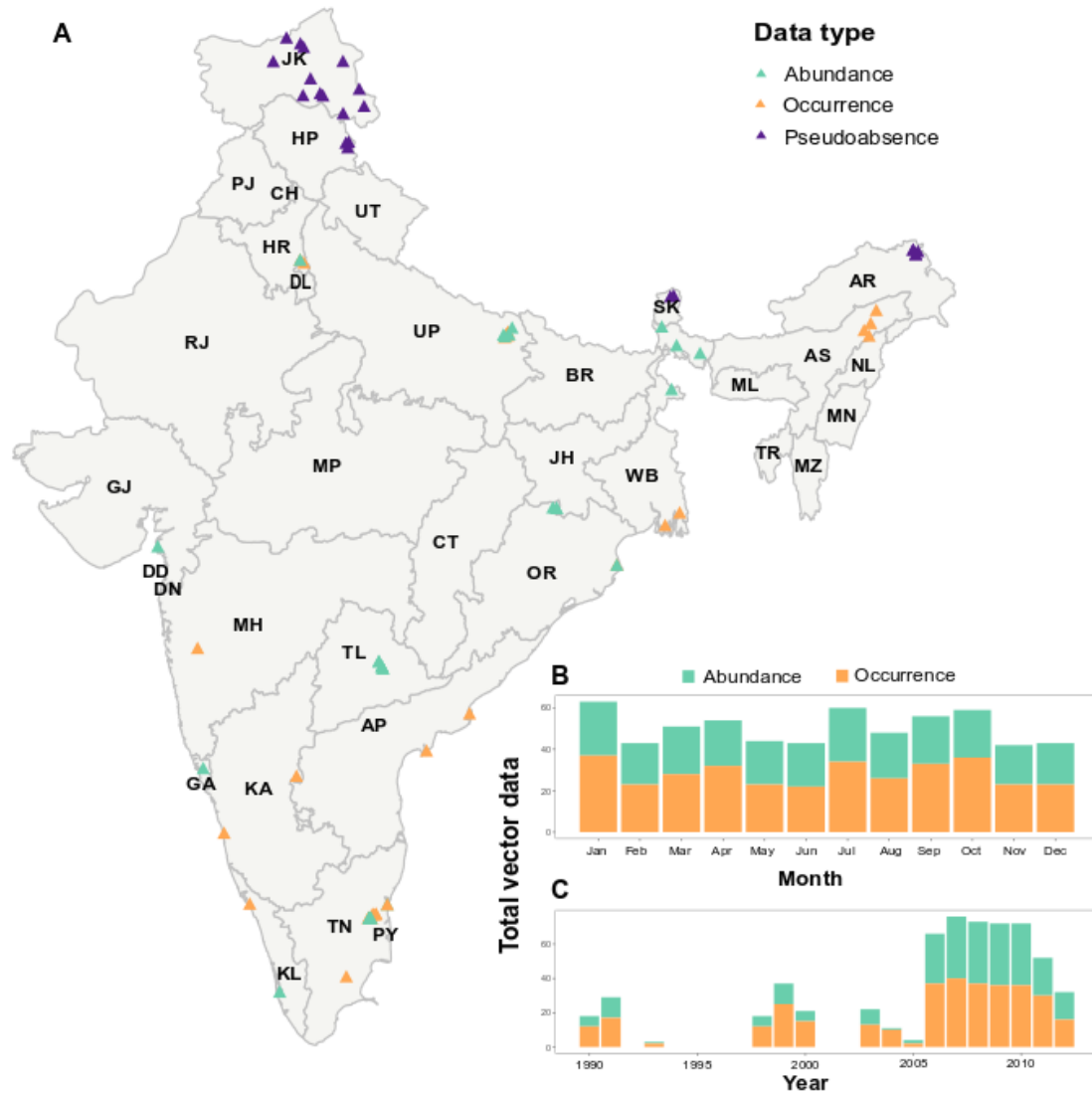
Figure 3.1. Spatial and temporal distribution of vector surveillance dataset used in model.

(A) Points show the geographical sampling locations (n= 57) of the C. tritaeniorhynchus records across India*, with occurrence-only records coloured orange (n = 74), records which included occurrence and abundance data in green (n = 266), and pseudoabsence records in purple (n = 20). Stacked barplots show the temporal distribution of the total vector occurrence (orange) and abundance data (green) used in the analysis per month (B) and year (C). *Abbreviations for Indian states and union territories: AP - Andhra Pradesh, AR - Arunachal Pradesh, AS - Assam, BR - Bihar, CH – Chandigarh, CT- Chhattisgarh, DD - Daman and Diu, DL - Delhi, DN - Dadra and Nagar Haveli, GA – Goa, GJ – Gujarat, HP - Himachal Pradesh, HR - Haryana, JH - Jharkhand, JK - Jammu and Kashmir, KA - Karnataka, KL – Kerala, MH - Maharashtra, ML - Meghalaya, MN - Manipur, MP - Madhya Pradesh, MZ - Mizoram, NL - Nagaland, OR - Odisha, PJ - Punjab, PY - Puducherry, RJ - Rajasthan, SK - Sikkim, TL – Telangana, TN – Tamil Nadu, TR - Tripura, UP - Uttar Pradesh, UT - Uttarakhand, WB – West Bengal.

3.3.1.3 Seasonal, environmental, and land-use data

I selected environmental variables hypothesised or reported to influence the presence or abundance of *C. tritaeniorhynchus* populations (see Appendix 2 Table S3.2 and Figure S3.1). For instance, temperature is known to influence the development and survival rates of mosquito vectors and the availability of standing water provided from precipitation or irrigated agricultural practices is required for mosquito breeding (Niaz and Reisen, 1981; Bashar *et al.*, 2016; Raju *et al.*, 2018). The full suite of covariates tested across all analyses, data sources and associated hypotheses, including those considered but then dropped from the model, are described as follows:

Climate variability was incorporated through inclusion of TerraClimate (Abatzoglou *et al.*, 2018) high-spatial resolution rasters (1/24°, ~4-km) for monthly cumulative precipitation (mm), monthly maximum and minimum temperatures (ºC). I calculated monthly mean temperature (ºC) from the maximum and minimum temperature datasets. Mean monthly precipitation was log transformed to represent the nonlinear effect reported between rainfall and vector abundance (L D Valdez *et al.*, 2017). To represent the lag association between weather conditions and mosquito abundance (Tian *et al.*, 2015), I also calculated average temperature and precipitation data for the two months prior to the vector observation (henceforth referred to as two-month lagged variables in this study) to account for the period for mosquito larval habitat to increase and the development period of the mosquito.

I obtained annual land cover data from the European Space Agency (ESA) Climate Change Initiative Land Cover dataset (version 3.14) for 1992-2012 (ESA; http://maps.elie.ucl.ac.be/CCI/viewer/index.php) with a spatial resolution of 300m. The 37 original land cover classes were reclassified into six broad groups (agricultural, mixed agricultural, forest, mixed vegetation, urban and water) since the land cover types associated with the vector surveillance data were not varied enough to evaluate the importance of more diverse land classes (i.e., rainfed versus irrigated cropland). Zonal statistics function was used to determine the percent cover of each of land cover class within 1km buffer around each location, with the buffer size based on previous analyses (Trawinski and Mackay, 2010). Since ESA land cover data were missing for 1990 and 1991, I assessed changes in the proportion of land cover

classes for the period 1992 to 1995 and found strong significant correlation between the years (Mantel statistic R: 0.99, *p* = 0.001), so I used land cover data for 1992 for the missing years. Agricultural land-use intensity can be assessed via three categories: input metrics (e.g., irrigation), output metrics (e.g., yields) and system level metrics (e.g., actual vs. attainable yield) (Kehoe *et al.*, 2015). Due to the strong positive associations reported between *C. tritaeniorhynchus* abundance and rice paddy cultivation, I used the RiceAtlas database of global rice production (Laborte *et al.*, 2017) to extract district-level data for the agricultural intensification input metric of total annual rice area cultivated (hectares) and for the output metrics of total annual rice produced (tonnes) and average number of crops harvested per year. To assess seasonal variation in rice cropping practices, district-level data on the rice planting and harvesting months were also extracted from the RiceAtlas dataset.

All raster data layers were manipulated and resampled to a 0.208º (~23km) grid cell size using a World Geodetic System 84 projection using the *raster* package in R (Hijmans and van Etten, 2014). I examined all covariates for collinearity and excluded covariates that were collinear with one or more others (Pearson correlation coefficient >0.8).

3.3.1.4 Japanese encephalitis human case data

Monthly JE human cases recorded were retrieved from the Indian Government's Ministry of Health and Family Welfare (Ministry of Health & Family Welfare, Government of India, 2020). Data were obtained for the period January 2009 to December 2015 and were converted to geographic point locations (n= 123) from their village level description using online gazetteers (e.g., Google Maps). The data comprised of the number of confirmed cases rather than suspected cases since clinical signs for JE may overlap with several other diseases (Solomon *et al.*, 2000). Confirmed cases correspond to those confirmed by laboratory tests using JE-Enzyme-linked immunosorbent assay (ELISA) on serum or cerebrospinal fluid samples.

3.3.2 Statistical analysis

Statistical modelling was conducted using Bayesian hierarchical regression using Integrated Nested Laplace Approximation (INLA). This framework enables the development of spatiotemporal models that address data sparsity and spatial bias whilst also being computationally tractable (Rue, Martino and Chopin, 2009; Redding, Lucas, Blackburn and Jones, 2017).

3.3.2.1 Model specification

I developed a joint-likelihood Bayesian spatiotemporal model of *C. tritaeniorhynchus* with separate likelihoods for occurrence and abundance data. The first model tier estimates vector occurrence probability with species presence/absence (0, 1) as response y_{pa} using a Binomial distribution with a logit link function, such that p_i denotes the expected probability of vector occurrence and n_i is the observed survey sample size at observation i:

(1) $$y_{\text{pa}} \sim \text{Binom}(p_{i,} n_i)$$

p_i is modelled as a function of environmental covariates and spatial, seasonal, and random effects:

(2) $$\text{logit}(p_i) = \alpha + \alpha_{pa} + \sum_{k=1}^{K} \beta_k X_{k,i} + t_i + \gamma_i + u_i + v_i + \delta_i$$

where α is the intercept; α_{pa} is an occurrence data specific intercept; X is a matrix of the environmental covariates at each observation, with vector of linear coefficients β; t_i is a nonlinear effect for mean monthly temperature smoothed using a second-order random walk to represent expected nonlinear relationships between temperature and vector occurrence and abundance (Mordecai *et al.*, 2019); seasonality was included as an effect of reporting month specified as a second-order random walk (γ_i); and spatial variation was included using state-level spatially-structured (conditional autoregressive; v_i) and unstructured i.i.d. (u_i) effects jointly specified as a Besag-York-Mollie (BYM) model (Besag, York and Mollié, 1991). Finally, δ_i is an independent, identically distributed (i.i.d.) random effect of source study to enable the

model to account for between-study variation in sampling effort that might otherwise confound inferences.

The second tier in the joint-likelihood model estimated relative vector abundance as response variable y_{abun} using a Gaussian distribution such that μ_i denotes the expected mean of vector abundance with standard deviation, σ:

(3) $\qquad y_{\text{abun}} \sim \text{Norm}(\mu_{i,}\sigma)$

The same shared covariates and spatial, seasonal, and random effects parameters were included as for the first-tier model apart from the occurrence specific intercept:

(4) $\qquad \exp(\mu_i) = \alpha + \sum_{k=1}^{K} \beta_k X_{k,i} + t_i + \gamma_i + u_i + v_i + \delta_i$

Prior to being included in the model, all continuous predictor covariates were standardised (to mean= 0, standard deviation [SD] =1) and log vector abundance was rescaled from 0-1 (to preserve zero as a reference point) to help with assigning model priors (McElreath, 2020a). Weakly informative prior probability distributions (priors) were assigned for the intercept, $\alpha \sim$ N (0,0.6) and fixed effects, $\beta \sim$ N (0,0.3) to constrain the position and scale of the outcome of interest (y_{abun}) to fall within a reasonable range. The intercept for occurrence data α_{pa} is a single, fixed parameter that was only added in the first tier of the model when modelling occurrence data. It acts as a varying intercept so that all occurrence data are modelled as a separate cluster to abundance data and therefore allows some flexibility in the joint modelling of both data types. Fixed effects priors were centred on 0 to allow for positive or negative relationships between environmental covariates and vector abundance. I assigned penalized complexity (PC) priors (Simpson *et al.*, 2017) to hyperparameters of the month, state-level and study-level effects. PC priors were used to penalise the complexity resulting from deviating from a simple base model. The PC priors are defined such that the probability that a given hyperparameter (ρ) exceeds an upper limit (ρ₀) is χ (i.e., *P(ρ> ρ₀) = χ)*. The PC priors in the model include:

Seasonal effects: $\qquad\qquad\qquad\qquad$ P $(\rho_i> 0.05) = 0.01$

Unstructured state-level effects: P $(u_i > 0.175) = 0.01$

Study-level random effects: P $(\delta_i > 0.175) = 0.01$

These values were chosen by comparing the variance of the effect variables and the resulting difference in log vector abundance observed. For example, an i.i.d. effect with a SD of 0.175 would typically (95% probability interval) yield intercepts between -0.34 and 0.34. Transforming these values through a log link gives abundances between 0.71 and 1.4 and therefore the effect allows a variation in abundance of about 100%. I based the values on assumptions from the data that log vector abundance may vary by up to 33% between one month and the previous two months (order-two random walk), whereas it may vary by 100% between studies. A conservative PC prior (mean 0.5, precision 0.667) was assigned to the structured state-level effect to account for the assumption that the unstructured effect accounts for more of the variability than the spatially structured effect.

3.3.2.2 Model selection

Collinearity was detected between temperature variables therefore only monthly mean temperature was used in the final model to capture long term associations with vector abundance (i.e., reduced effect of temperature extremes). I conducted model selection on model covariates (all fixed and spatial, seasonal and study-level random effects), evaluating their contribution to the model fit by removing each component in turn from the full model and examining the effect on the Bayesian pointwise diagnostic metric Watanabe-Akaike Information Criterion (WAIC) (Hooten and Hobbs, 2015). I tested 17 environmental variables (see Appendix 2 Table S3.2). I screened variables using a single pass whereby I removed each variable in turn from the model and assessed the change in WAIC. Covariates that did not improve model parsimony by a threshold of at least 2 WAIC units were excluded. I used this screening procedure to remove variables which were not improving model parsimony rather than searching for a best subset of variables as is performed in stepwise selection. The models were examined for fit and adherence to assumptions which included testing the model residuals for spatial autocorrelation using Moran's *I* (Cliff and Ord, 1973). Temporal autocorrelation could not be assessed since the data were not sampled at regular intervals over the whole study period. In addition, to assess

the influence of additional inferred absence data on model fit, I repeated the process of randomly selecting 20 inferred absence data points 25 times and examined the impact on WAIC.

I further evaluated the predictive ability of the models using random (10-fold) cross-validation which involved fitting separate models holding out data from each fold in turn. The random assignment of data to folds was chosen to represent the spatiotemporal variation in predictor space in all folds. The spatial clustering in abundance data meant that spatially structured cross-validation by state was not used for model evaluation (Roberts *et al.*, 2017). The final model was selected by comparing models of increasing complexity, in terms of input variables and model structure, to a baseline model which only included spatial effects and study-level random effects. This baseline model represents static vector abundance predictions that do not account for seasonality. I compared the baseline model to a seasonal model which also included the addition of a seasonal effect to account for seasonality in vector abundance and an environmental model which included spatial, seasonal, and random effects and environmental covariates. The ability of the models to predict log vector abundance (unscaled) was compared using the mean absolute error (MAE) between the predicted posterior mean values and the corresponding observed log vector abundance (Willmott and Matsuura, 2005) where lower values indicate a smaller difference between the predictions and the observations. In addition, I used conditional predictive ordinates (CPO) (Pettit, 1990) and predictive integral transform (PIT) (Marshall and Spiegelhalter, 2003) as cross-validatory criterion for model assessment. For CPO, a value is computed for each observation with small values indicating a bad fitting of the model to that observation and the potential for it to be an outlier. Predictive integral transform provides a version of CPO that is calibrated so that values like between 0 and 1. A histogram of PIT values that appears approximately uniform indicates the model represents the observation well. I also compared the direction and magnitude of fixed effects for hold-out models to examine the robustness of vector-environment relationships. The fixed effects parameter estimates were assessed using the posterior mean and 95% credible interval which is interpreted as the interval that covers the true parameter value with a probability of 95%, given the evidence provided by the observed data.

3.3.2.3 Spatiotemporal predictions of JE vector abundance and uncertainty

The best-fitting model was used to predict seasonal relative vector abundance (logscale) per (0.208º) grid cell across India for the three main seasons: winter (October to February), summer (March to May), monsoon (June to September). The seasons were chosen for their distinct climatic characteristics with heavy rainfall in central regions and the eastern coast during the winter, heavy rainfall in southwestern and north-eastern India during monsoon and high temperatures with little to no rainfall during summer (Kingwell-Banham, 2019). I evaluated the uncertainty in model predictions by mapping the SD in estimated vector abundance per grid cell for each season. A narrow SD (SD < 1) indicated low uncertainty and a wide SD (SD > 1) indicated high uncertainty.

3.3.2.4 Model-outbreak data comparison

To examine whether predicted mosquito abundance is correlated to JE cases, I compared observed human outbreaks of JE with model predictions for vector abundance at the same geographic location and calendar month. I define a JE outbreak as one or more confirmed or suspects cases of JE occurring in the same village within the same month. I converted JE outbreak data to binomial (presence/absence) data that a JE outbreak occurred in a particular geographic location and calendar month. I randomly generated pseudoabsence JE case data for 1000 locations for the 12 months (n=12000) to assess the ability of the model to correctly predict the probability that an outbreak occurred (which I describe as JE outbreak probability). I fitted a logistic regression of the probability of JE outbreak occurrence as a function of model-predicted vector abundance with and without a one-month lag using glm in R (R Core Team, 2020) . A null model (i.e., intercept only) was developed to represent predictions expected at random so that the effect of vector abundance predictions in explaining JE outbreaks could be assessed via comparing model Akaike Information Criterion (AIC) values. All data processing was conducted in R v.4.0.3 (R Core Team, 2020) with the packages *R-INLA* (http://r.inla.org) (Lindgren and Rue, 2015) and *raster* (Hijmans and van Etten, 2014).

3.3.3 Data availability

The vector data underlying the results presented in this chapter are archived at Figshare (https://figshare.com/s/377b76b6b79ffa2561cf). This dataset includes all vector data collected including records that pooled observations for more than one month. Sources for all freely available environmental datasets are described in Appendix 2 Table S3.2. Health data are available from the Ministry of Health & Family Welfare, Government of India:

https://www.idsp.nic.in/index4.php?lang=1&level=0&linkid=406&lid=3689.

3.4 Results

3.4.1 Model selection

Table 1 shows model predictive accuracy statistics for a series of models of increasing complexity. The most complex model structure (Model 3), which contained spatial, seasonal, and random effects and environmental factors, achieved superior model fit (ΔWAIC from baseline model = -77.53) (and see Appendix 2 Figure S3.2). Comparison of out-of-sample predictive ability showed that the inclusion of seasonality in the model (Model 2) improved predictions of vector abundance by decreasing MAE by 15% (ΔMAE = -0.14) when compared to the baseline model (Model 1). The addition of environmental covariates (Model 3) led to a further 40% decrease in MAE when compared to seasonal Model 2 (ΔMAE = -0.32). As well as spatial, seasonal, and random effects, the final selected environmental model (Model 3) included six covariates after accounting for collinearity and covariate selection as described. The fixed effects in the final model included two-month lagged precipitation, proportion of land under agricultural use in 1km radius, annual number of rice crops, rice area cultivated, and rice produced per district and a nonlinear function for mean temperature. The CPO and PIT histograms demonstrated that addition of environmental covariates in Model 3 led to a better fit of the model to the data and a superior representation of the observations when compared to the other models (Appendix 2 Figure S3.3). Model residuals displayed no significant (p <0.05) spatial autocorrelation among sites. The random selection of inferred absence data points was found to have no substantial impact on the ΔWAIC values for the different models (Appendix 2 Table S3.3).

Table 3.1. Model selection results for models of increasing complexity.

The table details the structure of the joint-likelihood models and their corresponding within-sample predictive accuracy assessed on Watanabe-Akaike Information Criterion (WAIC) values. Best models were selected based on minimising WAIC while adhering to model assumptions. Out-of-sample predictive accuracy was compared using mean absolute error (MAE) statistic for random cross validation. Fixed effects included two-month lagged precipitation, proportion of land under agricultural use in 1km radius and district-level measures for annual number of rice crops and total rice area cultivated and rice produced per year. Mean temperature was included as a second-order random walk function to represent the nonlinear relationship between temperature and vector population dynamics. Non-environmental effects considered were for month (M) and state-level spatial (ST) effects specified as a BYM model and study-level (S) random effects.

Model		Non-environmental effects	Environmental effects	WAIC	MAE
1	Baseline model	ST, S	-	722.15	0.95
2	Seasonal model	M, ST, S	-	651.14	0.81
3	Environmental model	M, ST, S	Precipitation, Agricultural land proportion, Annual rice crops, Annual rice area, Annual rice production, Nonlinear temperature function	644.62	0.48

3.4.2 Associations between environmental variables and vector abundance

I found that *C. tritaeniorhynchus* abundance was associated with climatic and land-use factors (Figure 3.2B). I found positive associations between vector abundance and two-month lagged precipitation, number of rice crops and annual rice production. The annual area under rice cultivation had a negative relationship with vector abundance and the proportion of land under agricultural use had a weakly positive but uncertain association. Annual rice area and annual rice production had relatively

wide credible intervals (CIs) for their parameter estimates when compared to the other covariates making the effect of these parameters on vector abundance more uncertain. These fixed-effects estimates were robust to randomly structured sensitivity tests (Appendix 2 Figure S3.4). I found that the inclusion of a nonlinear effect for mean monthly temperature without a lag improved model predictive ability when compared to the nonlinear effect with two-month lagged temperature (ΔWAIC = -81.83). The resulting temperature function suggests an increase in vector abundance from 9ºC with a peak at around 23ºC (Figure 3.2C). CI widths were narrow for this function at high temperature values.
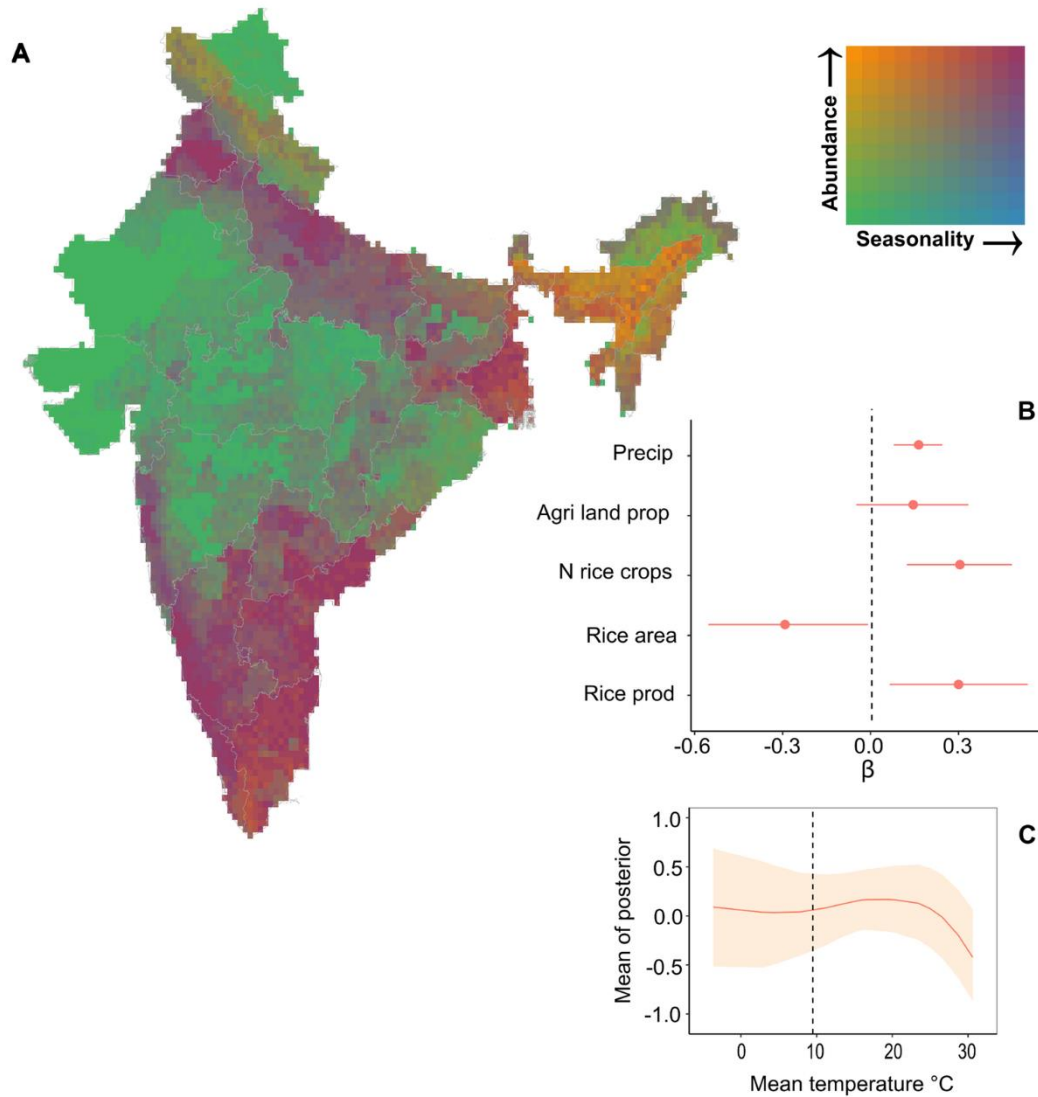
Figure 3.2. Spatiotemporal correlates of JE vector abundance across India averaged over the period 1990–2012.

Map to show predicted *C. tritaeniorhynchus* abundance (maximum annual value) and vector seasonality (intra-annual variance in abundance) (A). These measures were calculated from the scaled abundance predictions and ranged from 0 to 7 logscale for maximum abundance and 0 to 3 logscale for seasonality. The map displays areas of high perennial vector abundance as orange, high seasonal vector abundance as pink, low perennial vector abundance as green and low seasonal vector abundance as blue. The fixed-effect parameter estimates and 95% credible intervals for the joint likelihood model (B) show that vector abundance is associated with climatic and land-use variables. The nonlinear relationship between monthly mean temperature and vector abundance for the observed range of temperatures (ºC) where 95% CI is shown shaded and peaks at around 23ºC and then declines. The reported thermal minima (9.5ºC) for important *Culex* species life history traits (Mordecai *et al.*, 2019) is indicated with a dashed line.

3.4.3 Spatiotemporal predictions of JE vector abundance and uncertainty

Spatially projecting the final model predictions revealed differences in predicted areas of high (i.e., hotspots) or low (i.e., coldspots) *C. tritaeniorhynchus* abundance between seasons (Figure 3.3). Peaks in vector abundance were found in the northern, eastern, north-eastern, and southern regions, with highest levels predicted during the winter months (October to February) and lowest levels during the summer months (March to May). Hotspots of vector abundance were predicted with low uncertainty (i.e., narrow SD) in northern, southern, and north-eastern India during the winter (Figure 3.3A) and in north-eastern and southern India during the summer (Figure 3.3B) and monsoon (June to September) seasons (Figure 3.3C). By contrast, hotspots were predicted with high uncertainty (i.e., wide SD) for all seasons in the northern state of Punjab, the eastern state of West Bengal and the south-eastern state of Andhra Pradesh. Areas predicted with low vector abundance (i.e., coldspots) were predicted throughout the year in the Himalayas, and in central and north-western states, and eastern state of Odisha. Uncertainty in coldspot predictions was low for the Himalayas throughout the year (likely as a result of inferred absence data) whereas summer predictions for Odisha, central and north-western states and monsoon predictions for Rajasthan were more uncertain (represented as increased transparency in Figure 3.3). Assessing vector abundance and seasonality simultaneously reveals hotspots of high perennial vector abundance in north-eastern areas and the southern tip of the country (Figure 3.2A). Conversely, high seasonal vector abundance is predicted in northern and southern regions (Figure 3.2A).
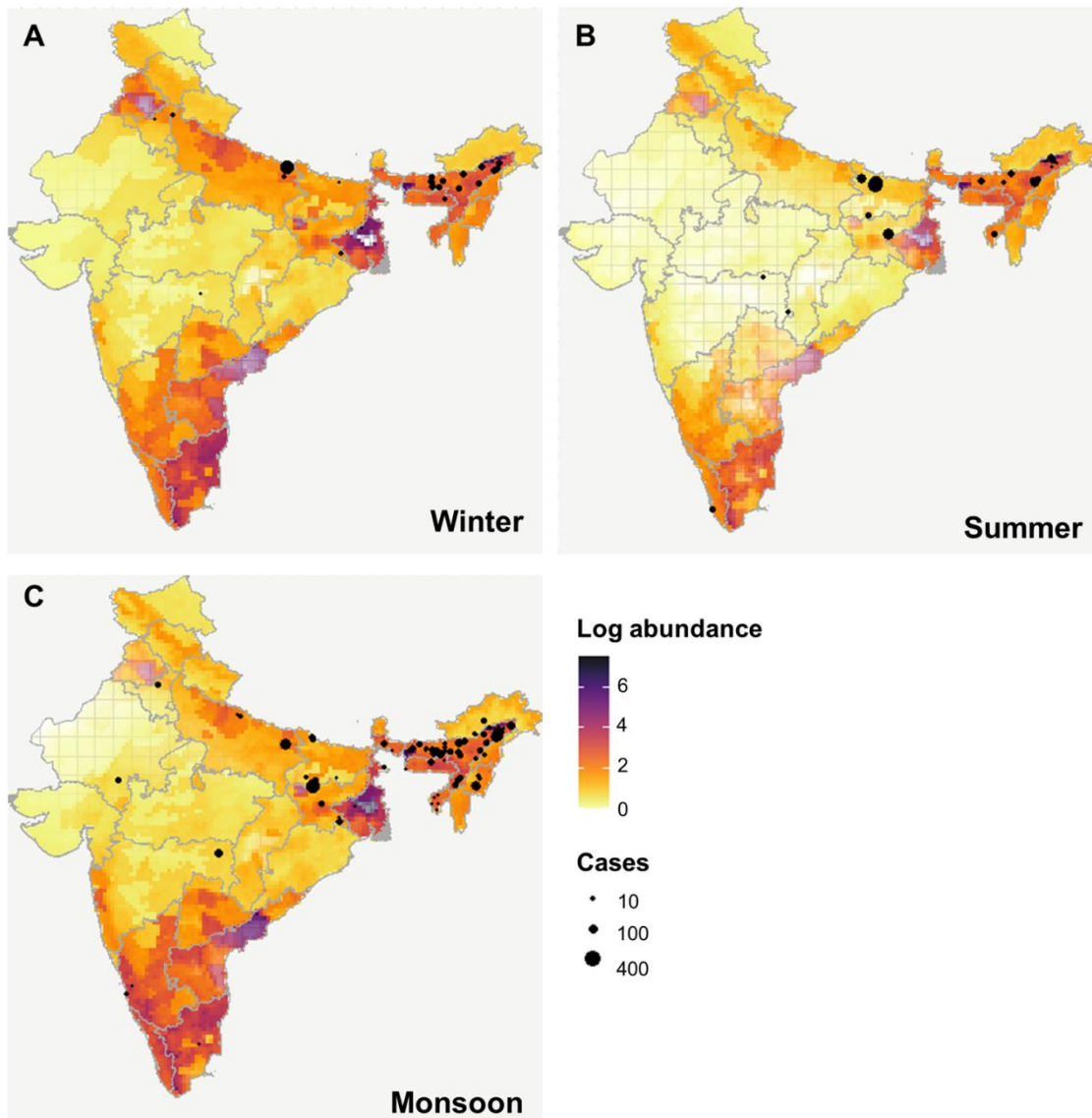
Figure 3.3. Predicted seasonal abundance of *C. tritaeniorhynchus* across India for the period 1990–2012.

Average vector abundance (logscale) for the (A) winter (October to February), (B) summer (March to May) and (C) monsoon (June to September) seasons. The figure legend is scaled from 0 to 7 logscale, with light yellow colours signifying low vector abundance and dark purple emphasising high abundance. Uncertainty in predictions was estimated from standard deviation (range 0-2 SD) and is represented in the maps by transparency (high uncertainty is more transparent). The black circles represent the location and magnitude (i.e., number of cases) for JE human outbreaks per season during the period 2009-2015 across India (Ministry of Health & Family Welfare, Government of India, 2020).

3.4.4 Model-outbreak data comparison

The results for the comparison between predicted mosquito abundance and JE cases is summarised in Appendix 2 Table S3.4. Logistic regression of JE outbreak probability as a function of model predicted vector abundance with a one-month lag month showed superior predictive ability (AIC = 144.17) when compared to the same analysis with vector abundance predicted in the same month as the outbreak (AIC = 147.66) and to the null model (AIC= 168.02). Both model-predicted vector abundance with and without a one-month lag had a significant positive effect on human JE outbreaks however, the lagged variable had a stronger association (odds ratio [OR] 2.45, 95% confidence interval: 1.52-4.08) than the variable without a lag (OR 2.25, 95% confidence interval: 1.35 -3.74) (see Appendix 2 Table S3.4). Plotting predicted JE outbreak probability against log-scaled vector abundance for the best-fitting model (Appendix 2 Figure S3.5) illustrates that the strong association between these variables is non-linear and plateaus at high levels of vector abundance lagged by one month.

3.5 Discussion

This study describes a novel approach for the prediction of spatiotemporal patterns in *C. tritaeniorhynchus* abundance – a key component of JE hazard - using a joint-likelihood modelling technique that leverages information from sparse vector surveillance data. I show that the addition of environmental covariates in the model substantially improved out-of-sample predictive ability, highlighting the importance of environmental and climate data in driving JE vector abundance. This provides a strong justification for producing spatiotemporal vector predictions to help focus future work efforts and build towards accurate forecasts of JE risk. This framework provides a powerful and flexible method which will help to define seasonal JE vector abundance over large spatial scales and assist in guiding future surveillance efforts where long-term and large spatial scale data are not available or cannot be practically acquired. This analysis builds on previous correlative studies of *C. tritaeniorhynchus* which have mapped vector occurrence but have overlooked seasonal variation in population dynamics and have not accounted for uncertainty

within the predictions (Masuoka *et al.*, 2010; Miller *et al.*, 2012; Longbottom *et al.*, 2017; Samy *et al.*, 2018).

A distinct temporal pattern was observed across India in predicted vector abundance, with peaks in the winter (October to February), reductions during the summer (March to May) and increased vector abundance again during the monsoon (June to September). This temporal pattern can be explained by seasonality in climatic factors during the year which supports findings in previous studies (Reisen, Aslamkhan and Basia, 1976; Murty, Rao and Arunachalam, 2010; Kumari and Joshi, 2012) and my hypothesis that vector abundance will be strongly influenced by seasonal rainfall. During the monsoon, heavy rainfall moving in a south-westerly direction across the country has been reported to enhance the availability of vector breeding habitats (Balasubramanian and Nikhil, 2015) and causes a reduction in local temperatures (Das Bhowmik, Suchetana and Lu, 2019) which provides suitable environments for vector development. The peaks in vector abundance observed during the winter months probably reflect the post-monsoon rice cultivation period when water availability is high in the paddy fields (Shukla, Chakraborty and Joshi, 2017). This translates to the strong positive association between lagged precipitation and JE vector abundance found in this analysis and in other studies (Tian *et al.*, 2015). Conversely, high temperatures and low rainfall during the summer months probably limits vector survival and breeding (Murty, Rao and Arunachalam, 2010), especially in areas with low levels of irrigated agriculture. Climatic conditions will also influence areas with predicted low perennial vector abundance such as arid regions in the northwest and northern states in the Himalayas which record temperatures beyond the thermal limit for *Culex* species vectors (Mordecai *et al.*, 2019).

In addition to precipitation and temperature, land-use and rice cultivation metrics were identified as important drivers of broad-scale spatiotemporal patterns of vector abundance. The importance of land-use factors is illustrated by comparing hotspots of JE vector abundance in southern and north-eastern India which have high levels of irrigated agriculture despite differing climates (i.e., tropical in south, temperate in northeast) (Beck *et al.*, 2018). Regions with high proportions of agricultural land allocated to intensive irrigated agriculture provide suitable vector breeding habitats for extended periods which undoubtedly influence vector abundance and seasonality.

Indeed, regions that cultivate rice biannually report lower vector seasonality compared with those that have a single annual crop (Gajanana *et al.*, 1997). The positive relationship between land-use intensity metrics for rice crop cultivation (i.e., number of rice crops cultivated and amount of rice produced per year) and vector abundance detected in this study, supports previous research that has found a strong positive association between vector abundance and rice irrigation practices at local scales (Kanojia, Shetty and Geevarghese, 2003; Keiser et al., 2005b; Richards *et al.*, 2010; Raju *et al.*, 2018). Surprisingly, I found that the annual area under rice cultivation was negatively associated with vector abundance, albeit with wide CIs. This result may be spurious due to data quality issues or could be explained by unmeasured underlying factors such as agrichemical use (i.e., fertilisers and pesticides) (Kibuthu *et al.*, 2016), methods of irrigation (i.e., surface, sprinkler or drip irrigation) or use of fallow periods between crops which may lead to changes in local ecology (e.g., biotic interactions such as competition and predation) (Ohba, Matsuo and Takagi, 2013). Indeed, local changes in ecology due to rice crop phenology are also likely to influence the presence of JE hosts since wading bird use irrigated rice paddies as feeding habitat (Elphick, 2015) and fallow fields may be used to graze livestock. Understanding these relationships would require improved understanding of rice crop phenology together with biodiversity monitoring in rice fields. My findings highlight the strong association between land-use practices and JE vector abundance which may have implications for the predicted expansion of flooded areas for rice cultivation needed to improve food security (Keiser et al., 2005b; Alexandratos and Bruinsma, 2012) and the ongoing intensification of rice production in India (Song *et al.*, 2018).

Spatiotemporal patterns in JE vector abundance varied widely across India with seasonal hotspots predicted in northern, eastern, and southern regions and perennial hotspots predicted in north-eastern regions and the southern tip of India (Figure 3.2). These results support the spatial pattern in endemic regions of India which report particularly high endemicity in the states of Uttar Pradesh in the north, Bihar and West Bengal in the east, Assam in the northeast, and Tamil Nadu in the south (Government of India, 2014). In addition, vector abundance predictions reflected the described seasonality in JE transmission with increased outbreaks reported during the monsoon and winter seasons (Figure 3.3). However, predicted seasonal hotspots

in the southeast did not correspond to high cases, which could reflect factors not accounted for in the analysis such as unmeasured environmental factors affecting transmission, spatial biases in different datasets or differing vaccination and vector control measures. In addition, it may also reflect the importance of vertical transmission for this disease which is selected for when there is seasonality in vector abundance (Lequime, Paul and Lambrechts, 2016). I found a positive correlation between one-month lagged vector abundance predictions and the occurrence of human JE outbreaks when using a simple correlative analysis. This analysis assumes that the location of the vector abundance will also be the location in which exposure occurred which may be inaccurate. Indeed, to fully gauge the strength of this association and assess the usefulness of vector abundance as potential proxy for JE hazard would require a more complex model that accounts for temporal and spatial autocorrelation in model residuals and uncertainty in the model. The development of a reliable proxy for JE hazard would be invaluable since data on pathogen prevalence in both animal reservoir host populations and vector populations that is required to define areas of JE hazard remains scarce. The further translation of hazard to disease risk requires additional knowledge about the potential exposure and susceptibility of human populations. For example, data on human demography, socioeconomics and vaccination coverage will provide information on contact with pathogens (exposure) and likelihood of infection (susceptibility) (Hosseini *et al.*, 2017). Furthermore, potential lags between peak vector abundance and human cases that occur due to transmission dynamics or timeliness of reporting need to be considered (Parham *et al.*, 2015). Indeed, future studies could extend this analysis by including further information on hazard, exposure, and vulnerability of human populations as well as any potential time lags to determine spatiotemporal predictions of JE risk (Johnson, Escobar and Zambrana-Torrelio, 2019).

A significant limitation of this study was related to the spatial and temporal biases of available *C. tritaeniorhynchus* surveillance data which is probably connected to the high costs associated with vector sampling studies (ECDC and EFSA, 2018). Although data paucity leads to less accurate predictions in data-poor regions, I accounted for this by presenting the level of uncertainty within predictions on the vector abundance maps. Furthermore, it should be acknowledged that model predictions will not provide accurate data at the local level, instead they reveal broad

scale ecological patterns that can help to direct future research efforts. In addition, the generation of additional absence data assumes that vectors do not occur at altitudes above 3500m which may need to be reviewed overtime in future surveillance studies and the influence of expected climate change (Rocklöv and Dubrow, 2020). This study highlights the need for improved vector surveillance for JE, with the potential for future surveillance efforts to be targeted in those areas with high predicted vector abundance. This would help validate my results with the use of independent data and improve predictions in areas that have not been surveyed. In addition, I found that despite JE vector abundance predictions being relatively focal (Figure 3.2), the spatiotemporal distribution of vector sampling in the data were more evenly distributed across India (Figure 3.1), suggesting that spatial bias is not driving model predictions (Figure 3.3).

A further limitation of this study was the coarse spatial resolution of rice cultivation data used in the model (Laborte *et al.*, 2017). The data were provided at district-level which may have been too coarse to detect an accurate relationship between land-use intensity metrics and vector abundance (Parham *et al.*, 2015) and may have prevented the detection of a correlation between vector abundance and rice cropping calendar data (Raju *et al.*, 2016). Future studies could explore the use of vegetation datasets such as normalized difference vegetation index (NDVI) at high spatial and temporal resolution to provide more accurate information on rice cultivation metrics (Huang *et al.*, 2014) and rice crop phenology (Onojeghuo *et al.*, 2018) in India. Investigating the lagged effects of these land-use factors on vector abundance (Tian *et al.*, 2015) may also help to elucidate the unexpected negative association between area for rice crop cultivation and vector abundance. In addition, despite the results of this study highlight the importance of environmental factors on vector abundance, the observational datasets and correlative analytic methods used do not enable the identification of underlying causal mechanisms (Hernán, 2018; Kraemer, Reiner and Bhatt, 2019). This means the generalisability of these ecological associations across time and space may be inaccurate (Washburne *et al.*, 2019) and it precluded the ability to investigate the effects of insecticide control (White *et al.*, 2017).

Despite these limitations, this work provides a framework to help monitor and predict the seasonal abundance of JE vectors which will be crucial for public health bodies in

their objective "to strengthen surveillance, (and) vector control" (Government of India, 2014). In line with other vector studies, this analysis combines datasets from multiple sources to address issues of limited data coverage and to produce maps for public health decision-making (Ribeiro *et al.*, 2019). Current management for JE varies regionally across India depending on socioeconomic factors and whether areas have historically recorded high cases (Government of India, 2014). With ongoing environmental change, I believe the Indian public health bodies cannot afford to continue to focus their vector surveillance efforts on currently endemic regions, and instead need to establish a broader scanning surveillance system which can assist in the development of early warning signals for the prediction and mitigation of JE outbreaks nationally. The maps produced in this study will be especially useful for the guidance of public health actions in targeting future vector surveillance in understudied regions previously predicted, with varying uncertainty, to have high vector abundance. My data could be used to inform the model and improve and update predictions. My work may also be used to improve the effectiveness of vector control measures especially in areas predicted to have high seasonal vector abundance, instead of being employed solely during JE outbreaks, as is current practice (Government of India, 2014)..

In this study I provided estimates of the variation in vector abundance across space and time by leveraging different types of data sources for *C. tritaeniorhynchus,* an understudied JE vector. I showed that distinct spatiotemporal patterns of JE vector abundance were driven by seasonality and environmental factors and so demonstrated the limitations of previously available static vector distribution maps estimating vector occurrence across large geographic ranges (Miller *et al.*, 2012; Longbottom *et al.*, 2017; Samy *et al.*, 2018). In addition, I showed that model predictions of vector abundance were positively correlated with JE outbreaks, highlighting the possible development of vector abundance as a proxy for JE hazard. I propose that the joint-likelihood model used in my research will be easily adaptable for other mosquito vectors and enable other vector abundance estimations to be made from limited vector surveillance data. Furthermore, this novel approach can be used to help guide future vector surveillance programmes by targeting data collection. Understanding the timing and drivers of patterns in vector abundance and seasonality offers important insights into how and when intervention measures

should be applied to reduce JE risk and how disease risk may vary with future environmental changes.

Chapter 4:

Climate, land-use and socioeconomic factors predict spatiotemporal dynamics of Japanese encephalitis risk

In this chapter I conduct spatial and temporal epidemiological analyses of systematic, multiyear Japanese encephalitis (JE) surveillance data (northeast India 2009-2019), to identify the socio-ecological correlates of observed JE occurrence, predict endemic areas of JE transmission, and evaluate whether environmental factors and vaccination coverage can be used to predict temporal trends in JE incidence.

4.1 Abstract

Japanese encephalitis (JE) is the leading cause of child viral encephalopathy in Asia however, public health interventions remain hampered by limited understanding of the geographic distribution, timing and intensity of outbreaks and its underlying drivers. In this chapter, I used a spatial Bayesian hierarchical model to determine the association between socio-ecological variables and JE outbreak occurrence and to predict areas of endemic transmission. The model was applied to a binary outbreak indicator for 115 districts in northeast India between 2009 and 2019. I also extended the model temporally to predict the magnitude and timing of JE incidence in four endemic districts using environmental variables. I found that the spatial pattern of JE outbreak occurrence was significantly associated with the proportion of agricultural land, the poverty prevalence and the temperature suitability. The best-performing predictive spatial model of JE outbreak occurrence included linear effects of the proportion of agricultural land, precipitation, poverty, and healthcare access, and, a nonlinear effect of maximum temperature. The inclusion of these covariates improved out-of-sample (OOS) predictive error (Brier score = 0.063) when compared to a baseline model including just random effects (Brier score = 0.065). Twenty-four districts were predicted endemic despite low or absent reported cases and would benefit from an increased surveillance effort. Temporal predictive models of JE incidence in endemic states showed that the inclusion of nonlinear lagged climatic and land-use variables improved predictive accuracy (Root mean square error [RMSE] for random cross validation = 33.83) over a baseline model (RMSE = 53.37).

The inclusion of vaccination coverage information with a two-month lag further improved model predictive accuracy (RMSE = 28.80), suggesting that it has the potential for forecasting JE incidence in endemic areas and may be useful in informing vaccination programmes. This study emphasises the sensitivity of JE to environmental and socioeconomic conditions and highlights the importance of focusing surveillance efforts in areas outside established JE transmission zones to further our understanding of this understudied disease and help inform effective public health interventions.

4.2 Introduction

Japanese encephalitis is the leading cause of viral encephalopathy in children, accounting for over 100,000 cases and 25,000 deaths annually, and primarily affects people living in rural, economically deprived areas (Baig *et al.*, 2013; Quan *et al.*, 2020). The causative pathogen, Japanese encephalitis virus (JEV), is maintained in an enzootic transmission cycle between mosquito vectors (van den Hurk, Ritchie and Mackenzie, 2009; Pearce *et al.*, 2018) and vertebrate reservoir hosts including domestic pigs and ardeid wading birds (e.g. herons and egrets) (Buescher *et al.*, 1959; van den Hurk, Ritchie and Mackenzie, 2009; Le Flohic *et al.*, 2013). The dynamics of JEV transmission are influenced by ecological interactions involving the environment, vectors and reservoir hosts and human socioeconomic factors that determine pathogen exposure and susceptibility to infection. Although susceptible to the virus, humans are considered 'dead-end' hosts since they do not mount sufficient viraemia to infect mosquitoes. Since JEV was first isolated in Japan in 1935, it has spread across the region (Mackenzie, Gubler and Petersen, 2004) and now is endemic in 24 Asian and Western Pacific countries, exposing over 3 billion people to infection risk (Erlanger *et al.*, 2009; G. L. Campbell *et al.*, 2011; WHO, 2015a). However, 87% of JE cases in Asia are reported from just four countries: India, Nepal, China, and Vietnam (Heffelfinger *et al.*, 2017; Lindquist, 2018). In India, increasing JE incidence has been reported regionally over the past few decades particularly in the northeast (Sabesan, Raju Konuganti and Perumal, 2008; Kumari and Joshi, 2012; Dhiman, 2014; Ahmad *et al.*, 2015; Dev, Sharma and Barman, 2015; Kulkarni

et al., 2018) despite national vaccination efforts, prompting the classification of JE as a national emerging public health problem (Government of India, 2014).

India introduced a JE vaccination campaign in 2006 which first targeted 11 districts with high reported cases in the states of West Bengal, Assam, Karnataka and Uttar Pradesh (Government of India, 2014). From 2006 to 2011 the vaccination campaign gradually integrated into the Universal Immunisation Programme and increased its remit to cover 113 districts in 15 states that reported JE transmission (Government of India, 2014). Children in both rural and urban areas of the operational districts were targeted and the campaign achieved an average reported vaccination coverage rate of 82% (Ghosh, Haldar and Jacobson, 2022). From 2011, JE vaccination has been expanded to target further districts that are identified as endemic using the criteria of number of cases reported (i.e., suspected or confirmed JE), incidence of JE, serological evidence or epidemiological links to known areas of transmission (Government of India, 2014). The SA 14-14-2 live attenuated JE vaccine was originally administered as a single dose to children aged 1–15 years (Tandale *et al.*, 2018) and from 2013 it was administered in two-doses to children at nine months and then at 16-24 months (Government of India, 2014). Though the vaccine is reported to be 97.5% for a two-dose regimen (Hennessy *et al.*, 1996), studies have reported vaccine efficacy of 30% - 40% in India (Vashishtha and Ramachandran, 2015; Tandale *et al.*, 2018). Possible explanations for this may include challenges with cold chain transport (Saikia, 2017), differences in circulating JEV genotypes in India (Schuh *et al.*, 2013) or cross-reactive immunity to other flaviviruses. In addition, studies have shown JE vaccination coverage is lower than reported (Murhekar *et al.*, 2017). Poor JE surveillance data and a lack of trust in the Indian public health system are substantial challenges to the success of the national vaccination strategy (Government of India, 2014; Singh *et al.*, 2015; Saikia, 2017).

Risk factors for JE include environmental conditions due to their influence on the ecology of the vectors and hosts (Keiser et al., 2005b; Erlanger *et al.*, 2009; Borah *et al.*, 2013; Le Flohic *et al.*, 2013) and socioeconomic factors due to their impact on human exposure and susceptibility to disease (Badari, 1985; Luo *et al.*, 1995; Sarkar *et al.*, 2012; Hosseini *et al.*, 2017). Climatic conditions are reported to contribute to the timing and magnitude of JE transmission (Dev, Sharma and Barman, 2015;

Medhi *et al.*, 2017; Tu *et al.*, 2021), due to the influence on mosquito vector abundance and seasonality (Le Flohic *et al.*, 2013) (Chapter 3). For example, ambient temperature can impact mosquito-borne disease (MBD) transmission in multiple ways including effects on mosquito lifespan and the extrinsic incubation period (i.e., period between mosquito ingesting an infectious blood meal and becoming infectious) (Mordecai *et al.*, 2019). Although thermal response data have been generated for several vector species and their pathogens (Mordecai *et al.*, 2019), this information is not readily available for JE vectors which limits our ability to understand the effect of temperature on the disease. One recent study investigated the impact of temperature on JEV infection of UK *Culex pipiens* vectors however, this laboratory-estimated thermal performance was not validated by measurements in the field (Folly *et al.*, 2021).

In India, JE outbreaks typically coincide with the monsoon (June to September) and winter periods (October to February) (Dev, Sharma and Barman, 2015; Medhi *et al.*, 2017; Kulkarni *et al.*, 2018). Increased rainfall during the monsoon promotes vector and wading bird habitats particularly in rural areas (Sabesan, Raju Konuganti and Perumal, 2008). Conversely, heavy rainfall can result in vector larvae being washed away (ICMR, 2001). Another risk factor for JE transmission is agricultural land-use, specifically rice paddy cultivation (Keiser et al., 2005b; Sabesan, Raju Konuganti and Perumal, 2008) since it provides the preferred breeding habitat for JE vectors (Rajagopalan and Panicker, 1978; Richards *et al.*, 2010; Raju *et al.*, 2016, 2018), wildlife host feeding habitat (Solomon, 2006; Misra and Kalita, 2010; Le Flohic *et al.*, 2013; Elphick, 2015) and human exposure to infected vectors (Richards *et al.*, 2010; Shah *et al.*, 2019). In addition, studies have shown that pig farming is associated with increased JE transmission since pigs are an important reservoir and an amplifying host (Keiser et al., 2005b; Datey *et al.*, 2020). However, studies on the importance of various hosts in India remain limited (Desingu *et al.*, 2016; Datey *et al.*, 2020). Moreover, current knowledge on JEV transmission ecology is strongly influenced by the first investigations undertaken in the 1950s in Japan (Buescher, Scherer, Rosenberg, *et al.*, 1959; Scherer and Buescher, 1959; Scherer, Buescher and McClure, 1959). For example, it was during this research that *Cx. tritaeniorhynchus* was implied as the primary vector (Lord, Gurley and Pulliam, 2015) which has resulted in irrigated agriculture being regarded as an important driver since it is the

preferred habitat for this species. The results from this initial research are a product of that location and time and therefore may not be generalisable to other contexts (Lord, Gurley and Pulliam, 2015).

Socioeconomic status, religion (i.e., prohibition of pork) and living conditions are also reported risk factors for the disease, with increased cases being reported in economically deprived populations (Luo *et al.*, 1995; Halstead and Jacobson, 2003; Sarkar *et al.*, 2012). However, these associations have been detected from retrospective observational studies without controlling for confounding factors or identifying underlying mechanisms. One potential mechanism linking economic status with JE risk is that increased resources enable the funding of interventions and vaccination programs leading to a reduction in JE risk as seen in Japan, Korea and Taiwan (Halstead and Jacobson, 2003). Although vaccination programmes and public health interventions are important determinants of JE transmission (Muniaraj and Rajamannar, 2019; Quan *et al.*, 2020), their success also relies on effective targeting; something which has been disputed in India (Bagcchi, 2014; Vashishtha and Ramachandran, 2015; Murhekar *et al.*, 2017). Overall, the complexity and variability of socioeconomic factors and insufficient knowledge of the scale at which these processes act (Caminade *et al.*, 2014; Parham *et al.*, 2015; Booth, 2018) has impaired understanding of their impact on JE risk.

Despite improvements in JE surveillance data, comprehensive records are not widely available and laboratory confirmation has proved difficult. Therefore, the exact global incidence and burden of disease are not fully understood (Sabesan, Raju Konuganti and Perumal, 2008; WHO, 2015b; Quan *et al.*, 2020). In 2007, the Indian Government initiated a national JE surveillance programme (Government of India, 2014) but, the high ratio of clinical to subclinical infections (1:250) (WHO, 2015b) means reported cases are not likely to represent the true number of infections (Government of India, 2014). Furthermore, since JE cannot be distinguished clinically from other causes of encephalitis (e.g., malaria, dengue, scrub typhus), underreporting of cases in non-endemic areas is thought to occur, especially where the other diseases are common (McNaughton, Singh and Khan, 2018). This scenario is further impacted by the limited healthcare resources in India, which results in a high proportion of health costs having to be met by the patient (WHO, 2020b) and so

comprehensive diagnostic tests may not be performed. The paucity of JE surveillance data from India has impacted our understanding of potential endemic areas (Sabesan, Raju Konuganti and Perumal, 2008) and important drivers of this disease. Consequently, the national goal of "reducing morbidity, mortality and disability in children due to JE" has been compromised (Government of India, 2014).

In this study, I aim to address these gaps in data by using a long-term JE surveillance dataset to identify socio-ecological drivers of spatial JE outbreak occurrence and to predict the endemic area of JE transmission in northeast India between 2009 and 2019. Additionally, I aim to evaluate whether climatic variability, land-use factors and vaccination coverage can be used to predict the timing and magnitude of JE incidence in a subset of endemic districts.

4.3   Materials and methods

4.3.1   Study area

India is the second most populous country in the world, with a population of over 1.3 billion people. The country consists of 28 states and eight union territories (Figure 4.1) and currently has 742 districts, which have increased from the 640 districts listed in the last census (Government of India, 2011). India experiences a wide range of biomes and climate systems including tropical areas in the south and temperate and alpine (Himalayas) areas in the north (Zhang *et al.*, 2017) (Appendix 3 Figure S4.1). Although monsoon rainfall contributes to approximately 75% of the annual precipitation across India, there is considerable spatiotemporal variability (Guhathakurta and Rajeevan, 2008; Kishore *et al.*, 2016). Rainfall patterns are modulated by the topography of the western Ghats and the Himalayas (Kishore *et al.*, 2016), leading to high precipitation along the west coast and northeast regions of India and minimal precipitation in the northwest and southeast (Hrudya, Varikoden and Vishnu, 2021). Comparatively, the east coast (i.e., states of Odisha, Andhra Pradesh and Tamil Nadu) has two rainfall peaks, one in July–August and one in October–November (Kishore *et al.*, 2016). The second peak is due to the northeast monsoon (during October–December) which predominantly affects the east coast districts of India, providing 30–60% of their annual rainfall (Rajeevan *et al.*, 2012).

I focused my research in the endemic region of northeast India (Government of India, 2014) which is projected to undergo substantial changes in climate and land-use (Ravindranath *et al.*, 2011; Dutta, 2014; Prokop, 2020). The region includes the states of West Bengal, Sikkim, Assam, Arunachal Pradesh, Meghalaya, Nagaland, Tripura, Mizoram and Manipur (Figure 1), and shares international borders with Tibet, Bhutan, Nepal, Myanmar and Bangladesh. The region is divided into tropical, temperate and cold climates (Beck *et al.*, 2018) (Appendix 3 Figure S4.1A) and is recognised for its social marginality, inaccessibility, cultural and ethnical diversity, and rich biodiversity (Roy *et al.*, 2015). It is predominantly agrarian with paddy rice the primary crop, and over 70% of the population are engaged in the agricultural sector (Roy *et al.*, 2015; FAO, 2020).
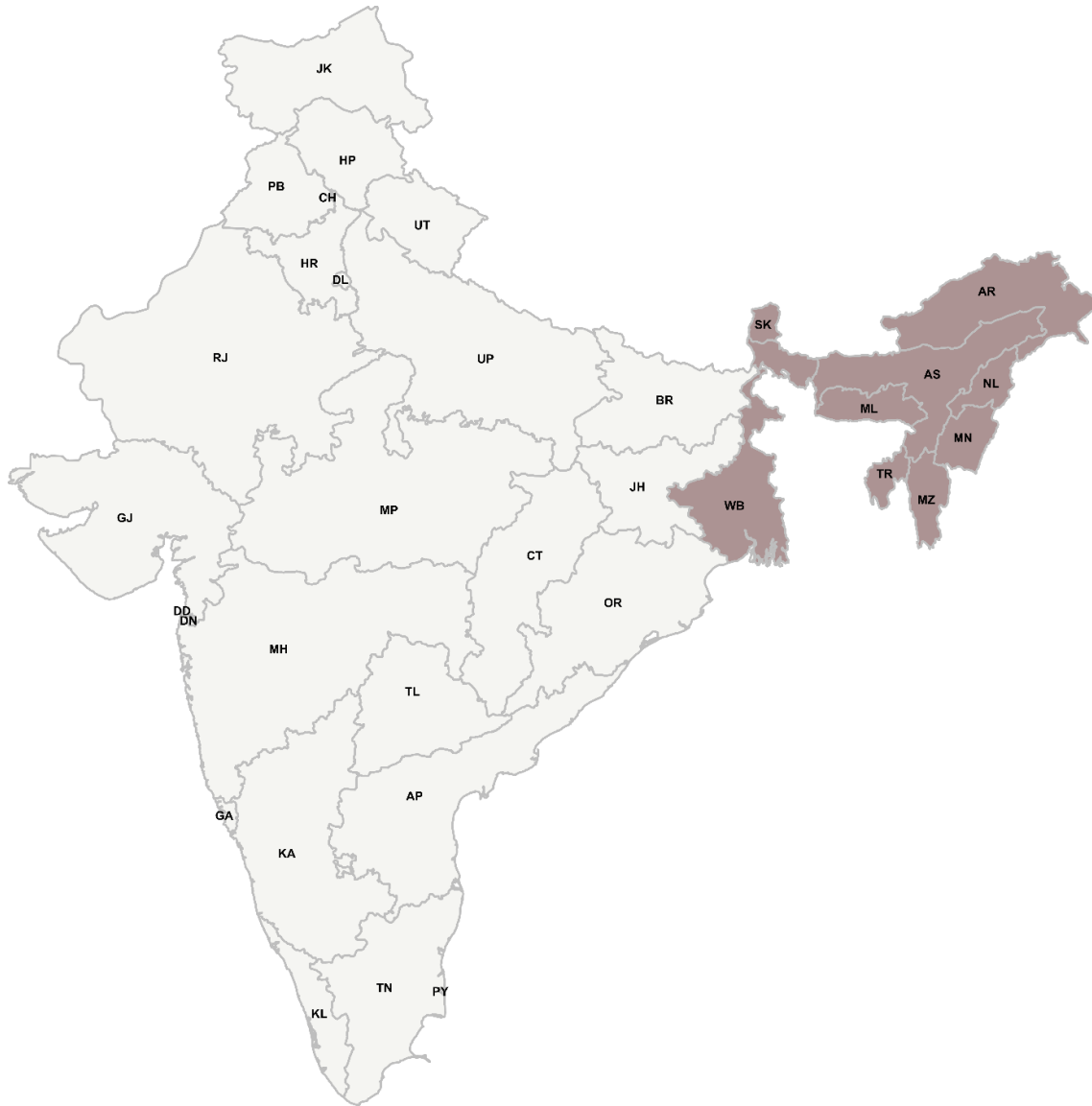
Figure 4.1. Map of India indicating states and union territories*.

The northeast region described in this study (nine states) is highlight in brown.

*Abbreviations for Indian states and union territories: AP - Andhra Pradesh, AR - Arunachal Pradesh, AS - Assam, BR - Bihar, CH – Chandigarh, CT- Chhattisgarh, DD - Daman and Diu, DL - Delhi, DN - Dadra and Nagar Haveli, GA – Goa, GJ – Gujarat, HP - Himachal Pradesh, HR - Haryana, JH - Jharkhand, JK - Jammu and Kashmir, KA - Karnataka, KL – Kerala, MH - Maharashtra, ML - Meghalaya, MN - Manipur, MP - Madhya Pradesh, MZ - Mizoram, NL - Nagaland, OR - Odisha, PJ - Punjab, PY - Puducherry, RJ - Rajasthan, SK - Sikkim, TL – Telangana, TN – Tamil Nadu, TR - Tripura, UP - Uttar Pradesh, UT - Uttarakhand, WB – West Bengal.

4.3.2 Datasets

4.3.2.1 Human Japanese encephalitis surveillance data

I obtained reported counts of suspected and confirmed human cases and deaths attributed to JE between 1st January 2009 and 31st December 2019, from across India (n=388). Weekly reports were provided at district level under the Indian government's Integrated Disease Surveillance Programme (IDSP) (Government of India, 2021b). IDSP requires weekly online reporting of suspected and confirmed cases of selected diseases, including JE, from each district; the information is reported by health workers, medical officers and laboratory technicians and is reviewed by a committee of epidemiologists and experts (Government of India, 2022). Prior to clinical confirmation of JE, suspected cases are reported under the umbrella term 'acute encephalitis syndrome' (AES) which is defined by the National Vector Borne Disease Control Programme as a person of any age, at any time of year with the acute onset of fever and a change in mental status and/or new onset of seizures (Kumari and Joshi, 2012). The clinical confirmation of the presence of JEV is done by testing the serum and/or cerebrospinal fluid samples of suspected cases by immunoglobulin (Ig)M enzyme-linked immunosorbent assay (ELISA) (Kumari and Joshi, 2012). Cases were aggregated by month of first symptom and district of residence to reduce zero-inflation in the data. I calculated JE incidence per 100,000 by dividing the monthly cases by population estimates for each district reported in the most recent census (Government of India, 2011).

Due to the systematic form-based reporting of JE cases (Government of India, 2022) and the classification of JE as a notifiable disease (i.e., required by law to be reported to government authorities) since 2016 (Kulkarni *et al.*, 2018), I assumed that no new cases had been detected when a district did not report any information for JE. To ensure I had monthly reported measures, reports were excluded if cases were reported as a cumulative number over a month duration from the start of outbreak date (n=102). In addition, data were only included if they provided district-wise case information (i.e., data reported at the level of state or multiple districts were excluded). Therefore another 21 reports were excluded (i.e., total = 265 [388 – (102 + 21)]). Reports of suspected JE which were later confirmed as negative for the virus were included in the dataset as confirmed negative cases. Between 2009 and 2019,

several new districts were created in India. To ensure data were consistent over the study period, I aggregated data to the 640 districts that were present in 2011 by combining the new districts with their parent districts

Since JE cases are relatively focal in India (Appendix 3 Figure S4.2), I decided to focus my analysis on the northeast region (nine states, 115 districts) of the country where many cases are reported (n=138/265), to better understand the processes driving transmission. Additional sources of human JE surveillance data for the northeast region of India were obtained from National Centre for Disease Control's (NCDC) Media Scanning and Verification Cell which monitors global and national media for health alerts (Sharma *et al.*, 2012), the India Health Management Information System (HMIS) data (Government of India, 2021a) and ProMED (International Society for Infectious Diseases, 2021). I also supplemented the data with published literature on JE outbreaks in the region. I performed a systematic literature search on PubMed using the search terms "Japanese encephalitis + (Arunachal Pradesh and/or Assam and/or Manipur and/or Meghalaya and/or Mizoram and/or Nagaland and/or Sikkim and/or Tripura and/or West Bengal" and selected a published data range from 2009 to present day, selecting journal articles published in English. These search terms provided 43 unique results, of which five articles were relevant after review. Case data were collected from all supplementary sources in the same method as described for the original surveillance data (Appendix 3 Table S4.1).

Due to the issue of variation in sampling effort when using multiple sources, I decided to use the single source of IDSP data to model spatial JE outbreak occurrence since fewer data were required to specify an outbreak occurrence. However, this single source did not provide enough non-zero data to model the seasonal JE incidence. Therefore, for the temporal model I first selected four neighbouring districts with the most data (i.e., Dibrugarh, Jorhat, Sivasagar and Tinsukia in Assam). I then supplemented IDSP data with data from supplementary sources for these districts. To reduce the potential for double counting and inflation of case numbers when using multiple sources, I only included supplementary data from a single source for months in which no data were reported in the IDSP dataset. The source of supplementary data was selected according to perceived case standardisation with Indian

government sources (i.e., HMIS data, NCDC data), followed by ProMED data and finally, published literature. The resulting temporal dataset of reported cases for the four districts of Assam included n=103 datapoints (IDSP [n=19], HMIS [n=32], NCDC [n=2], MED [n=15] and published studies [n=35]).

4.3.2.2 Meteorological data

Monthly mean daily minimum temperature (Tmin, °C), maximum temperature (Tmax, °C), precipitation (mm) and the Palmer drought severity index (PDSI) were obtained from Terraclimate (Abatzoglou *et al.*, 2018) for the period January 2009 to December 2019. The raster datasets were aggregated to each district using the *exactextractr* package in R (version 0.7.1) (Baston, 2021), by calculating the mean of the grid cells within each district, weighted by the fraction of the cell that lay within the district. The northeast region of India has clear seasonality in temperatures with cool winters, often falling below the thermal optima for Flavivirus transmission (between 23.9–26.4°C for *Culex* species. (Mordecai *et al.*, 2019) and below temperatures reported for optimal JEV transmission for predominant vector *Culex tritaeniorhynchus* (Tu *et al.*, 2021). The region receives an average annual rainfall of 2000 mm, accounting for about 10% of the country's total precipitation (Roy *et al.*, 2015) which primarily occurs during the summer monsoon (Guhathakurta and Rajeevan, 2008; Mahanta, Sarma and Choudhury, 2013). I used PDSI to determine the effect of unusually wet or dry periods on JE transmission since it provides a measure of drought or wetness conditions relative to the historical average by using soil moisture levels, expected evapotranspiration rate and precipitation (Alley, 1984; The National Center for Atmospheric Research, 2020).

4.3.2.3 Land-use type

I obtained annual land cover data from the European Space Agency (ESA) Climate Change Initiative Land Cover dataset (version 2.1.1) for 2009–2019 (ESA; http://maps.elie.ucl.ac.be/CCI/viewer/index.php). Data on the proportion of individual agricultural and natural land cover classes were extracted for each district from the datasets using the *raster* package in R (version 3.4.5) (Hijmans *et al.*, 2020). I also extracted data on seasonal proportion of land under rice paddy cultivation for northeast India in 2017 (Singha *et al.*, 2019). To provide more accurate information on natural vegetation and crop cultivation dynamics (Onojeghuo *et al.*, 2018),

monthly mean Normalized Difference Vegetation Index (NDVI) data were extracted from MODIS (Didan, 2015) for the period January 2009 to December 2019. The raster datasets were aggregated to each district using the *exactextractr* package as described for meteorological variables.

4.3.2.4 Animal reservoir host data

I used Gridded Livestock of the World (version 3) data for domestic pig population density in 2010 (Gilbert *et al.*, 2018) to calculate the mean number of pigs per grid cell in each district using the *raster* package. To estimate the geographical distribution of sylvatic reservoir host presence, I fitted species distribution models with Bayesian additive regression trees (Carlson, 2020) to Intermediate egret (*Ardea intermedia*), Little egret (*Egretta garzetta*), Cattle egret (*Bubulcus ibis*), Indian pond heron (*Ardeola grayii*) , and Black-crowned night heron (*Nycticorax nycticorax*) occurrence data from January 2009 to December 2019 identified from ebird (eBird, 2021) and Global Biodiversity Information Facility (GBIF) (GBIF, 2021f, 2021d, 2021b, 2021i, 2021e, 2021g, 2021h, 2021a, 2021c), using the *embarcadero* package in R (Carlson, 2021) (see Appendix 3 Text S4.1. for full method and Figures S4.3, S4.3, S4.5, S4.6 and S4.7 for results). I then extracted the mean predicted probability of presence for each species per district using the *raster* package.

4.3.2.5 Human socioeconomic and vaccine coverage data

I retrieved data on human socioeconomic factors hypothesised to influence JE transmission (see Appendix 3 Table S4.2). District-level data on the total human population of residents, the population living in rural areas, the number of children under six years old and the population practicing major religions (i.e., Hindus, Muslims, Sikh, Buddhists, Jain, Christians) were obtained from the 2011 census (Government of India, 2011). I retrieved data on the number of residents in each district living in poverty as defined by the Multidimensional Poverty Index (MPI) recorded for India in 2016 (Alkire, Oldiges and Kanagaratnam, 2018) which tracks poverty across several indicators of health, education and living standards. These socioeconomic covariates were then converted to proportions of the total population per district in 2011 (e.g., proportion of the population living in rural areas per district, proportion of the population under 6 years old) to make interpretation and comparison of model coefficients easier. Data on healthcare access (i.e., number of

primary health centres and first referral units) were retrieved from annual district-wise estimates for 2010-2018, reported by the Indian Government's HMIS (Institute for Health Metrics and Evaluation, 2021). I calculated average healthcare access per capita for each district by dividing the number of healthcare centres per district by district-wise data on the total human population of residents from the 2011 census. I used data from 2010 to represent missing healthcare access data for 2009, and data from 2018 were used for missing data in 2019.

Vaccination is predominantly administered during routine childhood immunisation targeting infants aged around nine months old in at-risk endemic states (Muniaraj and Rajamannar, 2019). Data on routine infant vaccination coverage were retrieved from annual district-wise estimates for 2009-2019, reported by the Indian Government's HMIS (Institute for Health Metrics and Evaluation, 2021). I used this data to calculate the proportion of the population who had received a JE vaccine for each district per year. I used data from 2010 to represent missing data for 2009, and data from 2018 were used for missing data in 2019.

The full suite of covariates considered in this analysis, data sources and associated hypotheses are described in Appendix 3 Table S4.2. All calculations were made using a World Geodetic (WGS84) geographic coordinate system and R software version 4.0.3 (R Core Team, 2020) through RStudio (RStudio Team, 2020).

4.3.2.6 Data availability

The case data underlying the results presented in this chapter are archived at Figshare (https://figshare.com/s/e24f74c13f934a82c689). Sources for all freely available environmental datasets are described in Appendix 3 Table S4.2. Health data are available from the Ministry of Health & Family Welfare, Government of India: https://www.idsp.nic.in/index4.php?lang=1&level=0&linkid=406&lid=3689.

4.3.3 Statistical analysis

Statistical model inference and selection were conducted using Bayesian hierarchical regression using Integrated Nested Laplace Approximation (INLA) in R (Rue, Martino and Chopin, 2009; Lindgren and Rue, 2015). This framework enables the development of spatially and temporally-structured regression models that address data sparsity and spatial bias whilst also being computationally tractable (Rue, Martino and Chopin, 2009; Redding *et al.*, 2017).

4.3.3.1 Evaluative spatial model of JE outbreak occurrence in northeast India

To define the endemic area for JE and determine the spatial, socio-ecological correlates of disease in northeast India, I aggregated JE cases by districts and created a binary JE outbreak indicator. Initially I used a threshold of one per district-year to define a JE outbreak occurrence. I also modelled an alternative outbreak threshold of three confirmed cases per district-year. I developed a binomial spatial Bayesian hierarchical model using the binary outbreak indicator as the response variable for 115 districts in nine states in the northeast of India from January 2009 to December 2019. I modelled annual JE outbreak occurrence (n=115 districts over 11 years) where $Y_{i,t}$ is the binary presence (1) or absence (0) of a JE outbreak in district *i* during year *t,* and $p_{i,t}$ denotes the probability of JE outbreak occurrence, such that:

$$Y_{i,t} \sim \text{Bern}(p_{i,t}) \tag{1}$$

JE outbreak occurrence ($p_{i,t}$) is modelled as a function of socio-ecological covariates and random effects:

$$\text{logit}(p_{i,t}) = \alpha + \sum_{j} \beta_{\text{j}} X_{j,i} + \sum_{k} \delta_{k,i} + \gamma_i + u_i + v_i \tag{2}$$

where, α is the intercept; X is a matrix of socio-ecological covariates with linear coefficients given by β; $\delta_{k,i}$ are nonlinear effects for climatic predictors (specified as second-order random walks); interannual variability is included as an effect of reporting year specified as a first-order random walk (γ_i); and spatial reporting trends at district level are accounted for using spatially-structured (conditional autoregressive;(v_i) and unstructured i.i.d. (independent and identically distributed)

(u_i) random effects jointly specified as a Besag-York-Mollie model. I considered the following linear coefficients (β) that are hypothesised to influence JE transmission (see Appendix 3 Table S4.2): annual mean precipitation, annual mean Tmax, annual mean Tmin, probability of presence for sylvatic reservoir hosts (for individual species and combined), mean pig population density, proportion rainfed and irrigated agricultural land cover, proportion water bodies land cover, proportion mosaic vegetation land cover, proportion of the human population living in rural areas, proportion of population working in agriculture, proportion of the population under 6 years old, healthcare access per capita and proportion of the population living in poverty. I also considered nonlinear (random walk) terms for temperature and precipitation covariates because past studies of climatic factors and JE incidence suggest that these relationships may be nonlinear (Liu *et al.*, 2020; Tu *et al.*, 2021). Continuous covariates were rescaled using the z-score (to mean 0, s.d. 1) prior to fitting linear fixed effects. Weakly informative prior probability distributions (priors) were assigned for the intercept, $\alpha \sim N (0,1.5)$ and fixed effects, $\beta \sim N (0,0.5)$ to constrain the position and scale of the outcome to fall within a reasonable range. I assigned penalized complexity (PC) priors (Simpson *et al.*, 2017) to hyperparameters of the year and district-level effects and the nonlinear climatic covariates to penalise the complexity resulting from deviating from a simple base model.

I first constructed a baseline model comprising year and district-level spatial random effects to allow for interannual variability in unobserved factors (e.g., public health funding, vector control measures) and dependency structures (e.g., shared environmental and socioeconomic factors) between districts. I then conducted univariate selection on model covariates, examining the effect of each covariate on model adequacy measures, including the widely-applicable information criterion (WAIC) which balances model accuracy with complexity by penalising for the number of effective parameters in the model (McElreath, 2020b), and the mean cross-validated log score which measures the predictive power of the model when excluding each datapoint in turn (Gneiting and Raftery, 2007). For both measures, smaller values indicate better fitting models. Any covariates that did not improve both measures of model adequacy when compared to the baseline were excluded. For temperature and precipitation variables, I included linear and nonlinear effects in the univariate analysis to see which effects would perform best. I excluded covariates

that were highly collinear with one or more other others (Pearson correlation coefficient >0.8) and omitted potential collider variables (i.e., causally influenced by two or more variables) which might block associations between other variables. The remaining covariates were included in a full model on which I conducted multivariate selection by removing each covariate in turn and excluding any that did not improve fit by a threshold of at least five WAIC units. All posterior parameter distributions and residuals were examined for adherence to distributional assumptions. The fixed effects parameter estimates were assessed using the posterior mean and 95% credible intervals (CIs) which represents the interval that covers the true parameter value with a probability of 95%, given the evidence provided by the observed data. I examined the robustness of the relationships by evaluating the sensitivity of the model to k-fold cross validation by comparing the direction and magnitude of fixed and nonlinear effects for hold-out models. This involved randomly dividing the data into five folds (i.e., 20% of data), then fitting separate models holding out data from each fold in turn and extracting out of sample (OOS) predicted JE outbreak occurrence probability for the holdout fold (Valavi *et al.*, 2019). Despite the spatial structure in the data, spatial cross validation was not suitable (Roberts *et al.*, 2017), because data paucity in certain states caused substantial variation in the training data fold size.

4.3.3.2 Predictive spatial model of JE outbreak occurrence in northeast India

Compared to the goal of identifying socio-ecological drivers of JE outbreak occurrence, the goal of predicting endemic areas of JE transmission focuses on producing predictions that generalise well without explicit concern in understanding relationships between quantities of interest (Hofman *et al.*, 2021). Therefore, to accurately predict endemic areas, I subset the JE outbreak occurrence data to the last six years of the study period (i.e., 2014 to 2019) when most outbreaks were reported (Appendix 3 Figure S4.8). I conducted model selection on OOS prediction by identifying the model that minimised OOS predictive error using the same 5-fold split as described for the evaluative model. Model OOS predictive error for the whole region was calculated using the Brier score which is the mean squared difference between the observed outcome and the predicted probability of the outcome (Brier, 1950), whereby smaller values indicate better predictions. The final model was selected by comparing models of increasing complexity (with regard to input

covariates) to the baseline model and selecting the model with the lowest Brier score. Predictive ability was also evaluated by assessing the spatial variation in the Brier score (Colón-González *et al.*, 2021b) per district to understand areas where the model had improved outbreak detection ability. To determine the potential endemic areas of JE transmission using the JE outbreak occurrence probability, a threshold was defined by the value that maximized sensitivity and specificity when classifying outbreak occurrence and background data. This was calculated using a receiver operating characteristic (ROC) curve which plots the true positive rate against the true negative rate at different thresholds to select the threshold that maximises sensitivity and specificity. Any district with a predicted JE outbreak occurrence value above 0.08 was considered endemic.

4.3.3.3 Temporal model of JE incidence in endemic districts of Assam

I developed a temporal model to quantify the lagged climatic and environmental conditions that predict JE incidence (monthly confirmed case counts) in four neighbouring endemic districts in the state of Assam (i.e., Dibrugarh, Jorhat, Sivasagar and Tinsukia) from January 2009 to December 2019. I focused my analysis on these districts since they reported the most cases (Appendix 3 Figure S4.9) and Assam is a known endemic state with high surveillance effort relative to other states in the region. A zero-inflated negative binomial distribution was assumed to account for potential overdispersion in JE case counts and the generation of zeros from two processes (McElreath, 2020c): true JE absence and undetected cases. Data source-level and temporal random effects were included to account for unobserved and unmeasured sources of variation and temporal dependency structures. I included variables lagged at 0 to 3 months before reporting to account for exposure-lag response associations between environmental conditions and JE incidence (Liu *et al.*, 2020; Tu *et al.*, 2021). I did not include the other temporally invariant covariates included in the spatial models, since the focus on one state in this phase of the analysis provides low comparative power to detect any spatial effects on incidence.

I modelled monthly JE confirmed case counts in four districts of Assam Z_i (n=4 districts over 11 years; total 528 observations) as a zero-inflated negative binomial process (which models zero observations as a mixture of true and false negatives):

$$y_i \sim \text{ZINegBin}(\mu_i, \pi_i, \varphi) \tag{3}$$

where π_i is the zero-inflation probability, μ_i is the expected number of cases during month *i*, and φ is the overdispersion parameter. I used the "zeroinflatednbinomial1" distribution in *R-INLA* (https://inla.r-inla-download.org/r-inla.org/doc/likelihood/zeroinflated.pdf) which considers multiple sources of zero-inflation (i.e., structural zeros and excessive zeros). I selected a zero-inflated negative binomial model since it very flexible by allowing for over-dispersion arising from excess zeros and heterogeneity in count data, whereas a zero-inflated Poisson model only accommodates over-dispersion from excess zeros (Feng, 2021). Population effects were accounted for by including log population per 100 000 in the model as an offset at the linear predictor scale to give JE incidence rate per 100 000 population. I modelled JE incidence as a log-link function of a linear combination of temporally structured random effects and environmental covariates:

$$\log(\mu_i) = \alpha + P_i + \Upsilon r_i + t_i + s_i + \sum_k \delta_{k,i} \tag{4}$$

where, α is the intercept, P_i is log human population included as an offset, and several random effects are included: Υr_i is a temporal effect of year (first order random walk to account for ongoing changes in reporting effort and other interannual variability), t_i is a temporal effect of epidemiological month to account for seasonality (second order random walk to capture dependency between months) and, s_i is an i.i.d. random effect of data source to enable the model to account for between-source variation in sampling effort that might otherwise confound inferences. Additionally, $\delta_{k,i}$ are nonlinear effects of climatic predictor variables (specified as second-order random walks). I assigned weakly informative priors for the intercept, $\alpha \sim$ N (2,0.5) and fixed effects, $\beta \sim$ N (0,0.07) and PC priors to hyperparameters of the month, source, and nonlinear climatic effects.

I considered candidate models for lagged combinations of all covariates and identified the model that minimised OOS predictive error compared to the baseline model containing only random (year, month and source) effects. I performed temporal cross-validation by refitting the selected model 22 times, excluding all

observations for sequential six-month holdout windows across the study period and compared observations to OOS predicted case counts for the holdout window. Model predictive error was calculated as root mean square error (RMSE) of the difference between observed and OOS predicted case counts across the whole time series (2009–2019).

4.4 Results

4.4.1 Trends in JE surveillance data

Between January 2009 and December 2019, there were 2293 suspected and 1259 confirmed cases of JE reported by the Indian government's IDSP from 115 districts in northeast India. Over the 11-year period, significant outbreaks (i.e., outbreaks of more than 10 confirmed cases reported in one month) were reported from 2013 to 2016, particularly in the states of Assam, West Bengal and Meghalaya (Figure 4.2). Outbreaks were more widespread across the region from 2014 to 2019 (Appendix 3 Figure S4.8) with around 19% (22/115) of districts experiencing more than one outbreak throughout the study period (Figure 4.3). Most outbreaks occurred in the states of Assam and West Bengal, with a few outbreaks reported in Arunachal Pradesh, Meghalaya, Manipur, and Tripura (Figures 4.2, 4.3). No outbreaks were reported in the states of Sikkim, Nagaland, and Mizoram.
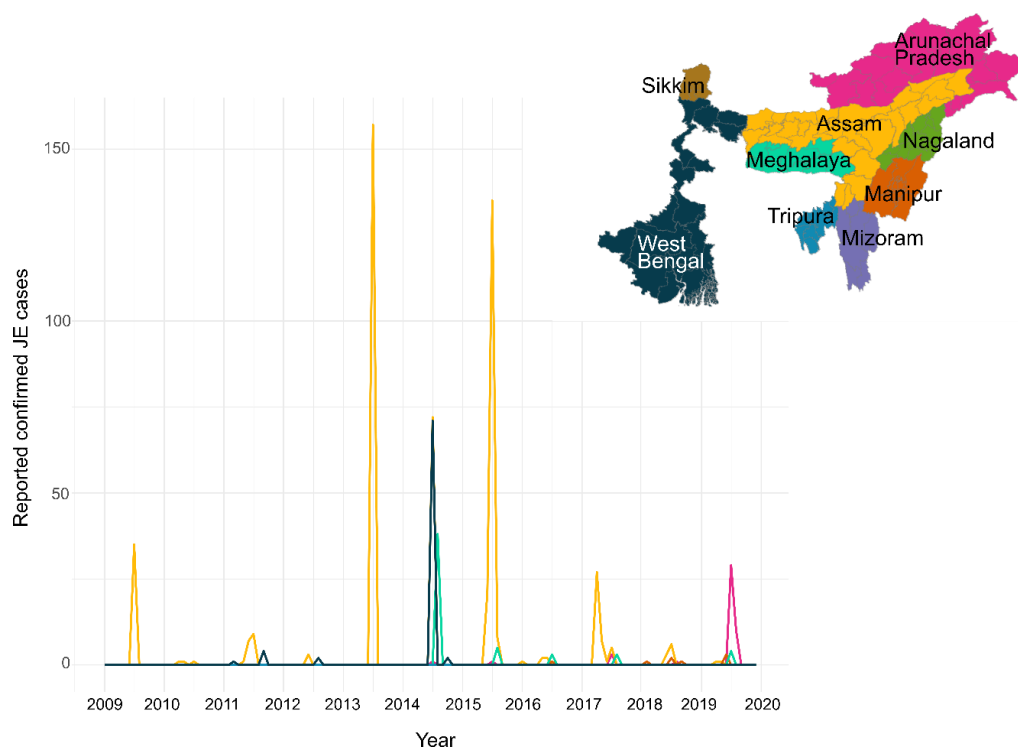
Figure 4.2. Reported confirmed Japanese encephalitis cases by state in northeast India 2009–2019.
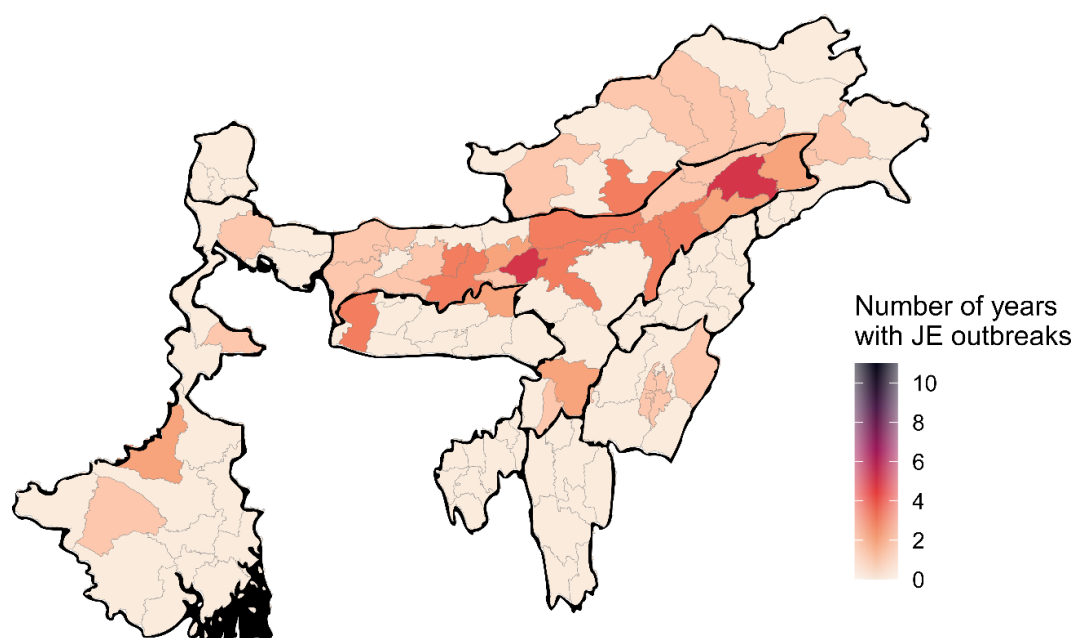
Figure 4.3 The number of years each district experienced a Japanese encephalitis outbreak (threshold of one confirmed case) between 2009 and 2019 in northeast India.

Although Assam had the highest number of JE cases over the 11-year study period, reports were concentrated in a small number of districts, particularly in the east (i.e., Dibrugarh, Jorhat, Sivasagar and Tinsukia) (Appendix 3 Figure S4.9). Focusing on JE cases from these four neighbouring districts showed that peak transmission generally occurred in the middle of the year and the largest outbreaks were reported in 2013, 2015 and 2017; of these, the outbreak in 2017 was the most significant (Figure 4.4).
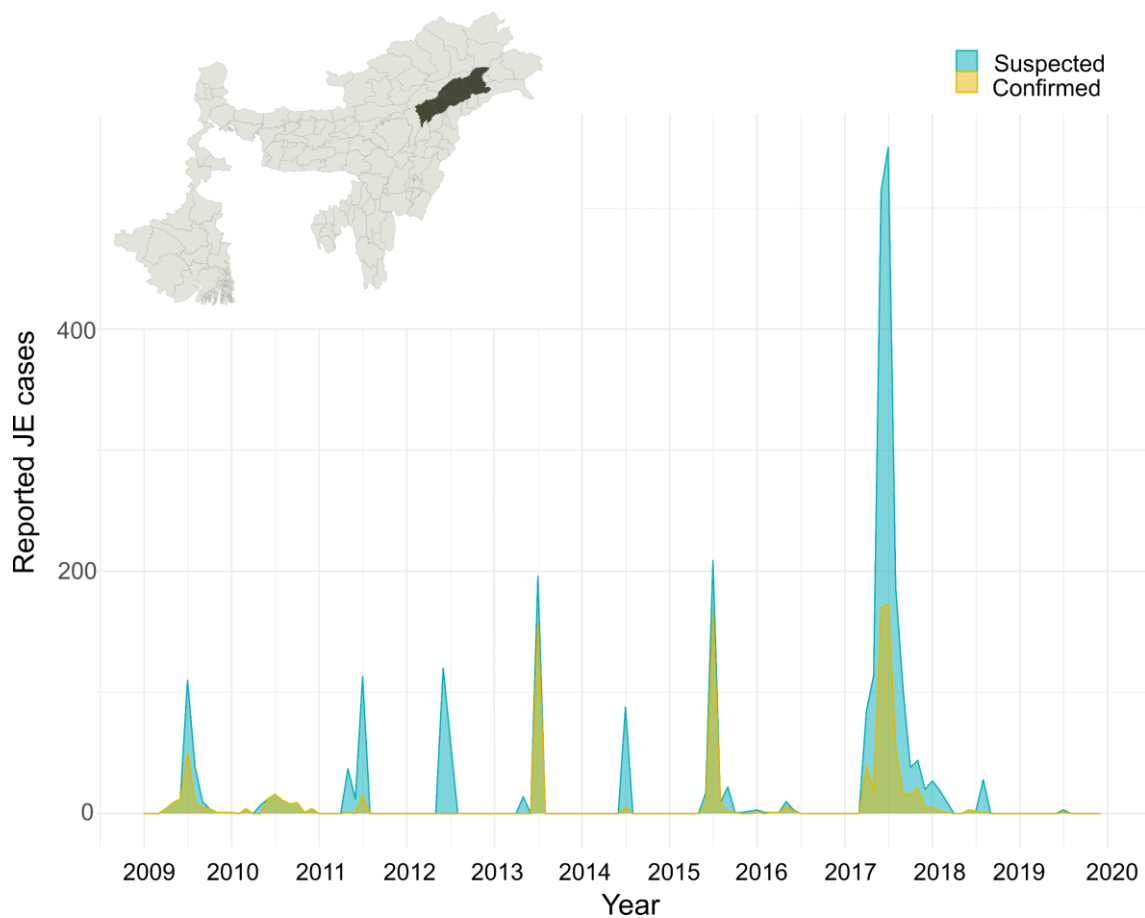
Figure 4.4. Monthly suspected and confirmed Japanese encephalitis cases in four endemic districts of Assam (i.e., Dibrugarh, Jorhat, Sivasagar and Tinsukia), 2009–2019.

4.4.2 Evaluating the spatial correlates of JE outbreak occurrence in northeast India

The results of the univariate (Appendix 3 Table S4.3) and multivariate selection (Appendix 3 Table S4.4) indicated that the best-fitting spatial model of JE outbreak occurrence included linear effects of agricultural land proportion, mean annual precipitation, mean pig population density, healthcare access per capita, proportion of the population living in poverty (Figure 4.5A) and a nonlinear effect of mean Tmax (Figure 4.5B). Districts with a high proportion of agricultural land (irrigated and rainfed) and a high poverty prevalence had a significantly increased probability of an outbreak (Figure 4.5A, Appendix 3 Table S4.7). Analysis showed that JE outbreak occurrence was influenced by climatic conditions, peaking in areas with mean Tmax levels around 26–28ºC, and declining sharply above 30ºC (Figure 4.5B). Although non-significant, mean precipitation was negatively associated with JE outbreak occurrence and pig density positively influenced JE outbreak occurrence (Appendix 3 Table S4.7). Despite their non-significant effects, mean precipitation, pig density and healthcare access were included in the model since they were considered important *a priori* factors. The covariate relationships were consistent under sensitivity analysis using an alternative outbreak threshold of three confirmed cases (Appendix 3 Figure S4.10). However, the nonlinear effect for mean Tmax appeared different with higher JE outbreak occurrence associated with low temperatures (Appendix 3 Figure S4.10C). The individual and combined presence of the sylvatic reservoir hosts were highly correlated (Pearson correlation coefficient r >0.8) with temperature and cropland covariates so these variables were not included in the model despite their *a priori* relevance.

The socio-ecological model explained substantially more of the variation in the data relative to a random effects-only baseline model (ΔWAIC= -40.58; Δlog score= -0.09; Table 4.1) Fixed and nonlinear effects direction and magnitude were robust in all hold-out models (Appendix 3 Figure S4.11).
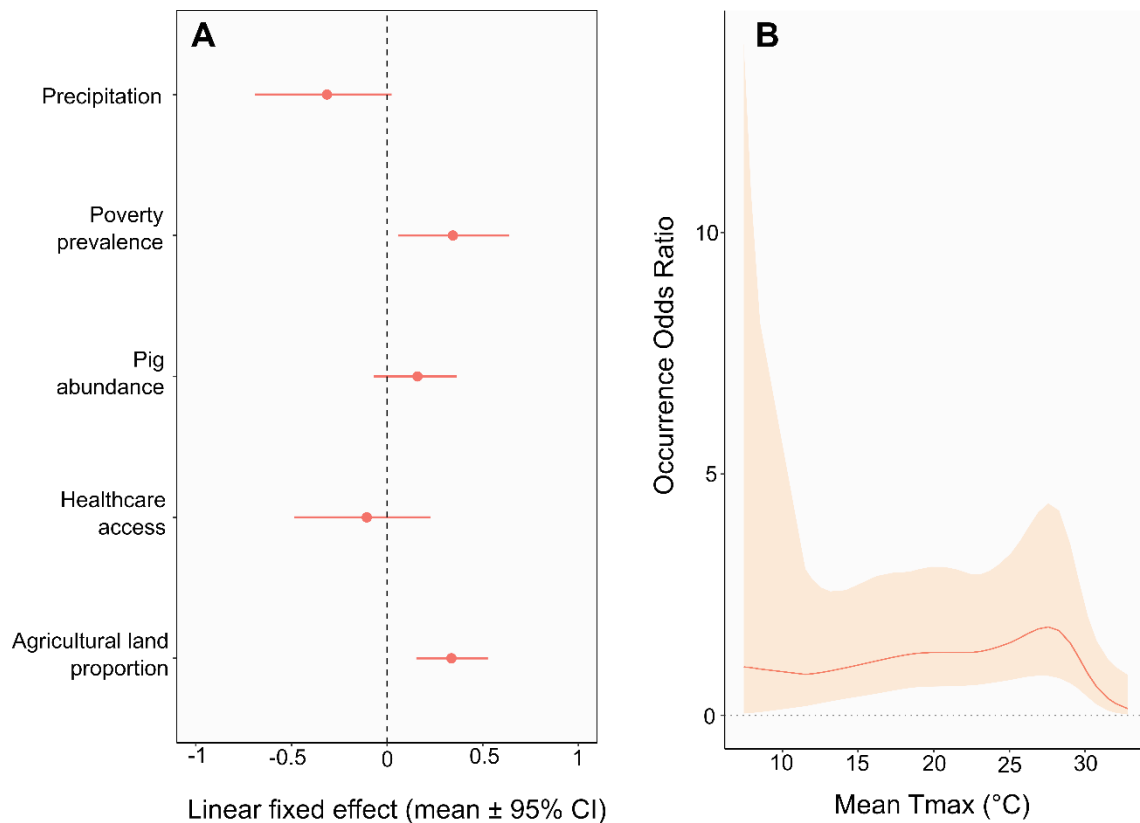
Figure 4.5. Correlates of annual Japanese encephalitis occurrence in northeast India 2009–2019.

(A) The mean and 95% credible interval (CI) of the posterior distribution for each model covariate for the best fitting model with a threshold of one confirmed case. The linear fixed effects are displayed on the standardised z-score scale, so parameters measure the effect of 1 scaled unit change in the covariate (1 standard deviation) on log odds of occurrence. (B) Curve shows nonlinear effects of mean Tmax on JE outbreak occurrence (odds ratio).

Table 4.1. Model selection results for models determining socio-ecological drivers of spatial Japanese encephalitis outbreak occurrence in northeast India.

The table shows the differences in structure and within-sample model fit (WAIC and log score) for the baseline (random effects only) and best-fitting socio-ecological model.

Model	Random effects	Socio-ecological effects	WAIC	Log score
Baseline	Year, district-level spatial random effects	-	226.20	0.49
Socio-ecological	Year, district-level spatial random effects	Precipitation, Pig population density Proportion of the population living in poverty, Healthcare access per capita, Agricultural land proportion, Nonlinear Tmax function	185.62	0.40

4.4.3 Predicting the spatial distribution of JE endemic areas in northeast India

The results of the model selection (Appendix 3 Table S4.5) indicated that the best performing predictive spatial model of JE outbreak occurrence included linear effects of agricultural land proportion, mean annual precipitation, proportion of the population living in poverty, healthcare access per capita, and a nonlinear effect of mean Tmax. The inclusion of these covariates marginally improved OOS predictive error according to the Brier score when compared to a baseline (random effects only) model (Table 4.2). These findings were consistent when modelling an alternative outbreak threshold of three confirmed cases (Appendix 3 Table S4.8). When comparing the difference in Brier score between the baseline and socio-ecological model per district (Appendix 3 Figure S4.12), the socio-ecological model performed better in many known 'high JE priority' districts of Assam (Government of India, 2014), suggesting the ability of the socio-ecological model to define high JE risk areas.

Table 4.2. Model selection results for models predicting spatial Japanese encephalitis outbreak occurrence in northeast India.

The table shows the differences in structure and out-of-sample model fit (Brier score) for the baseline (random effects only) and best-fitting socio-ecological model of JE outbreak occurrence.

Outbreak threshold	Model	Random effects	Socio-ecological effects	Brier score
1 confirmed case	Baseline	Year, district-level spatial random effects	-	0.065
	Socio-ecological	Year, district-level spatial random effects	Precipitation, Proportion of the population living in poverty, Healthcare access per capita, Agricultural land proportion, Nonlinear Tmax function	0.063

Spatially projecting the predicted probability of JE outbreak occurrence suggests that large areas of northeast India are suitable for JE transmission especially in the states of Assam and West Bengal (Figure 4.6A). The predictive model identified likely endemic districts (i.e., with the average probability of an outbreak above 0.08) across most of Assam and localised regions in Manipur, Meghalaya, Nagaland, Tripura, Arunachal Pradesh, and West Bengal (Figure 4.6B). When compared to the Indian Government's 'high JE priority' district list (Government of India, 2014), the model predicted several districts in these states that are not currently considered to be a priority for JE surveillance or intervention (Figure 4.6B). However, the model did not predict endemicity in the some districts considered high JE priority by the Indian government (Government of India, 2014) (Figure 4.6B).
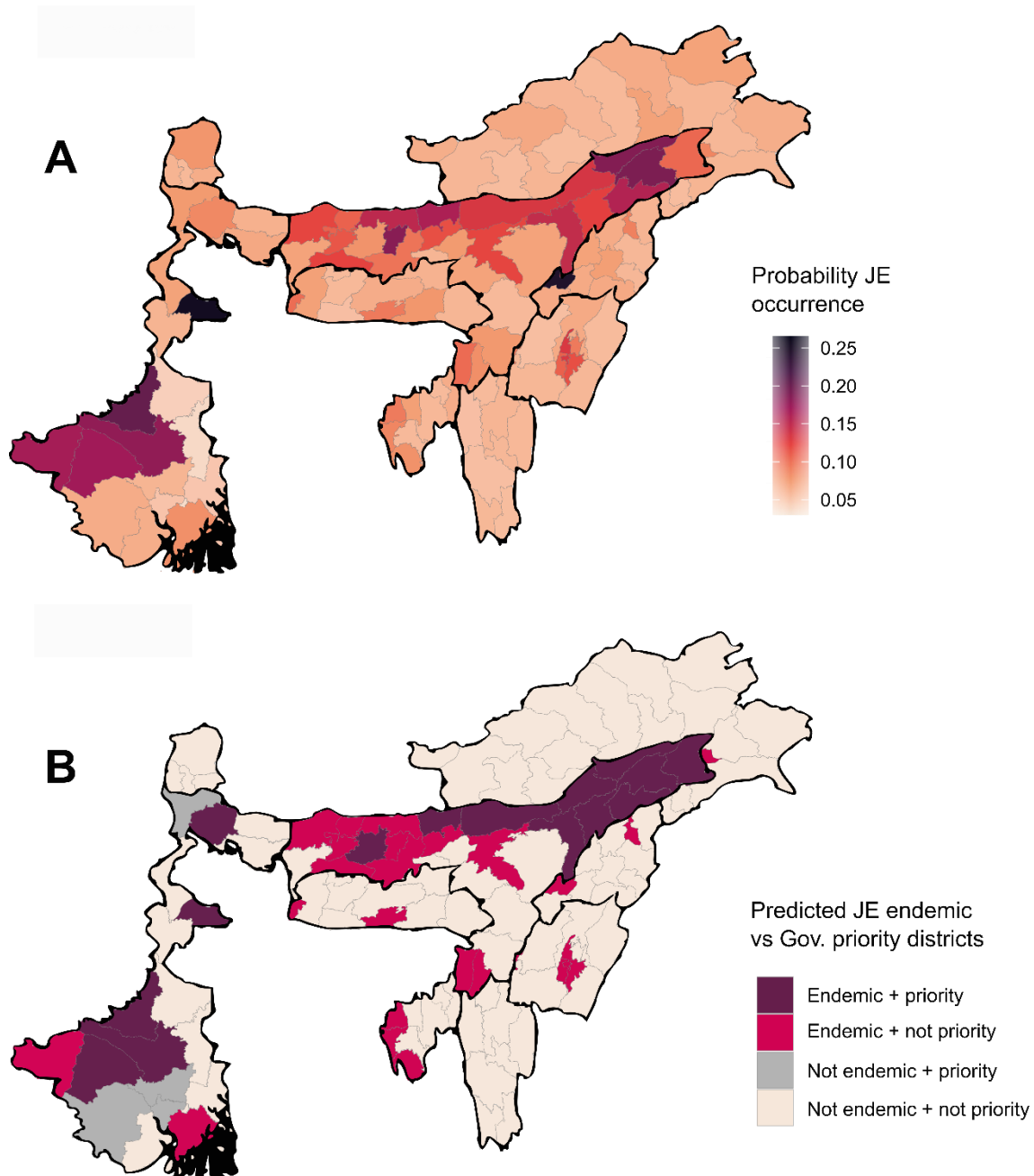
Figure 4.6 Maps of predicted Japanese encephalitis outbreak probability and endemic districts for northeast India, 2009–2019 (see Figure 1 for delineation of states).

(A) Map of predicted probability of JE outbreak occurrence for the region. (B) Map of predicted endemic states (i.e., with JE outbreak occurrence probability >0.08), whereby dark purple signifies predicted endemic districts that are reported "JE high priority" districts by the Indian Government (Government of India, 2014), red signifies predicted endemic districts that are not reported "JE high priority", grey signifies "JE high priority" districts that were not predicted endemic and pale pink signifies districts that are not predicted endemic or reported "JE high priority".

4.4.4 Predicting seasonal JE incidence in endemic districts of Assam

Model selection results (Appendix 3 Table S4.6) indicated that the best combination of environmental predictors included nonlinear effects of Tmean (1 month lag), precipitation (1 month lag), PDSI (1 month lag), and a linear effect for area of land under rice cultivation. This environment-driven model (Model 2) reduced OOS predictive error relative to the random effects only baseline model (36.6% reduction in RMSE; Table 5). The inclusion of vaccination data at a two-month lag in the environment and vaccine-driven model (Model 3) further improved OOS predictive error relative to the baseline model (46.0% reduction in RMSE; Table 5). When evaluating the added predictive accuracy of including vaccine data in the environment and vaccine-driven model, the RMSE was clearly optimised at a two-month lag (Appendix 3, Figure S4.13).

Table 4.3. Predictive accuracy of Japanese encephalitis incidence models.

The table shows the differences in structure and out-of-sample (OOS) model fit (root mean square error; RMSE) for the baseline (random effects only), the best-fitting environment-driven model and best-fitting environment and vaccine-driven model of JE incidence.

	Model	Random effects	Environmental covariates	Posterior mean (95% CI) of linear effects	RMSE	Δ RMSE
1	Baseline	Data source Month Year	-	-	53.37	-
2	Environment-driven	Data source Month Year	Nonlinear precipitation 1-month lag function, Nonlinear PDSI 1-month lag function, Nonlinear Tmean 1-month lag function, Rice area under cultivation	- - - -0.72 (-1.55, 0.19)	33.83	-19.54
3	Environment and vaccine-driven	Data source Month Year	Nonlinear precipitation 1-month lag function, Nonlinear PDSI 1-month lag function, Nonlinear Tmean 1-month lag function, Rice area under cultivation, Vaccination 2-month lag	- - - -0.88 (-1.66, 0.00) -0.47 (-0.96, 0.00)	28.80	-24.57

Model 2 and 3 accurately predicted the timing of JE incidence across the districts. However, neither model captured the magnitude of the large outbreaks in 2013 and 2015 (Figure 4.7A and B). Overall, both models overestimated the magnitude of outbreaks, especially for 2009, 2017, 2018 and 2019 but the disparity between reported confirmed cases and predicted cases may reflect underreporting during these periods. The inclusion of vaccination data in Model 3 dampened some of high predicted peaks (maximum OOS posterior mean predicted cases = 400) when compared to Model 2 (maximum OOS posterior mean predicted cases = 287) (Figure 4.7A and B).

Results from Models 2 and 3 suggest that seasonal JE risk in the four endemic districts of Assam (i.e., Dibrugarh, Jorhat, Sivasagar and Tinsukia) is linked to the

distribution of rainfall (both non-extreme conditions [as determined from PDSI], and mean precipitation), mean temperature in the preceding month (Figure 4C-D), area of rice-cropland under cultivation and vaccination coverage in the preceding two months. Incidence relative risk was highest when PDSI in the preceding month was between -2 and 0 (Figure 4.7C), indicating non-extreme precipitation conditions, and when mean monthly precipitation was approximately 400mm in the preceding month (Figure 4.7D). JE risk was influenced by average monthly mean temperature in the preceding month with a peak around 20ºC and then a steady incline above 28ºC. However, the relationship had large CIs which infers a large margin of error (Figure 4.7E). In addition, the area of rice-cropland under cultivation and vaccination coverage in the preceding two months were both negatively associated with JE risk in Model 3 (Table 4.3). Together with the spatial models of JE outbreak occurrence, these results indicate a substantial association between environmental factors and patterns of JE occurrence and incidence across northeast India. Furthermore, the results suggest that vector and host ecology – which constitute the hazard component of JE risk - play a significant role in JE transmission. In addition, seasonal rice cultivation appears to be an important factor in JE transmission which may be due to its influence on exposure to JE hazard.
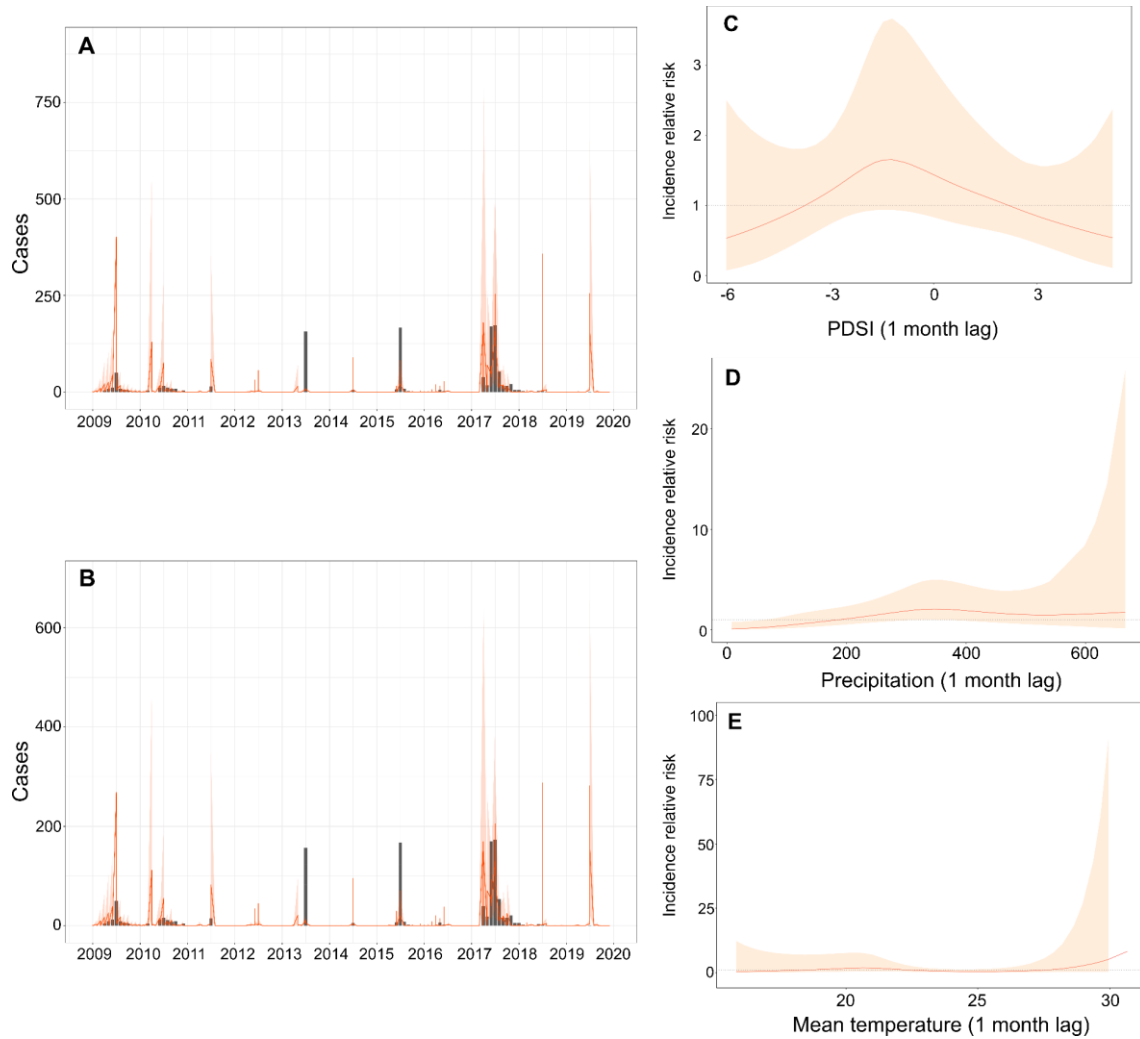
Figure 4.7. Modelled temporal dynamics and drivers of confirmed Japanese encephalitis cases in endemic districts of northeast India, 2009–2019.

Case time series show observed and out-of-sample (OOS) predicted monthly case counts from (A) an environment-driven model, and (B) an environment and vaccine-driven model. Time series graphs (A-B) show observed counts summed across four neighbouring endemic districts in Assam (i.e., Dibrugarh, Jorhat, Sivasagar, and Tinsukia) from 2009 to 2019 (grey bars), OOS posterior mean predicted cases (red line) and OOS 95% (orange shading) posterior predictive intervals. OOS predictions were made while holding out sequential 6-month windows across the full time series. Panels show nonlinear fitted effects of (C) Palmer Drought Severity Index (PDSI) at 1 month lag, (D) average monthly precipitation at 1 month lag, and (E) average monthly mean temperature at 1 month lag on relative risk, showing posterior mean and 95% credible interval.

4.5   Discussion

I found that JE outbreak occurrence is associated with climatic suitability, agricultural practices, healthcare access and poverty and that potential JE endemic areas in northeast India may be more extensive than previously thought. Highest JE outbreak occurrences appear to be in areas experiencing mean maximum annual temperatures of approximately 26–28ºC with a high proportion of land dedicated to rainfed and irrigated crops and a high poverty prevalence. The inclusion of climatic suitability, agricultural practices, poverty, and healthcare access in the predictive model of JE outbreak occurrence improved OOS predictive ability when compared to a baseline (random effects only) model, highlighting the importance of these socio-ecological factors in defining the JE endemic region in northeast India. In several districts of Assam, West Bengal, Meghalaya, Tripura, and Manipur, I identified areas that may experience underreporting of JE outbreaks and highlighted potential endemic districts that are currently not perceived to be of high JE priority. Furthermore, in a subset of endemic districts in Assam, I found that lagged climatic conditions, cultivated rice area, and lagged vaccination coverage could be used to predict the temporal dynamics of JE incidence. These findings substantiate the description of JE as an environmentally sensitive disease (Erlanger *et al.*, 2009; van den Hurk, Ritchie and Mackenzie, 2009; Le Flohic *et al.*, 2013; Tian *et al.*, 2015; Pearce *et al.*, 2018) and support the prospect of developing an early warning system for JE incidence which would inform public health efforts in endemic areas (Government of India, 2014).

JE outbreak occurrence is positively associated with increasing agricultural land-use, which may influence the populations of vectors and reservoir hosts (Keiser et al., 2005b; Sabesan, Raju Konuganti and Perumal, 2008; Erlanger *et al.*, 2009; Borah *et al.*, 2013; Le Flohic *et al.*, 2013) and human exposure to infected vectors as a consequence of the large numbers of people engaged in agricultural work in the region (Roy *et al.*, 2015; FAO, 2020). This current study is in agreement with previous findings that have shown a strong positive association between agricultural land-use and JE transmission in northeast India (Phukan, Borah and Mahanta, 2004; Sarkar *et al.*, 2012; Borah *et al.*, 2013) and in surrounding countries (Cao *et al.*, 2010; Impoinvil *et al.*, 2011; Robertson *et al.*, 2013). This association has

implications for the projected irrigated agricultural expansion in Asia required to improve food security (Keiser et al., 2005b; Alexandratos and Bruinsma, 2012). I found annual mean maximum temperatures of approximately 26–28ºC are associated with JE outbreak occurrence, which support the findings from previous studies (Bi *et al.*, 2003) and reflect the thermal optima reported for the transmission of other flaviviruses by *Culex* spp (Mordecai *et al.*, 2019) and optimal JEV vector temperatures reported in India (Murty, Rao and Arunachalam, 2010; Borah *et al.*, 2013). Poverty prevalence determined by the MPI (Alkire, Oldiges and Kanagaratnam, 2018) is also positively associated with JE outbreak occurrence, and is in agreement with previous studies that have reported JE as a disease of poverty (Badari, 1985; Luo *et al.*, 1995; Sarkar *et al.*, 2012). Therefore, public programmes aimed at poverty alleviation may have a positive impact in terms of reducing JE risk. However, since MPI is a compound metric (UNDP and OPHI, 2021), the effect of poverty on JE occurrence will likely be mediated by several factors which may vary by district (i.e., health, education and living standards).

Interestingly, the best-fitting predictive model used to define endemic areas did not include pig density which suggests that the influence of this covariate on JE outbreak occurrence may be regional and not generalisable across northeast India. Indeed, extensive serosurveillance data are required to better understand the epidemiological significance of pigs as a reservoir host for JEV in India (Desingu *et al.*, 2016; Datey *et al.*, 2020). Unfortunately, data on the presence of the sylvatic reservoir hosts were not included in this study due to high correlation with environmental variables. However, other studies have reported a strong association between habitat suitability of ardeid birds and JE outbreak risk in India, highlighting the importance of considering both irrigated agriculture and water bodies when predicting risk (Walsh *et al.*, 2021). Although there was a trend for a negative relationship between precipitation and JE outbreak occurrence, the results were non-significant. This finding was surprising since rainfall facilitates vector habitat formation. Nevertheless, other studies have reported similar results (Impoinvil *et al.*, 2011; Bai *et al.*, 2014). One study found that the effect of precipitation on JE risk was positive up to 350 mm/day, above which vector habitats were likely destroyed (Chen *et al.*, 2012). Therefore, my results may have reflected the high average annual rainfall received in this region (2000mm; 10% of India's total precipitation) (Roy *et al.*, 2015; Singha *et*

al., 2019) and the influence of heavy monsoon rainfall (Guhathakurta and Rajeevan, 2008; Mahanta, Sarma and Choudhury, 2013) which may have resulted in the destruction of vector habitats.

The predicted spatial pattern of JE outbreak occurrence (Figure 5A) mirrored the pattern of reported JE outbreaks (Figure 2), with high outbreak probability predicted across the majority of Assam, the western regions and Dakshin Dinajpur district in West Bengal and localised districts of Manipur and Meghalaya. Many of these districts border with neighbouring countries such as Bhutan, Nepal and Bangladesh where JE cases are often reported (Hossain *et al.*, 2010; Impoinvil *et al.*, 2011; Paul *et al.*, 2011; Robertson *et al.*, 2013; Khan *et al.*, 2014; Wangchuk *et al.*, 2020). Owing to the difficulty of classifying JE endemic areas (Sabesan, Raju Konuganti and Perumal, 2008), I decided to define districts as endemic when the average probability of an outbreak throughout the study period was above a threshold of 0.08, as determined by ROC curve. This classification led to the identification of 24 potentially endemic districts across seven states that are not currently considered by the Indian government to be high priority for JE surveillance or interventions (Government of India, 2014) (Figure 5B). However, there is substantial evidence to support the classification of these districts as endemic and requiring increased surveillance. For example, predicted endemic districts in the west, south and central region of Assam have reported increased cases of JE over the last few years (Malakar and Choudhury, 2014; Ahmad *et al.*, 2015, 2017; Dev, Sharma and Barman, 2015; Government of India, 2021b) and Purulia district in West Bengal (Chatterjee *et al.*, 2004; Das *et al.*, 2016) and the central districts of Manipur have reported significant seropositivity in the population (Singh *et al.*, 2019).

Despite the majority of predicted endemic districts corresponding to the Indian government's reported 'high JE priority' districts (Government of India, 2014), the model did not predict endemicity in four districts in West Bengal that were previously considered high priority. This disparity may relate to the reduced predictive performance of the spatial model in this state (as determined spatial variation in the Brier score) when compared to its superior predictive ability in the high priority districts of Assam. Furthermore, the selected threshold for endemicity may have been too conservative to identify all endemic areas. This threshold was selected to

maximise sensitivity (i.e., the chance of detecting a true positive) and specificity (i.e., the chance of detecting a true negative) and therefore prevent overestimation. However, for an underreported disease, maximising these values may not be desirable since it is valuable to predict occurrence when it has not been observed.

Overall, predicted JE endemic areas in northeast India appear to be associated with environmental conditions that influence vector and host ecology (i.e., components of JE hazard) and facilitate human contact with infected vectors such as irrigated agricultural systems (i.e., components of JE exposure). Indeed, the majority of predicted endemic districts have a warm and humid climate, with higher precipitation during the monsoon (CWA and AW types in Köppen climate classification) (Appendix 3 Figure S4.1). They also have a large proportion of irrigated agricultural land (Roy *et al.*, 2015) owing to the Brahmaputra river that flows through Assam (Immerzeel, van Beek and Bierkens, 2010; Samaranayake, Limaye and Wuthnow, 2016) and the Damodar river in West Bengal (Singh *et al.*, 2020). Dependence on the agricultural sector (Roy *et al.*, 2015; FAO, 2020) and projected expansion in irrigated agriculture (Keiser et al., 2005b; Alexandratos and Bruinsma, 2012) may result in public health interventions focused on reducing human-vector contact not being effective in northeast India. Instead, targeted vaccination programmes may be more beneficial at reducing JE risk in this region.

The temporal model of JE incidence in the four endemic districts of Assam showed substantial improvement in OOS predictive error with the inclusion of environmental variables when compared to the random effects only baseline model. Moreover, the inclusion of vaccination coverage data lagged by two months further improved model predictive ability, dampening the predicted peaks in JE cases to more reasonable levels. This suggests the possibility of developing an environment-driven forecasting model for JE incidence for endemic areas of India which can be used to pre-emptively inform when to target vaccination drives and therefore reduce JE risk. This may help to address the low vaccine efficacy (Vashishtha and Ramachandran, 2015; Tandale *et al.*, 2018) and coverage (Murhekar *et al.*, 2017; Vannice *et al.*, 2021) reported in India by facilitating management of vaccines cold chain logistics (Saikia, 2017). With the exception of underestimating peaks in cases in 2013 and 2015, the environment and vaccine-driven model was able to predict the accurate timing of JE

119

cases across the endemic area but often overestimated their magnitude. The disparity between the magnitude of confirmed and predicted cases may be explained by underreporting which is possibly due to several factors that include: the high subclinical to clinical ratio of disease presentation (WHO, 2015b); non-specific clinical symptoms associated with JE (McNaughton, Singh and Khan, 2018); high incidence of other encephalitis aetiologies in the region (Khan *et al.*, 2011; Chowdhury *et al.*, 2014; Dev, Sharma and Barman, 2015); possible test cross reactivity with other flaviviruses and vaccines (Maeki *et al.*, 2019; Quan *et al.*, 2020); limited healthcare resources (WHO, 2020b).

Climatic factors including temperature, precipitation and PDSI at one month lag appear to be important for predicting JE incidence as confirmed by other studies (Borah *et al.*, 2013; Singh, Singh and Mall, 2020; Tu *et al.*, 2021). The lag period probably reflects the time taken for vector development (7-10 days for *Culex* spp.) (CDC, 2020), the extrinsic incubation period (i.e., the time period for the virus to develop within a vector and become transmissible; 7-14 days) (Schuh *et al.*, 2014; Tu *et al.*, 2021), and the human incubation period (median of 8.4 days) (Turtle and Solomon, 2018). There may also be a time lag between the onset of clinical symptoms and healthcare access, which has been reported to vary between 1–12 days in Assam (Kakoti *et al.*, 2013). I found that rice area cultivated was also an important predictor of JE incidence reflecting the importance of rice paddy agriculture to the JE disease system (Keiser et al., 2005b; Erlanger *et al.*, 2009; Pearce *et al.*, 2018).

Although this study extends our understanding of endemic areas and important drivers of JE in northeast India, it has several limitations. For example, the predominant source of JE case data used in the analysis was obtained from the Indian government's IDSP, which may be influenced by the differences in reporting efforts of the various districts depending on whether JE is considered a high priority disease or not (Government of India, 2014). This will have meant JE incidence calculations will be subject to substantial underreporting and heterogeneity in reporting effort. Furthermore, 2011 census data was used to calculate incidence which will mean calculations are increasingly inaccurate over time. To overcome the significant zero-inflation in the data and reduce the impact of reporting bias in the

model, I used a JE outbreak indicator rather than case data as a response variable in the spatial models. An outbreak indicator of one confirmed case per district year was chosen to capture JE occurrence despite the relative underreporting of the disease (Quan *et al.*, 2020) and to achieve consistency with previous definitions of endemicity in India (Sabesan, Raju Konuganti and Perumal, 2008). The outbreak may not be conservative enough to capture the accurate relationships between JE occurrence and spatial drivers or the endemic areas. However, when compared to a higher threshold of three confirmed cases per district year, I found the direction and magnitude of spatial drivers and the ability of the model to predict outbreaks was consistent with the lower threshold. While the inclusion of socio-ecological variables improved the OOS predictive error (i.e., Brier score) of the spatial model when compared to the baseline (random effects only) model, the overall improvement was modest. This may have resulted from the fact that the Brier score penalises deviations from the observed outcome, therefore predictions of occurrence in unobserved areas (e.g., potential areas of underreporting) will result in higher predictive error. Nevertheless, assessing the spatial variation in OOS predictive error revealed that the socio-ecological model performed better than the baseline in many reported JE priority districts of Assam (Government of India, 2014).

The use of observational datasets and correlative analytic methods in this study precluded the identification of underlying causal mechanisms (Hernán, 2018; Kraemer, Reiner and Bhatt, 2019) which may limit the generalisability of the results across time and space (Washburne *et al.*, 2019). To infer causal relationships requires further empirical research investigating underlying socioecological processes that influence JE risk. Another limitation was that the temporal model failed to predict some trends in the data, which may have reflected the inability of the coarse scale of predictors (i.e., mean monthly values per district) to capture important statistical associations (Parham *et al.*, 2015) required to forecast accurate outcomes. Indeed, it is possible that JE risk is highly discontinuous and localised and so future research would benefit from modelling case data at finer resolutions to describe heterogeneity in JE incidence. Owing to limited data, this study did not consider the role of human factors which are critical in shaping patterns of disease risk such as behaviour, population immunity, and age distribution (Funk, Salathé and Jansen, 2010). Behavioural risk factors for JE include the proximity of dwellings to rice

paddies and livestock (Borah *et al.*, 2013), the use of insecticide-treated mosquito nets (Dutta *et al.*, 2011), and scepticism surrounding immunisation (Saikia, 2017; Sakamoto *et al.*, 2019). Since JE is predominantly a disease of childhood, the age distribution of the population and the associated JEV seroprevalence in different age groups also has a major impact on the spatiotemporal distribution of JE cases (Li *et al.*, 2016; Kwak, Hong and Kim, 2021). Future research would benefit from analysing targeted serosurveillance data stratified by age and vaccination status which would capture subclinical cases and reduce data biases associated with the effects of test cross-reactivity, variations in healthcare diagnostics and differences in reporting effort.

Despite these limitations, I have shown that JE outbreak occurrence is driven by environmental and socioeconomic factors that influence the different components of disease risk (i.e., hazard, exposure and vulnerability) (Hosseini *et al.*, 2017). Using passive surveillance data, I have predicted potential areas for endemic JE transmission in northeast India and identified districts that are likely to be experiencing underreporting and would benefit from increased surveillance effort. Targeting future surveys outside of the current 'high JE priority' districts (Government of India, 2014) will also provide further information on the importance of environmental and socioeconomic factors influencing JE risk. I also demonstrated that climatic variability and land-use factors can be used to predict the temporal pattern of JE incidence in endemic areas, revealing the potential to develop a desired early warning system to inform public health efforts (Government of India, 2014). In this study I have shown the sensitivity of JE to environmental and socioeconomic conditions and highlighted the importance of focusing surveillance efforts in areas outside of the established JE transmission zone. Improved knowledge on the burden and drivers of JE in India will help policymakers to communicate and develop effective and efficient interventions to safeguard public health with ongoing global changes.

Chapter 5:

Predicting Japanese encephalitis risk under different scenarios of global change

This chapter focuses on medium-to-long term forecasting, applying the spatial predictive model of JE outbreak occurrence developed in the previous chapter to evaluate how future climatic, agricultural, and socioeconomic change may differentially impact trends in JE risk in northeast India. My goal in this chapter is to move towards incorporating MBD risk into not only public health but also environmental policy decisions to identify trade-offs across land-use, climate, food security and human health.

5.1   Abstract

Forecasting the impacts of global change on mosquito-borne disease (MBD) risk is a key component of public health preparedness. Japanese encephalitis (JE) is a MBD that has spread throughout Asia and the West Pacific over the past 70 years, exposing more than 3 billion people to risk of infection. Environmental and socioeconomic drivers impact JE risk but knowledge on how these processes may influence disease risk in the future remains unclear. I applied a Bayesian model of JE outbreak spatial occurrence to project the spatial extent of JE risk across northeast India in 2030, 2050 and 2070 based on different global change scenarios. Specifically, JE outbreak occurrence probability and human population at risk were projected using four alternate socioeconomic and greenhouse gas concentration pathways (Shared Socioeconomic Pathways and Representative Concentration Pathways [SSP-RCPs]) and compared to a 2009-2019 reference period. The population at risk of JE is projected to substantially diverge from present-day levels under different SSP-RCP scenarios. By 2070, the population at risk is predicted to increase by over 45,000 for SSP3-RCP6.0 (i.e., 'regional rivalry' scenario) and by 3500 for SSP2-RCP4.5 (i.e., 'middle of the road' scenario). By contrast, when compared with present-day, declines in population at risk are predicted for SSP1-RCP2.6 (i.e., sustainability scenario) and SSP5-RCP8.5 (i.e., rapid growth scenario) resulting in reductions of over 22,000 and 25,000 people at risk, respectively. I

showed scenario differences in the contraction, stability, and expansion of the population at risk for different states in the region. The currently "high JE priority" states of Assam and West Bengal show the greatest between-scenario differences, justifying the ongoing public health focus in these regions. My study provides evidence for the changing threat of JE risk in northeast India under future global change. The projections can be used to inform future surveillance and public health efforts (e.g., vaccination) and to evaluate the consequences of different policy pathways for JE risk and burden across the region.

5.2   Introduction

Global change processes such as climatic, land-use and socioeconomic change are significant drivers of global mosquito-borne disease (MBD) risk. While environmental factors, such as temperature, precipitation, and land-use predominantly influence the ecology of vectors, hosts, and pathogens (Keiser et al., 2005b; Erlanger *et al.*, 2009; Borah *et al.*, 2013; Le Flohic *et al.*, 2013; Mordecai *et al.*, 2019), socioeconomic factors (e.g., travel, demographics and poverty) impact human exposure and susceptibility to disease (Badari, 1985; Luo *et al.*, 1995; Sarkar *et al.*, 2012; Hosseini *et al.*, 2017). The recent Intergovernmental Panel on Climate Change (IPCC) report provides overwhelming evidence for the strong links climate has to land-use and socioeconomics, and their combined effects on environmentally sensitive diseases such as MBDs (IPCC, 2022). Therefore, these global change processes need to be considered simultaneously when tackling complex problems such as the burden of MBD. Although many studies have reported the predicted effects of individual global change processes on future MBD distributions and populations at risk (Caminade *et al.*, 2014; Ryan *et al.*, 2015; Monaghan *et al.*, 2018; Colón-González *et al.*, 2018; Ryan, Colin J. Carlson, *et al.*, 2019; Iwamura, Guzman-Holst and Murray, 2020), there is limited analysis of their combined effects (Chapter 2; Franklinos *et al.*, 2019). This is true for other vector-borne diseases (VBDs) such as those transmitted by ticks or sandflies, whereby projections of disease risk are often based on climate-driven models with other drivers of change less explored (González *et al.*, 2010; Moo-Llanes *et al.*, 2013; Ogden *et al.*, 2014a; Parham *et al.*, 2015; Williams *et al.*, 2015; Alkishe, Peterson and Samy, 2017; McPherson *et al.*, 2017). Understanding

how VBD risk may vary under future global change scenarios is critical for effective public health and environmental decision making (Campbell-Lendrum *et al.*, 2015; Moritz U. G. Kraemer *et al.*, 2019a; Messina *et al.*, 2019).

Japanese encephalitis (JE) is a MBD of high public health concern in Asia and the West Pacific, where more than 3 billion people are exposed to risk of infection (Erlanger *et al.*, 2009; G. L. Campbell *et al.*, 2011; WHO, 2015a). Spatiotemporal trends in JE risk are associated with socio-ecological factors (i.e., climate, agricultural practices, poverty, healthcare access) that affect vector and host populations and human-vector contact (see Chapter 4). Therefore, the geographic distribution and population at risk of JE is likely to be impacted by future environmental and socioeconomic changes over the coming decades (Metelka, Robertson and Stephen, 2015; Pearce *et al.*, 2018). India may be particularly susceptible because it already has a high burden of JE (Heffelfinger *et al.*, 2017; Kulkarni *et al.*, 2018; Lindquist, 2018), diverse bioclimatic zones (MOEF, 2019) and is predicted to expand its irrigated agriculture (Alexandratos and Bruinsma, 2012). Although some anecdotal reports suggest JE incidence will increase with climate change (Rahman, 2016), there has been limited research into the future effects of global change processes on JE risk. A recent modelling study suggested that overlapping human population expansion and growth in pig populations in Asia may lead to significant geographical expansion of JE risk by 2050 (Metelka, Robertson and Stephen, 2015). However, the consequences of different climatic, land-use or socioeconomic scenarios for JE risk were not explored in that research.

The paucity of knowledge on future trends of JE risk under alternative policy scenarios hinders the ability of decision-makers to target effective adaptation options (e.g., vaccination, surveillance, early warning systems) and plan mitigation strategies (IPCC, 2022). In this present study, I use a statistical model of outbreak risk to project the combined effects of future climatic, agricultural, and socioeconomic change on JE risk. I focus my research in the endemic region of northeast India which is projected to undergo substantial changes in climate and land-use (Ravindranath *et al.*, 2011; Dutta, 2014; Prokop, 2020). Building on the methods I developed in Chapter 4, I implemented a spatial Bayesian hierarchical model to predict present-day (i.e., 2014-2019) geographic distribution of JE outbreak

occurrence probability (henceforth referred to as JE risk). Using present-day data as baseline, I then used this model to project the distribution of JE risk across northeast India in 2030, 2050 and 2070 under four socioeconomic-climatic scenarios with projections based on Representative Concentration Pathway (RCP) scenarios and Shared Socioeconomic Pathways (SSPs) (O'Neill *et al.*, 2016). I aim to evaluate the degree to which projected pathways may impact the population at risk of JE in northeast India. In addition, I aim to identify which areas are consistently projected to expand or contract in their suitability for JE transmission across all global change scenarios. This information can be used to inform future surveillance and public health efforts to reduce the burden of JE.

5.3   Materials and methods

5.3.1   Scenario narratives

Scenarios form an essential part of global change research and assessment. The RCPs are a set of four future emission pathways developed as a basis for the development of new climate change projections (van Vuuren *et al.*, 2011). The four RCPs span the range of end-of-century radiative forcing values (2.6, 4.5, 6.0, and 8.5 W m^2) by accounting for altering future greenhouse gas emissions and changing underlying socioeconomic projections (van Vuuren *et al.*, 2011). The SSPs are a set of five future scenarios (SSP1 to SSP5) which span a range of future socioeconomic narratives (Riahi *et al.*, 2017). SSP1 ('sustainability scenario') represents a world of sustainable growth and equality with low challenges to mitigation and adaptation; SSP2 ('middle of the road' scenario) represents a world where trends follow the *status quo* with medium challenges to mitigation and adaptation; SSP3 ('regional rivalry' scenario) is a fragmented, nationalist world with high challenges to mitigation and adaptation; SSP4 (inequality' scenario) represents an increasingly inequitable world with low challenges to mitigation but high challenges to adaptation; and SSP5 ('rapid growth' scenario) represents a world of rapid and unconstrained economic growth with high challenges to mitigation and low challenges to adaptation (i.e., due to rapid technological progress). Socioeconomic and land-use projections provided for these different scenarios represent plausible outcomes under the assumptions of each scenario narrative. The RCP-SSP framework combines RCP scenarios with

SSPs to form a set of future global change scenarios which provide the basis to explore the space of future mitigation pathways in terms of different levels of mitigation stringency and different assumptions about socioeconomic development (O'Neill *et al.*, 2016). In this study, I selected four SSP-RCP pathways that represent varying climate and socioeconomic assumptions: SSP1-RCP2.6 (low challenges for mitigation and adaptation, low climate impacts, low population growth, high equity, 'sustainability' scenario), SSP2-RCP4.5 (medium challenges and medium-high climate change, moderate equity, 'middle of the road' scenario), SSP3-RCP6.0 (high challenges, medium-high climate change, high population growth, low equity, 'regional rivalry' scenario), and SSP5-RCP8.5 (high challenges to mitigation, low challenges to adaptation, high climate change, low population growth, high equity, 'rapid growth' scenario) (Table 5.1).

Table 5.1. Key features of the socioeconomic and climatic scenarios (RCP-SSPs).

Information derived from studies on the RCP and SSP scenarios (van Vuuren *et al.*, 2011; Popp *et al.*, 2017; Riahi *et al.*, 2017).

SSP	RCP	SSP socioeconomic narrative	Climate policy features	Agricultural and land-use features	Population by 2050 in northeast India (100,000)	Population economic vulnerability
1	2.6	Sustainability	Low challenges to mitigation and adaptation, strongly declining emissions	Strong regulation of land-use change (e.g., deforestation) to reduce environmental trade-offs. High improvements in agricultural productivity shared across countries. Moderate international trade.	15.0	Low
2	4.5	Middle of the road	Medium challenges to mitigation and adaptation, slowly declining emissions	Medium regulation of land-use change with slow declines in rate of deforestation. Medium improvements in agricultural productivity. Moderate international trade.	16.6	Moderate
3	6.0	Regional rivalry	High challenges to mitigation and adaptation, stabilising emissions	Limited regulation of land-use change with high rates of deforestation. Low improvements in agricultural productivity. Low international trade.	18.6	High
5	8.5	Rapid growth/ fossil-fuelled development	High challenges to mitigation, low challenges to adaptation, rising emissions	Medium regulation of land-use change with slow declines in rate of deforestation. Highly managed and intensive practices with rapid improvements in agricultural productivity. High international trade. Increased livestock and feed crop production.	14.9	Low

5.3.2 Datasets

5.3.2.1 Human Japanese encephalitis case data

I obtained the Indian government's Integrated Disease Surveillance Programme (IDSP) (Government of India, 2021b) human JE surveillance data for the period between 1st January 2009 to 31st December 2019 and processed the data as described in Chapter 4 (see Chapter 4 methods for further details). I used monthly confirmed JE case data from the last six years (2014-2019) from the full dataset because this is when most cases were reported (see Appendix 3 in Chapter 4 Figure S4.8). Since the case data were zero-inflated and overdispersed, I aggregated JE cases by year at the district level and created a binary JE outbreak indicator. I used a threshold of one confirmed case per district per year to define a JE outbreak occurrence. I believe this low threshold of outbreak occurrence is justified because of the high levels of underreporting predominantly due to the high subclinical to clinical ratio of disease presentation (WHO, 2015b). The resulting dataset included district-wise annual JE outbreak occurrence data for the northeast region of India (nine states, 115 districts) (Appendix 4 Figure S5.1) between 2014 and 2019.

5.3.2.2 Present-day environmental and socioeconomic covariates

In this analysis, I used the same suite of environmental and socioeconomic covariates as described in Chapter 4. However, instead of using European Space Agency Climate Change Initiative (ESA-CCI) land cover data, I used land-use data for 2020 derived from the Global Change Analysis Model (GCAM) and a land-use spatial downscaling model (Demeter) (Chen *et al.*, 2020) to follow the same land-use scheme as used for future projections. ESA-CCI land cover data were found to be highly collinear with GCAM-Demeter land-use data (Pearson correlation coefficient >0.8), justifying the use of this dataset. Terraclimate data used in Chapter 4 were also used in this analysis for present-day meteorological variables since the data are compatible with future climate projections provided by Worldclim (Abatzoglou *et al.*, 2018). I also explored the inclusion of gross domestic product (GDP) data in the model as a measure of poverty since GDP projections that are

compatible with the different SSPs are available for this dataset (Murakami, Yoshida and Yamagata, 2021).

5.3.2.3 Climate and land-use and poverty projections under different socioeconomic and climate adaption scenarios

Land-use projections were obtained from the GCAM-Demeter land-use dataset (Chen *et al.*, 2020). The data includes projected land cover for the period of 2015-2100 at five-year time steps produced for 15 SSP-RCP scenarios driven by five general circulation models (GCMs) (i.e., gfdl, hadgem, ipsl, miroc, and noresm). I obtained land-use projection data driven by the five GCMs for each of my four specified SSP-RCP scenarios for 2030, 2050 and 2070. I obtained data on the land-use classes of rainfed and irrigated rice-cropland to match the covariates selected in the best-fitting model of present-day JE outbreak occurrence.

Monthly average values for minimum temperature (Tmin, °C), maximum temperature (Tmax, °C), and precipitation (mm) were obtained from WorldClim v2.1 (https://www.worldclim.org/data/cmip6/cmip6_clim10m.html) for the time periods: 2021-2040, 2041-2060 and 2061-2080. The Worldclim data are downscaled projections from the 6th climate model intercomparison project (CMIP6) (O'Neill *et al.*, 2016) for nine GCMs and four SSP-RCP scenarios (i.e., SSP1-RCP2.6, SSP2-RCP4.5, SSP3-RCP6.0 and SSP5-RCP8.5). I obtained climate projection data for each of the four SSP-RCP scenarios for the same five GCMs used for the land-use projection data (Chen *et al.*, 2020).

Poverty projections were obtained from a global gridded GDP dataset (Murakami, Yoshida and Yamagata, 2021). The data includes projected GDP for the period of 2010-2100 at 10-year time steps produced for five SSP scenarios. I obtained GDP projection data for each of my four specified SSP scenarios for 2030, 2050 and 2070.

5.3.2.4 Human population projections under different socioeconomic scenarios

To quantify a measure of population at risk comparable between current and future global change scenarios, I obtained spatially explicit global population scenarios consistent with SSP scenarios (Jones and O'Neill, 2016). The data includes projected human populations for the period of 2010-2100 at 10-year time steps produced for five SSP scenarios. I obtained human population projection data for each of my four specified SSP scenarios for 2030, 2050 and 2070 (Appendix 4 Table S5.1).

All raster datasets used in this study were aggregated to each district using the *exactextractr* package in R (version 0.7.1) (Baston, 2021) by calculating the mean of the grid cells within each district, weighted by the fraction of the cell that lay within the district. Then mean district-level values for the whole study period were calculated for all data. All calculations were using R software version 4.0.3 (R Core Team, 2020) through RStudio (RStudio Team, 2020).

5.3.3 Statistical analysis

5.3.3.1 Predictive spatial model of present-day JE outbreak occurrence in northeast India

I developed a binomial spatial Bayesian hierarchical model using the binary outbreak indicator as the response variable for 115 districts in nine states in the northeast of India from January 2014 to December 2019. I modelled JE outbreak occurrence (n=115 districts over six years) where Y_i is the binary presence (1) or absence (0) of a JE outbreak in district *i* and p_i denotes the probability of JE outbreak occurrence, such that:

$$Y_i \sim \text{Bern}(p_i) \tag{1}$$

JE outbreak occurrence (p_i) is modelled as a function of socio-ecological covariates and random effects:

$$\text{logit}(p_i) = \alpha + \sum_j \beta_j X_j + \sum_k \delta_{k,i} + u_i + v_i \qquad (2)$$

where, α is the intercept; X is a matrix of socio-ecological covariates with linear coefficients given by β; $\delta_{k,i}$ is a nonlinear climatic effect (specified as second-order random walk); and reporting trends at district level are accounted for using a spatially-structured (conditional autoregressive;(v_i) and unstructured i.i.d. (independent and identically distributed) (u_i) random effects jointly specified as a Besag-York-Mollie (BYM) model (Besag, York and Mollié, 1991). I considered the same linear coefficients (β) as described in Chapter 4 that are hypothesised to influence JE transmission (see Appendix 3 Table S4.2). In addition, I used different land-use data than in Chapter 4 to follow the same land-use scheme as used for future projections and I considered GDP as a covariate to represent poverty. Continuous covariates were rescaled using the z-score (to mean 0, s.d. 1) prior to fitting linear fixed effects. Present-day and future projection data were combined before rescaling the continuous covariate data and before specifying nonlinear climatic effects to ensure that future covariate data were on the same scale when performing projections. Weakly informative prior probability distributions (priors) were assigned for the intercept, $\alpha \sim$ N (0,1.5) and fixed effects, $\beta \sim$ N (0,0.5) to constrain the position and scale of the outcome to fall within a reasonable range. I assigned penalized complexity (PC) priors (Simpson *et al.*, 2017) to hyperparameters of the district-level effects and nonlinear climatic covariates to penalise the complexity resulting from deviating from a simple base model.

I conducted model selection on 'out of sample' (OOS) prediction by identifying the model that minimised OOS predictive error when compared to a baseline (i.e., random effects only) model, as described in Chapter 4. Model predictive error for the whole region was calculated using the Brier score which is the mean squared difference between the observed outcome and the predicted probability of the outcome (Brier, 1950), whereby a lower score represents superior model fit.

5.3.3.2 Projection of JE risk across future global change scenarios

I used the projected climate, land-use, poverty, and human population datasets (as described above) as input data for the best-fitting predictive spatial model of JE outbreak occurrence, and projected district-level JE risk (e.g., probability of JE outbreak occurrence) for each of the four SSP-RCP scenarios and three epochs (2030, 2050 and 2070). I propagated uncertainty in future climate and land-use data into the JE risk predictions by using data for the different epoch and SSP-RCP combinations from each of the five GCMs. I made separate model predictions for each GCM and then calculated the mean and uncertainty bounds (95% credible intervals [CIs]) across all the GCMs within each scenario-epoch combination. To calculate the change in population at risk, JE outbreak occurrence probability predictions were multiplied by total population per district for each scenario and epoch and compared to present-day predictions. The projected human population data used for these calculations did not consider the proportion of the population moving in (inflow migration) or out (outflow migration) of a district. Since outflow migration will affect the number of people at risk of JE transmission, I calculated migration inflow and outflow proportions per state from the latest census which provides data on movement of people within India between states (Government of India, 2011). I then subtracted the proportion of migration outflow from the population projections and multiplied these projections by predicted JE outbreak occurrence probability to calculate the minimum projected population at risk.

5.4   Results

5.4.1   Predicting the present-day spatial distribution of JE risk in northeast India

The best performing predictive spatial model of JE outbreak occurrence included linear effects of rice (irrigated and rainfed) cropland proportion, mean precipitation, poverty prevalence, and a nonlinear effect of mean Tmax. Districts with a high proportion of rice-cropland (irrigated and rainfed) had a significantly increased probability of an outbreak (Figure 5.1A).

Analysis showed that JE outbreak occurrence probability was associated with climatic conditions, increasing with mean Tmax levels however, this relationship was relatively uncertain (Figure 5.1B). The inclusion of these covariates improved OOS predictive error according to the Brier score (Brier score = 0.061) when compared to a baseline (random effects only) model (Brier score = 0.064) (Appendix 4 Table S5.2). The inclusion of GDP as an indicator for poverty prevalence did not improve model predictive ability which precluded the use of future poverty projection data in this study.
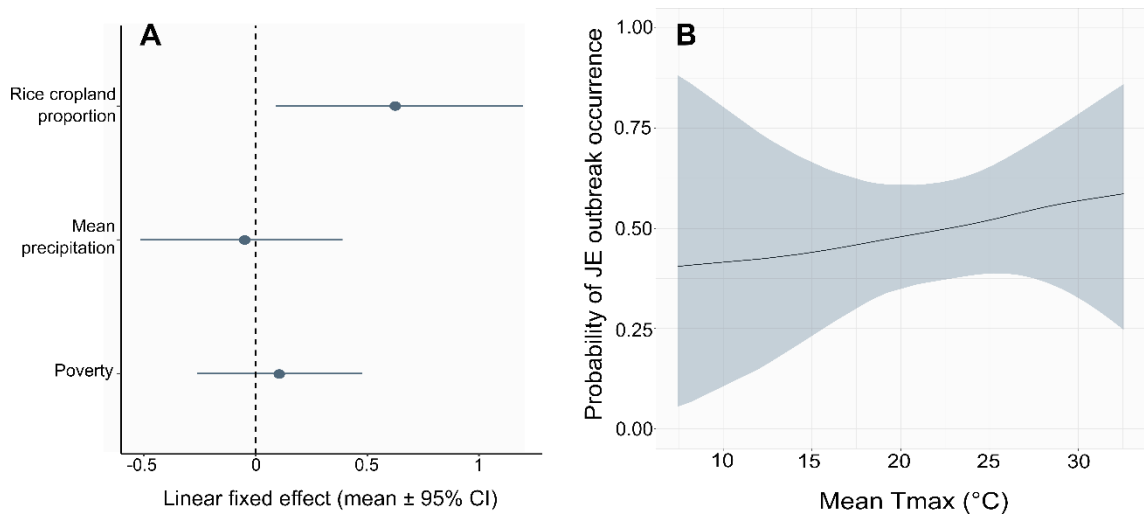
Figure 5.1. Temporal correlates of Japanese encephalitis outbreak occurrence across northeast India for the period 2009-2019.

(A) The fixed-effect parameter estimates and 95% credible intervals (CIs) for the spatial model of present-day JE outbreak occurrence. (B) The nonlinear relationship between mean maximum temperature and probability of JE outbreak occurrence where 95% CI is shown shaded.

5.4.2   Projected changes in environmental drivers by the 2070s under combined climate and socioeconomic scenarios
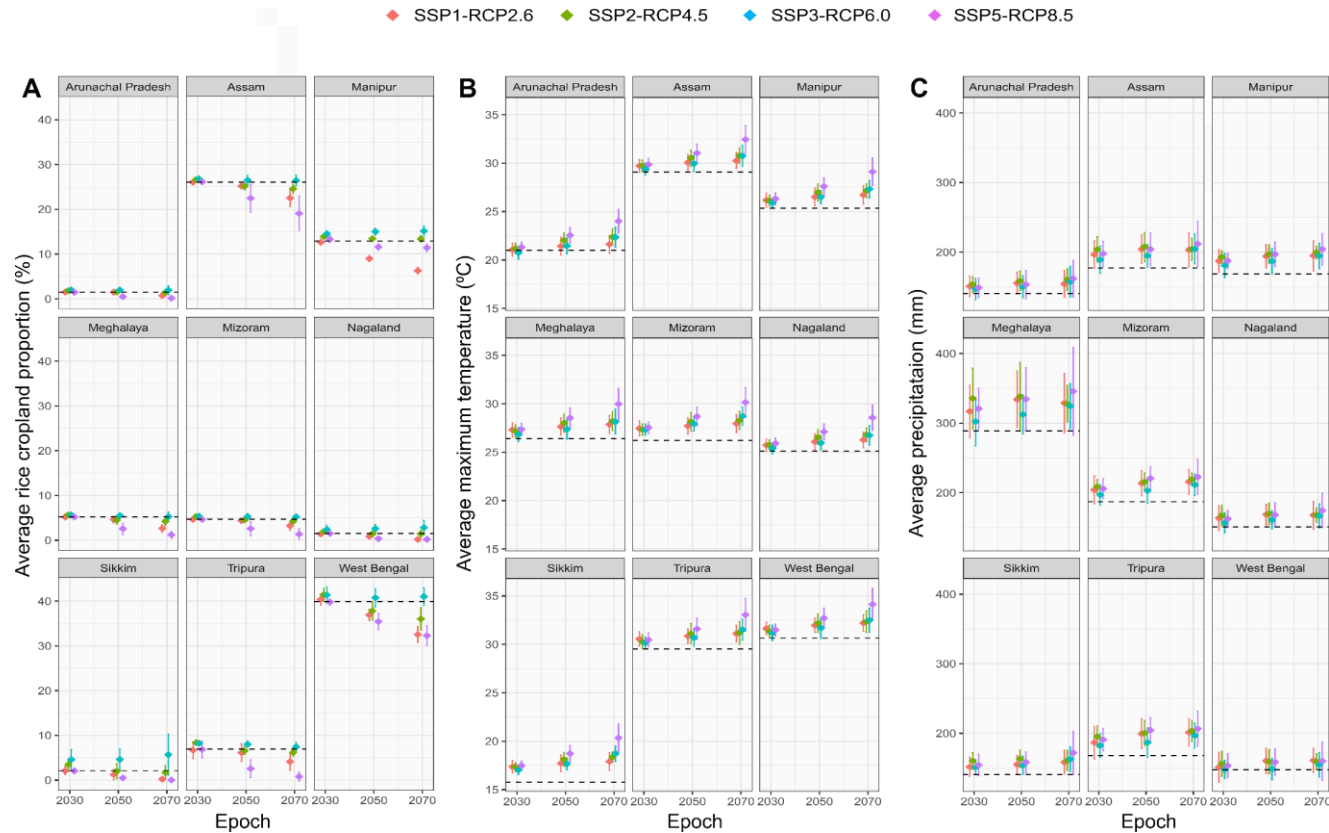
Figure 5.2. Projected change with 95% credible intervals in (A) average rice cropland extent (%), (B) average maximum temperature (ºC), and (C) average precipitation (mm) per state from present-day (dashed line) to 2070 for each RCP-SSP scenario.

Taking averaged projections for each SSP-RCP scenario, rice cropland proportion is predicted to decline in NE India under most scenarios apart from marginal increases in some states under SSP3-RCP6.0 and SSP2-RCP4.5 (Figure 5.2A). Declines in rice cropland proportion are especially high for the states of Assam and West Bengal which have high levels of present-day rice cropland. The increase in rice cropland under SSP3-RCP6.0 was simulated because this scenario favours further land-use conversation for agricultural use and low improvements in agricultural productivity (Table 5.1). Combined with a higher population and reduced food imports, this would result in more land area being needed for food production under this scenario. Comparatively, the decrease in rice cropland extent under SSP1-RCP2.5 and RCP5-RCP8.5 scenarios relates to projected improvements in agricultural productivity and moderate to high international trade which reduces the need for agricultural land expansion (Table 5.1). In comparison, the average maximum temperature is expected to increase for all states under all SSP-RCP scenarios with the most dramatic increases under SSP5-RCP8.5 and the lowest increase under SSP1-RCP2.5 (Figure 5.2B). For the states of Assam, Tripura and West Bengal which report present-day average maximum temperatures at around 30°C, all projected temperatures are significantly higher than the thermal optima for Flavivirus transmission for *Culex* species (between 23.9–26.4°C) (Mordecai *et al.*, 2019). Projected increases precipitation occurred in all states under all scenarios, with the greatest increases predicted for Meghalaya (Figure 5.2C).

5.4.3 Projected change in population at risk of JE under different scenarios

The population at risk of JE in northeast India is projected to substantially diverge from present-day levels under different SSP-RCP scenarios (Figure 5.3A, Appendix 4 Table S5.3). For all scenarios except SSP3-RCP6.0, the population at risk will fall below present-day levels by 2030. By 2050, further declines are projected for SSP1-RCP2.6 and SSP5-RCP8.5, whereas a dramatic increase in population at risk is reported for SSP3-RCP6.0, and a more modest increase for SSP2-RCP4.5 to just above present-day levels. In

2070, this divergent trend continues for the different scenarios with a further dramatic increase for SSP3-RCP6.0, additional projected declines below present-day levels for SSP1-RCP2.6 and SSP5-RCP8.5 scenarios, and a plateau in population at risk for SSP2-RCP4.5. Predictions from the model suggest that by 2070, over 45,000 more people will be at risk of JE in northeast India when compared to the present-day under SSP3-RCP6.0, compared to approximately 3500 under SSP2-RCP4.5 (Figure 5.3A, Appendix 4 Table S5.3). Whereas there will be reductions in over 22,000 people at risk under SSP1-RCP2.6, and approximately 25,000 for SSP5-RCP8.5. When assuming only population changes and holding environmental factors constant at present-day levels, the population at risk is projected to increase for all scenarios (Figure 5.3B). Although these results mirror the population differences projected for the different pathways (Appendix 4 Table S5.1), they also reveal how environmental change is projected to dampen the potential population at risk, especially for SSP1-RCP2.6 and SSP5-RCP8.5 scenarios. Indeed, rice-cropland proportion is projected to decrease under both these scenarios, especially in the states of Assam and West Bengal (Figure 5.2A). However, other environmental and socioeconomic factors that are associated with JE risk such as future pig production, and poverty conditions are missing from these projections.
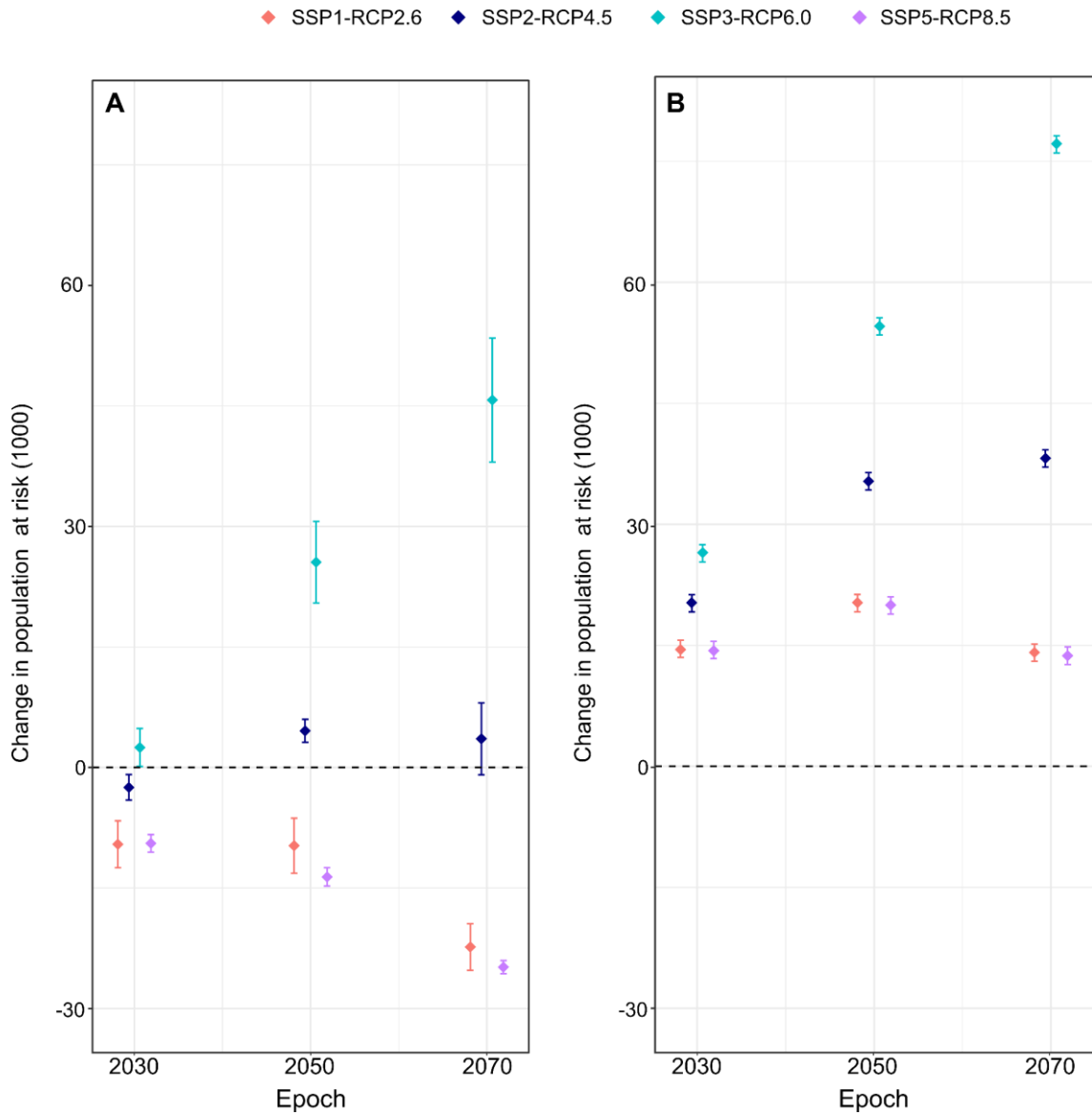
Figure 5.3. Projected changes in population at risk of Japanese encephalitis in northeast India under different SSP-RCP scenarios from 2030 to 2070.

Points and error bars show (A) the change population at risk of JE in thousands under different SSP-RCP scenarios from a present-day baseline to 2030, 2050 and 2070 (mean, 95% credible intervals (CIs) per scenario). (B) The change population at risk of JE in thousands when environmental factors are held constant at present-day levels.

5.4.4 Projected change in the geographic distribution of JE risk under different scenarios

By 2070, there is a projected overall decrease in JE outbreak occurrence probability under all SSP-RCP scenarios when compared to present-day levels (Figure 5.4), with greatest reductions predicted for the states of Assam and Meghalaya (see Appendix 4 Figure S5.1 for map of different states in northeast India). The SSP1-RCP2.6 scenario is projected to have the greatest decline in JE outbreak occurrence probability, followed by SSP2-RCP4.5, with SSP3-RCP6.0 and SSP5-RCP8.5 scenarios having comparable predictions across the region. Some districts in central Assam, northern West Bengal and in Arunachal Pradesh are projected modest increases in JE outbreak occurrence probability, most notably under SSP3-RCP6.0 and SSP5-RCP8.5 scenarios. The concurrent geographic distribution of human populations at risk under different scenarios are projected to vary throughout the region under different SSP-RCP scenarios (Figure 5.5). Scenarios SSP1-RCP2.6 and SSP5-RCP8.5 are comparable, with reductions projected across most of the region, focal areas of moderate increases in population at risk in Assam and West Bengal, and many states remaining stable when compared to present-day levels (e.g., Arunachal Pradesh, Manipur, Nagaland, Sikkim). These results are likely to reflect the projected declines in human population and rice-cropland proportion under these pathways. Under SSP2-RCP4.5, increased populations at risk are expected for the state of Assam and a combination of increases and declines are predicted in West Bengal. By contrast, the highest increases in populations at risk are predicted for the SSP3-RCP6.0 pathway, particularly for Assam and West Bengal. When considering the effect of outflow migration on the projected population at risk of JE, states with high outflow migration such as Assam and West Bengal will have greater disparity in the projected populations at risk under different global change scenarios compared to other states in the region (Table 5.2).
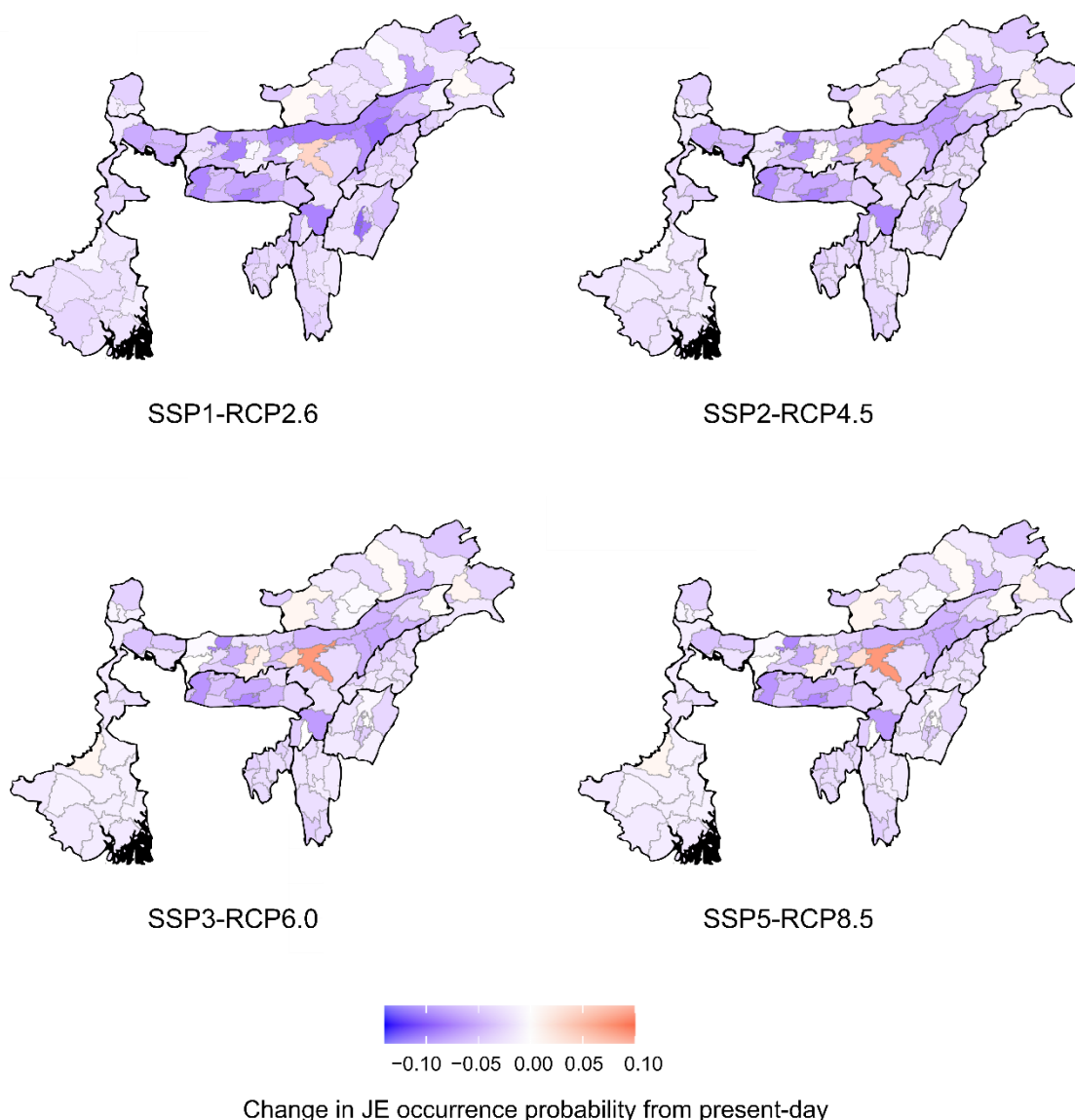
Figure 5.4. Change in projected probability of Japanese encephalitis outbreak occurrence per district in northeast India for 2070 for different SSP-RCP scenarios.

Change in probability of JE outbreak occurrence per district when compared to present-day predictions where zero (white) indicates no change, negative values (blues) indicate a decrease, and positive values (reds) indicate an increase.

SSP1-RCP2.6   SSP2-RCP4.5

SSP3-RCP6.0   SSP5-RCP8.5

-20   0   25   50   75

Change in population at risk from present-day (1000)
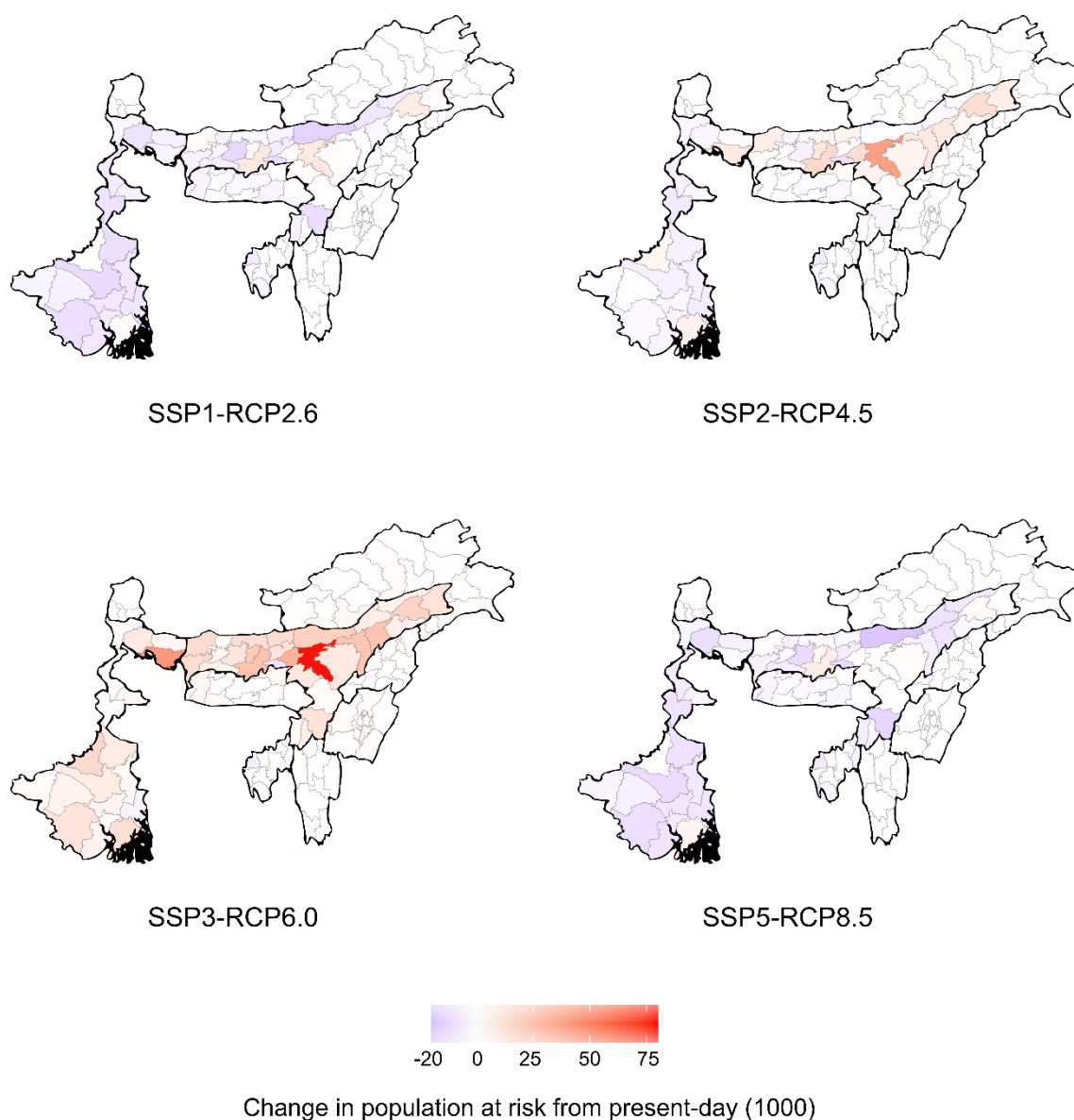
Figure 5.5. Change in projected population at risk (1000s) per district in northeast India for 2070 for different SSP-RCP scenarios.

Change in population at risk of JE in thousands per district when compared to present-day predictions where zero (white) indicates no change, negative values (blues) indicate a decrease, and positive values (reds) indicate an increase.

141

Table 5.2 Projected human population (in thousands) at risk of JE transmission per state in northeast India in 2070 under different scenarios of global change when considering migration.
I calculated migration inflow and outflow proportion per state from the latest census (Government of India, 2011). I calculated the maximum projected population at risk (and 95% credible intervals) by multiplying the projected human population (absolute number of the population moving in or out of a state) by predicted JE outbreak occurrence probability. I then calculated the minimum projected population at risk (and 95% credible intervals) using the same method but first I subtracted the proportion of migration outflow from the population projections.

State	Migration inflow proportion	Migration outflow proportion	Present day population (2011)	Maximum projected population at risk in 2070 (Total projected population x probability of JE occurrence)				Minimum projected population at risk in 2070 ([Total projected population - outflow migration] x probability of JE occurrence)			
				SSP1-RCP2.6	SSP2-RCP4.5	SSP3-RCP6.0	SSP5-RCP8.5	SSP1-RCP2.6	SSP2-RCP4.5	SSP3-RCP6.0	SSP5-RCP8.5
Arunachal Pradesh	0.50	0.18	85	5.3 (5.2-5.4)	7.4 (7.2-7.5)	10.0 (9.8-10.2)	5.3 (5.2-5.4)	4.4 (4.3-4.4)	6.0 (5.9-6.1)	8.2 (8.0-8.4)	4.4 (4.3-4.4)
Assam	0.32	0.36	1126	196.1 (192.5-199.6)	242.9 (238.5-247.2)	319.2 (313.5-324.9)	195.5 (191.9-199.0)	125.5 (123.3-127.7)	155.4 (152.6-158.2)	204.3 (200.6-208.0)	125.1 (122.8- 127.3)
Manipur	0.03	0.09	314	29.0 (28.0-29.9)	35.0 (33.1-36.9)	43.4 (42.1-44.8)	28.9 (28.0-29.8)	26.4 (25.5-27.2)	31.8 (30.8-32.8)	39.5 (38.3-40.8)	26.3 (25.5-27.1)
Meghalaya	0.10	0.07	332	22.5 (21.7-23.3)	28.2 (27.2-29.2)	37.5 (36.2-38.8)	22.4 (21.6-23.2)	20.9 (20.2-21.7)	26.2 (25.3-27.2)	34.9 (33.6-36.1)	20.8 (20.1-21.6)
Mizoram	0.04	0.04	134	3.8 (3.8-4.0)	5.1 (4.9-5.3)	6.8 (6.6-7.1)	3.8 (3.7-4.0)	3.7 (3.5-3.8)	4.9 (4.7-5.1)	6.6 (6.3-6.8)	3.7 (3.5-3.8)
Nagaland	0.18	0.08	205	9.8 (9.5-10.1)	13.0 (12.6-13.4)	17.4 (16.9-17.9)	9.8 (9.5-10.1)	9.0 (8.8-9.3)	12.0 (11.6-12.3)	16.0 (15.6-16.4)	9.0 (8.8-9.3)
Sikkim	0.07	0.07	128	0.7 (0.7-0.7)	1.2 (1.2-1.2)	1.6 (1.5-1.6)	0.7 (0.7-0.7)	0.7 (0.6-0.7)	1.1 (1.1-1.1)	1.5 (1.4-1.5)	0.7 (0.6-0.7)
Tripura	0.08	0.07	464	10.8 (10.4-11.1)	13.3 (12.8-13.7)	17.3 (16.8-17.9)	10.7 (10.4-11.1)	10.0 (9.7-10.3)	12.3 (11.9-12.7)	16.1 (15.6-16.6)	10.0 (9.6-10.3)
West Bengal	0.16	0.16	4476	167.7 (164.0-171.3)	193.5 (189.3-197.7)	235.9 (230.7-241.0)	166.8 (163.2-170.4)	140.9 (137.8-143.9)	162.5 (159.0-166.1)	198.1 (193.8-202.4)	140.1 (137.1-143.2)

142

5.5   Discussion

The spatial distribution and burden of MBDs are driven by climatic, land-use and socioeconomic factors. This study suggests that these factors may impact the geographic suitability and population at risk of JE within the next century. I found the inclusion of rice-cropland proportion, poverty prevalence and climatic factors improved the predictive ability of present-day JE outbreak occurrence in northeast India relative to a simpler baseline (random effects only) model. When projecting the environmental model to 2030, 2050 and 2070 under four different global change scenarios, I found that the population at risk of JE is projected to substantially diverge from present-day levels under different SSP-RCP scenarios. After an initial decline for all scenarios except SSP3-RCP6.0 in 2030, the population at risk of JE is predicted to increase for SSP3-RCP6.0 (i.e., 'regional rivalry' scenario), decline below present-day levels for SSP1-RCP2.6 (i.e., 'sustainability' scenario) and SSP5-RCP8.5 (i.e., 'rapid growth' scenario), and increase and then plateau for SSP2-RCP4.5 (i.e., 'middle of the road' scenario). The results equate to the number of people at risk of JE in 2070 increasing by over 45,000 from present-day levels under SSP3-RCP6.0 scenario and by over 3500 under the SSP2-RCP4.5 scenario. By contrast, when compared with present-day, declines in population at risk are predicted for the SSP1-RCP2.6 and SSP5-RCP8.5 scenarios, resulting in reductions of over 22,000 and 25,000 people at risk, respectively.

The future trajectory of JE burden in northeast India, depends on which SSP-RCP scenario is realised. Unsurprisingly, future population projections under different SSP scenarios will have an extremely strong influence on future populations at risk whereas the influence of environmental conditions is more subtle. However, the influence of environmental factors on JE risk were revealed when holding present-day environmental conditions constant and only assuming projected population changes. This led to predicted increases in populations at risk above present-day levels for all scenarios and revealed the potential negative relationship that future environmental conditions may

have on JE risk. This was especially evident for SSP1-RCP2.6 and SSP5-RCP8.5 scenarios which are both projected dramatic reductions in populations at risk by 2070 when future environmental factors are included in the models. Although SSP1-RCP2.6 and SSP5-RCP8.5 differ dramatically in their projected climatic conditions (Figure 5.2) (van Vuuren *et al.*, 2011), they both represent high equity pathways whereby reductions in agricultural land will occur either due to sustainable practices or technological advancement. These findings suggest that, irrespective of climatic or socioeconomic conditions, reducing rice-cropland extent may be important in limiting the future impact of JE. Conversely, JE risk is projected to increase to 2070 for the 'regional rivalry' scenario (SSP3-RCP6.0) which involves medium-high climate change, high agricultural expansion, high population growth and low equity. By comparison, the 'middle of the road' scenario (SSP2-RCP4.5) results in more moderate increases in JE risk by 2030 when compared to 'regional rivalry' scenario (SSP3-RCP6.0). My findings are in line with a other VBD research which has shown that projected temperature increases may not always amplify disease risk (Li *et al.*, 2019). An integrative modelling study projecting Lyme disease risk in Europe projected risk to be greatest under intermediate (RCP4.5) rather than high (RCP8.5) climate change scenarios and predicted reduced risk under a sustainable scenario (SSP1-RCP2.6) (Li *et al.*, 2019).

I found that present-day JE risk in northeast India is associated with climatic suitability, rice crop agricultural practices and poverty prevalence, supporting the results in Chapter 4. The predictive models used in both chapters substantiate the potential importance of rice crop cultivation and climatic conditions in driving JE risk in the region, both of which are strongly associated with vector and host ecology (Keiser et al., 2005b; Erlanger *et al.*, 2009; Borah *et al.*, 2013; Le Flohic *et al.*, 2013). Accordingly, the future geographic distribution of JE risk may be influenced by both by present-day environmental conditions and prospective land-use and climate conditions projected for the various scenarios. When assessing geographic patterns of JE outbreak occurrence probability under different pathways by 2070, I found an overall projected decrease under all SSP-RCP scenarios when compared

to present-day levels. The greatest reduction in JE occurrence was predicted for the reduced agricultural expansion and low emissions scenario, SSP1-RCP2.6. Predicted change in JE occurrence probability from present-day was comparable for the other scenarios despite their differences in projected agricultural expansion (Figure 5.2). This is likely to be due to the additional influence of projected temperature rise under these pathways (Figure 5.2). Predicted declines in JE occurrence were most prominent for the states of Assam and Meghalaya. The moderate present-day temperatures (25–28°C) and rice-cropland proportions (5–25%) reported in these states (Figure 5.2A) may mean projected environmental changes will have a greater influence on the probability of JE outbreak occurrence in these areas.

Assessing the projected spatial distributions of populations at risk of JE in northeast India reveals diverse differences in the contraction, stability, and expansion of risk under different SSP-RCP scenarios when compared to present-day levels. The greatest between-scenario differences are seen in the two current 'high JE priority' states of the region: West Bengal and Assam (Government of India, 2014). Both states are predicted an overall reduction in population at risk under SSP1-RCP2.6 and SSP5-RCP8.5 scenarios whereas other states are predicted to stay stable. By contrast, under SSP3-RCP6.0 and SSP2-RCP4.5 pathways, Assam and West Bengal are projected an increase in the population at risk. My results indicate that the states of Assam and West Bengal are likely to be priority targets for strengthening health systems and improving surveillance especially as they have high levels of migration. I predict that the human population at risk will remain stable for the other states except for focal areas of increased populations at risk in Manipur and Arunachal Pradesh under SSP3-RCP6.0. Currently Manipur and Arunachal Pradesh are not considered high priority for JE. This research suggests that surveillance should be strengthened in these states to obtain accurate baseline data from which to monitor trends in JE risk over time. Although JE is rarely reported in Arunachal Pradesh, the virus is increasingly being detected in the Himalayan highlands (Baylis *et al.*, 2016) and so could feasibly expand its range to higher elevations with associated warming trends, as predicted for other MBDs such as malaria in Africa and

Central America (Siraj *et al.*, 2014). Shifts towards higher altitudes may have major impacts on populations that are immunologically naive and public health systems with no previous experience in managing JE. Additionally, future increases in populations at risk are predicted to overlap with existing state-level infectious disease vulnerabilities such as socioeconomic factors (i.e., education, demography, poverty), vulnerability due to non-availability of health care (i.e., access to health insurance, public health facilities, availability of hospital beds) and housing and hygiene conditions (Acharya and Porwal, 2020). Therefore, these vulnerabilities will also need to be addressed in order to reduce the future burden of JE in northeast India.

Similar to all future projection analyses, this study is subject to a range of assumptions and limitations. For example, I have assumed that the effects of the global change processes on JE transmission will remain constant and that there will be no future improvements in JE diagnosis, treatment, and control practices. I have also assumed that migration will remain at the same level as recorded in 2011 which is not likely due to the projected effects of global change on human movement (Marotzke, Semmann and Milinski, 2020). Future studies would benefit from including movement models in their analyses since they may improve disease risk predictions when mobility data is unavailable (Kraemer *et al.*, 2019b). Another limitation of this study are the assumptions that the virus will not continue to evolve into further genotypes (Xu *et al.*, 2022) and that there will be no change to the ecology (Ramasamy and Surendran, 2012) or range of vectors or hosts of the disease (Lord, Gurley and Pulliam, 2015; Folly *et al.*, 2021). Future predictions of suitability for disease risk are inherently stochastic, and so the degree to which models resemble reality depends on uncertainty of the environmental and socioeconomic drivers of disease. I have attempted to account for the considerable uncertainty in the structure of the GCMs used to predict changes in future environmental conditions by propagating parameter uncertainty (e.g., uncertainty bounds in climatic and land-use parameters) from the climate models through to my predictions. Indeed, the high levels of uncertainty (i.e., wide CIs) for the maximum temperature parameter may suggest that this variable is not having that significant an effect in the model.

However, increasing the number of GCMs used in the analysis would produce better estimates of uncertainty intervals and provide further context for policymakers.

A significant limitation of this study is that the observational datasets and correlative analytic methods used do not enable the inference of mechanistic relationships between covariates and risk which may limit the model's ability to predict risk responses to novel settings (Getz *et al.*, 2018). For example, the upper thermal limits for optimal JE virus transmission (Mordecai *et al.*, 2019; Tu *et al.*, 2021) were not captured in this analysis due to uncertainty in the temperature parameter. However, in the absence of detailed biological knowledge and data required to specify mechanistic models, correlative approaches such as those used in this study, may be the most conservative approach in the projection of future disease risks (Messina *et al.*, 2015; Getz *et al.*, 2018). Another limitation of the study is the quality of the case data which was strongly influenced by the reporting effort (Government of India, 2014; Baylis *et al.*, 2016). This meant the analysis focused on predicting outbreak occurrence which is a coarse proxy for realised risk. Indeed, future research could extend this model to predict not only occurrence, but also incidence. In addition, this study did not consider the role of human factors which are critical in shaping patterns of disease risk such as behaviour, population immunity, and age distribution (Funk, Salathé and Jansen, 2010). Future studies could use age-stratified human population projections to consider how the age distribution of the population may impact the population at risk of disease (Li *et al.*, 2016; Kwak, Hong and Kim, 2021). Furthermore, future projections for important socio-ecological drivers such poverty (Luo *et al.*, 1995; Halstead and Jacobson, 2003; Sarkar *et al.*, 2012) were not captured in this study. A study on malaria risk found future socioeconomic status had a larger impact than climate change and the combined impact of both factors was even more significant than either factor alone (Béguin *et al.*, 2011). Water scarcity was also overlooked in my analysis despite its important relationship to irrigated agriculture and varied water demands predicted across different socioeconomic scenarios (Graham *et al.*, 2018, 2020). Indeed, climate change, population growth, and increased

dependence on irrigated agriculture are predicted to reduce the Brahmaputra basin which is likely to significantly impact irrigated agriculture in Assam (Immerzeel, van Beek and Bierkens, 2010).

Despite these limitations, the projections produced in this study provide an evidence base that can be used to improve surveillance systems, focus adaption strategies on vulnerable areas, and strengthen public health systems to reduce JE burden in the coming decades. Higher populations at risk are predicted for SSP3-RCP6.0 and SSP2-RCP4.5 scenarios which more accurately reflect current pathway trajectories, indicating that JE risk will continue to increase in the region with ongoing environmental and socioeconomic trends. Interestingly, I found that projected future environmental conditions may dampen the overall population at risk in northeast India when compared to present-day environmental conditions. This suggests that different climate and agricultural pathways could have distinctly different effects on disease risk, especially in already JE endemic areas such as northeast India. These results are in line with projections of future disease risk for other VBDs under scenarios of plausible future socioeconomic and climate change (Purse *et al.*, 2017; Li *et al.*, 2019). A study on leishmaniasis in the Americas projected that future disease patterns would be largely influenced by climatic factors however, the presence-only nature of the available disease data and the wide geographic scale of the study may have meant the impacts of land-use and social factors were difficult to detect (Purse *et al.*, 2017). In comparison Li *et al.* (2019) found that the projected impact of climate and land-use change of future Lyme disease risk were likely to be different, with climate warming projected to expand risk in northern Europe and agricultural land expansion projected to limit risk in southern Europe (Li *et al.*, 2019).

My study represents a step towards incorporating MBD risk into public health and environmental policy decisions to identify trade-offs across land-use, climate, food security and human health. Future research could extend this analysis to wider JE endemic areas across Asia and to include multiple MBDs (Colón-González *et al.*, 2021a). This research could provide a fuller

picture of future global change effects on MBD burden and enhance intersectoral coordination and collaboration on policy decisions, as has been performed for biodiversity and sustainability goals (Zabel *et al.*, 2019; Hinz *et al.*, 2020).

Chapter 6:
Discussion

Human exploitation of the environment has resulted in natural systems being degraded to an unprecedented extent, leading to dramatic environmental changes with deleterious impacts for human health (Whitmee *et al.*, 2015). The latest Intergovernmental Panel on Climate Change (IPCC) report (IPCC, 2022) provides a stark overview of the effects of human-induced environmental change on the health of nature and humans, signalling that the "people and ecosystems least able to cope are being hardest hit". The report provides overwhelming evidence for the strong links between climate, land-use, and socioeconomics and their effects on environmentally sensitive diseases such as mosquito-borne diseases (MBDs), emphasising the need to consider these processes simultaneously when tackling complex problems. Yet, despite the rapidly growing awareness of the influence of global change processes on the burden of MBDs, a lack of evidence on the effects of these drivers has hindered understanding of present-day MBD burdens and how disease risk may vary under future scenarios of global change (Campbell-Lendrum *et al.*, 2015). Broader perspectives that consider the combined influence of different socialecological pressures that are driving MBD risk are required to better understand the current and future impacts of global change processes on MBD systems.

To improve understanding of the effects of different global change processes on MBD risk, the research in this thesis has adopted a socio-ecological perspective on the effects of these pressures on the hazard (i.e., pathogen availability) and risk of MBDs both in general (Chapter 2) and, for a case study of Japanese encephalitis (JE) in India (Chapters 3 to 5). In Chapter 2, I reviewed the current evidence of the relative impact of global change processes on MBD risk and critically examined how these drivers have been incorporated into existing analyses. Despite growing evidence for the key role of other global change processes in modulating MBD risk, I found that in previous MBD research there has been a focus on the effects of climate

change (Figure 2.1). I suggested a holistic approach to the modelling of MBD risk whereby socioeconomic and environmental factors, and their interactions were considered (Figure 2.3). In so doing, I showed the need for better surveillance data, empirical research, use of novel data sources and enhanced statistical methods to improve the understanding of MBD drivers and risk.

In Chapter 3, I addressed some of the gaps identified in Chapter 2 by applying a novel statistical method to predict spatiotemporal patterns in vector abundance using sparse vector surveillance data. Measures of seasonal vector abundance – a key component of MBD hazard – are required to define potential hotspots of disease risk and target public health interventions. This is particularly important for understudied diseases such as JE because resources for disease surveillance and control are often limited. By combining different types of vector surveillance data in a joint-likelihood model, I was able to predict the seasonal abundance of the predominant JE vector *Culex tritaeniorhynchus* across India (Figure 3.3). I also identified important environmental drivers of seasonal vector abundance (Figure 3.2) and proposed the potential use of vector abundance as a proxy for JE hazard. In Chapter 4, by analysing long-term, surveillance data for JE in northeast India, I addressed knowledge gaps in the underlying drivers, geographic distribution, timing, and intensity of JE risk. I demonstrated the importance of environmental and socioeconomic factors in driving JE risk in this region (Figure 4.5) and used this knowledge to predict JE endemic areas (Figure 4.6) and temporal patterns in JE incidence (Figure 4.7). I then evaluated how future socioeconomic and greenhouse gas concentration pathways (Shared Socioeconomic Pathways and Representative Concentration Pathways [SSP-RCPs]) may differentially impact trends in JE risk in northeast India and found while population changes across all pathways are expected to influence JE risk, environmental conditions have the potential to either intensify or reduce these risks (Chapter 5).

In this final synthesis chapter, I discuss the contributions these studies make in improving knowledge on MBD risk and global change and highlight

outstanding questions. Firstly, I examine the methodological innovations and challenges I encountered in my research. Secondly, I consider how my results contribute to the understanding of the epidemiology and control of JE in India, and to the environmental and socioeconomic factors driving JE disease risk. Thirdly, based on my findings and the wider research contributions during this thesis, I review policy areas where ecosystem perspectives and transdisciplinary approaches could assist in enhancing human health outcomes. Finally, I discuss unresolved questions and limitations of the thesis before suggesting how my research could be extended to offer a broader perspective on MBD as an environmental nexus issue. I believe this approach is key to advance understanding and predictions of MBD risk under current and future scenarios of global change.

6.1   Methodological contributions

Quantifying and predicting the effects of different global change processes on MBD risk is hindered by the paucity of reliable, high quality surveillance data on vectors (ECDC and EFSA, 2018; Rund *et al.*, 2019), reservoir host populations (Britch *et al.*, 2013; Lord, Gurley and Pulliam, 2015; DeCarlo *et al.*, 2017; Pandit *et al.*, 2018) and human incidence (Lowe *et al.*, 2020; WHO, 2020a). Since JE is a relatively understudied disease, accounting for data gaps and surveillance biases has been a significant challenge throughout this thesis. I used Bayesian hierarchical modelling approaches in Chapters 3 to 5 to compensate for potential data biases (Redding, Lucas, Blackburn and Jones, 2017). In Chapter 3, I addressed gaps in vector surveillance data using a novel joint-likelihood Bayesian hierarchical model that leveraged spatial information from vector occurrence probability to estimate seasonal vector abundance for the principal JE vector, *Cx. tritaeniorhynchus* across India (Figure 3.3). This joint-likelihood modelling approach explicitly accounts for differences in data quality and structure (i.e., different probability distributions) and can handle and quantify sources of uncertainty associated with each data type (Amoah, Diggle and Giorgi, 2020; Lucas *et al.*, 2021). The framework provides a powerful and flexible method to define seasonal

vector abundance over large spatial scales and is easily adaptable for other MBDs also with limited vector surveillance data. The issue of limited robust long-term geographically extensive distribution data is also pertinent for other insect vectors. Indeed, a study using available long-term tick surveillance datasets compared the performance of three different data types (quantitative count data from scientific surveys; presence-only data from public submissions; and a combined dataset from multiple sources) in their ability to predict *Ixodes ricinus* tick distributions in the UK and inform public health policy (Ribeiro *et al.*, 2019). Although quantitative count data from scientific surveys are considered gold standard, their value was limited by poor data coverage and instead, combined datasets from multiple sources were found to be valuable in addressing issues of low coverage and producing maps for public health decision-making (Ribeiro *et al.*, 2019). Using varied data types to estimate spatiotemporal patterns in vector abundance and the uncertainty associated with the predictions will assist the targeting of future surveillance efforts where long-term and large spatial scale data are not available or cannot be practically acquired.

Similar to other understudied diseases (Lowe *et al.*, 2020; Purse *et al.*, 2020; WHO, 2020a), insufficient disease surveillance data has meant that the exact global incidence and burden of JE are not fully understood (Sabesan, Raju Konuganti and Perumal, 2008; WHO, 2015b; Quan *et al.*, 2020). Furthermore, the high subclinical to clinical ratio of disease presentation (WHO, 2015b), non-specific clinical symptoms (McNaughton, Singh and Khan, 2018), possible test cross reactivity with other flaviviruses and vaccines (Maeki *et al.*, 2019; Quan *et al.*, 2020) and limited healthcare resources (WHO, 2020b) has hindered the identification of drivers and accurate reporting of the distribution and dynamics of JE. In Chapter 4, I describe how I compensated for the patchy, zero-inflated surveillance data that were currently available, and any surveillance biases, by modelling binary outbreak indicators rather than incidence rates. It is common for vector-borne disease (VBD) case data to include excess zeros, either true or due to imperfect detection (i.e., sampling zeros), which pose modelling challenges (Neupane, Goldbloom-Helzner and Arab, 2021). The use of JE

outbreak occurrence thresholds allowed me to reduce the effects of bias introduced by differences in case reporting and health seeking behaviour and so distinguish the effects of socio-ecological factors on spatial JE risk (Figure 4.5). In addition, this approach enabled me to determine the potential endemic areas for JE transmission and identify areas that may be experiencing underreporting that could benefit from increased surveillance (Figure 4.6). The use of several outbreak thresholds for the binary outbreak indicator enabled me to perform a sensitivity test on the analysis and so avoid exaggeration or understatement of the results. However, the classification of outbreak thresholds must be performed and analysed with caution for underreported diseases because of the potential for predictions in unobserved areas (e.g., potential areas of underreporting) being penalised (see Section 4.5). Paucity of vector and disease surveillance data has led to the popularity of correlative models such as ecological niche models (ENMs; otherwise known as species distribution models) in VBD research to predict vector, pathogen and VBD risk distributions with future scenarios of global change (Tjaden *et al.*, 2018; Johnson, Escobar and Zambrana-Torrelio, 2019; Moritz U. G. Kraemer *et al.*, 2019a; Leta *et al.*, 2019; Messina *et al.*, 2019; Slatculescu *et al.*, 2020; Lule *et al.*, 2022). Although useful in instances of incomplete data or undefined environmental associations (Phillips, Anderson and Schapire, 2006; Redding *et al.*, 2016), these models often lack ecological information (Johnson, Escobar and Zambrana-Torrelio, 2019) and do not facilitate the identification of underlying causal relationships (Kraemer, Reiner and Bhatt, 2019); they tend to assume linear covariate associations (Washburne *et al.*, 2019) which reduces their applicability to novel settings (Campbell-Lendrum *et al.*, 2015; Parham *et al.*, 2015). Integrating ecological theory and approaches to modelling disease systems could significantly improve our understanding of how global change impacts disease risk (Gibb *et al.*, 2020b). Indeed, while modelling approaches that incorporate ecological processes are gaining traction in VBD research, they have tended to focus on the effects of climate change (Caminade *et al.*, 2014; Ogden *et al.*, 2014a; McPherson *et al.*, 2017; Kraemer *et al.*, 2019a; Ryan *et al.*, 2019).

The study I present in Chapter 5 focuses on incorporating scenarios of climate, land-use and socioeconomic change into future disease projections to evaluate the degree to which projected pathways may impact the population at risk of JE in northeast India. To do this, I applied a Bayesian model of JE outbreak spatial occurrence to project the spatial extent of JE risk across northeast India in 2030, 2050 and 2070 based on different global change scenarios (SSP-SSP scenarios). This study represents a step towards incorporating MBD risk into public health and environmental policy decisions to identify trade-offs across land-use, climate, food security and human health. Projections of future disease risk for other VBDs have also been performed under scenarios of plausible future socioeconomic and climate change (Purse *et al.*, 2017; Li *et al.*, 2019). A study on leishmaniasis in the Americas used correlative methods to determine present disease-environment relationships and project these onto a matrix of six alternative future scenarios of climate and land-use changes (Purse *et al.*, 2017). Climatic factors were found to have a strong influence on disease patterns however, the presence-only nature of the available disease data and the wide geographic scale of the study may have meant the impacts of landscape and social factors were difficult to detect (Purse *et al.*, 2017). In comparison Li *et al.* (2019) combined an agent-based model with host species distribution modelling and models of climates and land-use change to look at the impact of various climate and socioeconomic scenarios on the spread of Lyme disease in Europe. By integrating process-based and correlative methods, this study improves understanding on the mechanisms of Lyme disease transmission and how it may respond to combined future global changes. Future research could extend my analysis to include process-based models to enable a fuller picture of future global change effects on JE burden and enhance intersectoral coordination and collaboration on policy decisions, as has been performed for biodiversity and sustainability goals (Zabel *et al.*, 2019; Hinz *et al.*, 2020).

6.2 Contributions to the understanding of JE epidemiology and control

JE is an important arbovirus in Asia and the West Pacific (G. L. Campbell *et al.*, 2011; Quan *et al.*, 2020) with a high morbidity and mortality rate, affecting over three billion people (Moore, 2021). However, despite JE meeting the criteria of disproportionally affecting impoverished communities (Sarkar *et al.*, 2012), having a complex transmission cycle that is sensitive to environmental conditions (van den Hurk, Ritchie and Mackenzie, 2009; Le Flohic *et al.*, 2013) and causing serious health, social and economic consequences (Kulkarni *et al.*, 2018; Moore, 2021), the World Health Organization does not class it as a neglected tropical disease (NTD) (WHO, 2020a). The most likely reason for this decision is the availability of an effective vaccine in some countries (Abeysinghe and Neuzil, 2018); effective vaccination strategies have enabled countries such as Japan, Taiwan, and South Korea to reduce previously high JE burdens to almost zero (Erlanger *et al.*, 2009). Therefore, although the zoonotic source of transmission (i.e., animal reservoir hosts) remains in these more affluent countries, JE virus (JEV) spillover to humans has been significantly reduced (Moore, 2021). Nevertheless, large-scale vaccination programmes in other JEV-endemic countries may not be as achievable due to differences in demographics, resources, and healthcare access. Furthermore, it has been suggested that JEV genotypes may vary over time which may impede the success of any vaccination programme (Fang *et al.*, 2019). Although JE is not classed as an NTD, underreporting and ineffective healthcare provision for the disease necessitates the effective targeting of available resources and preventative measures towards the most at-risk regions and populations. Therefore, in Chapters 3 to 5, I aimed to determine the spatiotemporal distribution of disease hotspots in India and establish where future survey efforts should be directed to improve the knowledge of this understudied disease.

When predicting spatiotemporal variation in JE vector abundance across India, I found two distinct patterns; these were perennial hotspots in the northeast and southern regions, and seasonal hotspots in the north, east and

south of the country (Figure 3.2). My study showed the limitations of previously available static vector distribution maps which have used ENMs to define JE vector occurrence across large geographic ranges (Masuoka *et al.*, 2010; Miller *et al.*, 2012; Longbottom *et al.*, 2017; Samy *et al.*, 2018). Indeed, patterns in vector abundance and seasonality are important epidemiological factors that impact pathogen establishment, persistence and transmission (ECDC and EFSA, 2018; Tjaden *et al.*, 2018; Liu-Helmersson *et al.*, 2019) and, provide a detailed understanding of the hazard associated with JE transmission (i.e., JEV availability). Understanding the location and timing of peak vector abundance in India will certainly assist national public health bodies in their objective "to strengthen surveillance, (and) vector control" (Government of India, 2014). Accordingly, future vector surveillance should be guided by ecological understanding and empirical modelling (Chapter 3), focusing on predicted hotspots, especially in understudied regions predicted to have high vector abundance. These data could then be used to inform the model and improve and update predictions. This approach will help to better characterise geographical and seasonal JE vector abundance when compared to current surveillance strategies which are guided by socioeconomic factors and historical reported outbreaks (Government of India, 2014). Furthermore, model predictions could also be used to target preventative measures to reduce the disease incidence.

In Chapter 4, I built on my findings from Chapter 3 to model spatiotemporal JE risk and included information on contact with pathogen (i.e., exposure), likelihood of infection (i.e., susceptibility) (Hosseini *et al.*, 2017) in addition to environmental factors hypothesised to determine JE hazard. I focused my analysis on the northeast region of India, where most JE case data have been reported, and perennial JE vector abundance hotspots have been predicted (Chapter 3). My aim was to improve the understanding of the geographic distribution, timing and intensity of JE outbreaks and determine underlying drivers using long-term JE surveillance data. I predicted areas for potentially endemic transmission across many districts already considered high JE priority in the states of Assam and West Bengal (Government of India, 2014). However, I also identified several districts predicted endemic

despite low or absent numbers of reported cases (Figure 4.6B). These results indicate increased surveillance is required in these districts.

As suggested for vector surveys, future human JE surveillance should target areas predicted to be appropriate based on empirical models (Chapter 4) rather than on historic reporting of outbreaks to better characterise the distribution of the disease. Indeed, there are many factors that suggest that the targeting of surveillance to areas with high historical incidence is misguided. The factors include: the possibility that JE is mistaken for other causes of encephalitis (Khan *et al.*, 2011; Chowdhury *et al.*, 2014; Dev, Sharma and Barman, 2015; McNaughton, Singh and Khan, 2018); serological test cross reactivity with other flaviviruses and vaccines (Maeki *et al.*, 2019; Quan *et al.*, 2020); disparity in healthcare resources (WHO, 2020b). Furthermore, because of the influences of ongoing environmental changes, public health bodies must adapt and rather than focus their surveillance efforts on currently endemic regions, they should establish a broader scanning surveillance system to implement timely and appropriate health care strategies.

While the influence of environmental (Keiser et al., 2005b; Erlanger *et al.*, 2009; Borah *et al.*, 2013; Le Flohic *et al.*, 2013) and socioeconomic conditions on JE transmission (Badari, 1985; Luo *et al.*, 1995; Sarkar *et al.*, 2012), have been widely reported, the relative importance of these risk factors remains poorly understood. Chapter 3 provides strong evidence that not only climatic seasonality, but land-use and rice cultivation metrics are important drivers of vector abundance. These results reflect the influence of environmental covariates on vector ecology, with temperature and rainfall patterns influencing mosquito development and survival (Murty, Rao and Arunachalam, 2010; Kumari and Joshi, 2012; Mordecai *et al.*, 2019). In addition, intensive irrigated agriculture practices provide stable suitable vector breeding habitats for extended periods (Keiser *et al.*, 2005b; Baeza et al., 2011). Regions that cultivate rice biannually report reduced vector seasonality (i.e., higher vector abundance throughout the year) compared with those that have a single annual crop (Gajanana *et al.*, 1997).

My results in Chapter 4 further emphasise the sensitivity of JE to environmental conditions. I showed that within endemic areas climate and agricultural practices were crucial determinants of JE risk, both spatially and seasonally. These relationships probably reflect the critical roles of pathogen, vector and reservoir host population ecology in disease transmission dynamics (Keiser et al., 2005b; Erlanger *et al.*, 2009; Borah *et al.*, 2013; Le Flohic *et al.*, 2013). Temperature is linked to vector and pathogen development (Mordecai *et al.*, 2019) and seasonal rainfall and land-use practices are linked to habitat availability for vectors and hosts (Keiser et al., 2005b; Erlanger *et al.*, 2009; Borah *et al.*, 2013; Le Flohic *et al.*, 2013; Elphick, 2015). In endemic districts of northeast India, I found that JE risk was influenced by climatic factors (i.e., temperature, precipitation, and precipitation extremes) lagged by one month which probably represents the periods of vector development (CDC, 2020), viral replication in vectors (Schuh *et al.*, 2014; Tu *et al.*, 2021), and human incubation (Turtle and Solomon, 2018).

My findings also support the association between predicted vector abundance lagged by one month and JE outbreak occurrence detected in Chapter 3. Land-use covariates including area of land under rice cultivation and vegetation greenness (i.e., vegetation index NDVI) lagged by three months were also important predictors of JE risk in endemic areas, reflecting not only the importance of irrigated agricultural systems to the ecology of vectors and hosts (i.e., components of JE hazard), but also the contact between humans and infected vectors (i.e., JE exposure). The lag of three months between vegetation greenness and JE incidence may represent peak times of exposure during rice crop harvesting (Singha *et al.*, 2019) when increased human-vector transmission is likely to occur. However, the timing between vegetation greenness and potential human exposure has yet to be confirmed despite studies linking vegetation indices to JE cases (Wang *et al.*, 2014; Rattanavong *et al.*, 2020).

The distinct seasonality in JE incidence observed in districts of Assam described in Chapter 4 differs from the high perennial vector abundance

predicted across the state described in Chapter 3. This difference suggests that factors other than vector abundance are driving seasonal disease dynamics in the region. For example, although ardeid bird host populations in India are resident (i.e., spend the whole year in their breeding grounds) (SoIB, 2020e, 2020d, 2020b, 2020a, 2020c), they primarily forage in rice paddies during the rice growing season (King et al. 2010) and so their contact with vectors may be seasonal. Similarly, there may be a distinct seasonality in human exposure to infected mosquitoes due to behavioural practices such rice crop harvesting or seasonal use of vector control measures (e.g., fogging). Both these components of risk require further investigation, especially in understanding how human behaviour influences exposure over time and space. Although previous studies have attempted to develop potential indicators of human exposure to other MBDs (Monroe *et al.*, 2020; Fustec *et al.*, 2021), these are currently specific to other MBD systems and are unlikely to be useful for understanding JE exposure.

6.3 Contributions to the understanding of the impact of global change on MBD risk

Research on the effects of global change on MBDs have predominantly been explored through the lens of climate change due to well-documented effects of climate on vector life history traits (Gething *et al.*, 2010; Ryan *et al.*, 2015; Mordecai *et al.*, 2017; Mordecai *et al.*, 2019; Ryan *et al.*, 2019). This has resulted in policy narratives around MBD risk focusing on the direct effects of climate as a crucial driver of disease emergence and outbreak risk without considering the role of non-climatic drivers. Climate-driven models have also predominated in wider VBD research and other drivers of change have been less explored (González *et al.*, 2010; Moo-Llanes *et al.*, 2013; Ogden *et al.*, 2014a; Parham *et al.*, 2015; Williams *et al.*, 2015; Alkishe, Peterson and Samy, 2017; McPherson *et al.*, 2017). Importantly, the recent IPCC report on climate change impacts acknowledges that climate change is expected to expand and redistribute MBD burdens but also recognises that these effects are mediated by other impacts such as land-use change, travel,

socioeconomic conditions, and public health interventions (IPCC, 2022). My conclusions in Chapter 2 are consistent with the IPCC's assessment; considering the effect of climate change in isolation may result in inaccurate predictions of MBD risk. In Chapter 2, I reviewed climate-based modelling studies and found that climate change was predicted to have both a positive and negative effect on MBD risk. However, most reviewed studies were simple correlative analyses that did not account for key biological information (e.g., vector trait thermal optima) and needed to predict the climate dependence of transmission across vectors, pathogens, and environments (Mordecai et al., 2019). Although many studies have since used ecologically informed approaches that leverage information on thermal trait responses into models (Mordecai *et al.*, 2017; Ryan *et al.*, 2019), conflicting results on the effects of climate change on MBD risk exist between models. For example, malaria is projected to expand in some regions but also forecast to decrease in other areas (Caminade *et al.*, 2014; Ryan *et al.*, 2015; Murdock, Sternberg and Thomas, 2016; Endo and Eltahir, 2020; Mordecai *et al.*, 2020). One reason for this lack consensus is that some models have not captured how other global change processes might influence disease risk directly or indirectly via interactions with climate. Indeed, I found that only 28% of reviewed studies considered the effects of non-climate drivers in their analyses (Table 2.2). I suggest that future analyses need to consider other global change processes to understand and better predict MBD risk.

My results in Chapters 3 and 4 show the importance of land-use in shaping MBD risk. My findings suggest that vector populations and JE risk respond in consistently positive ways to agricultural land-use practices. In Chapter 3 I reported on the positive relationship I found between vector abundance and land-use intensity metrics for rice crop cultivation and in Chapter 4, I described how I found that crop growth phenology could be used to predict temporal trends in JE cases in endemic areas. My findings are supported by evidence from previous studies that have reported positive associations between agricultural intensity and vector abundance (Kanojia and Geevarghese, 2004; Keiser et al., 2005b; Richards *et al.*, 2010; Raju *et al.*, 2018), and correlations between vegetation greenness and JE cases (Wang

et al., 2014; Rattanavong *et al.*, 2020). My results also support broader conclusions on the importance of land-use change on infectious disease risk related to impacts on the interaction between people, pathogens, vectors and vertebrate hosts (Lambin *et al.*, 2010; Kilpatrick and Randolph, 2012; Gottdenker *et al.*, 2014; Johnson, de Roode and Fenton, 2015; Hassell *et al.*, 2017; Gibb *et al.*, 2018; Gibb *et al.*, 2020). These findings have implications for projected global expansion of land-use change (Chen *et al.*, 2020). Nevertheless, the impact of future land-use change will depend on factors such as the geographic region, the mode of the change and the specific disease system; these factors influence underlying ecological processes regulating disease transmission (Ladeau *et al.*, 2015; Gibb *et al.*, 2020a). Overall, my results highlight the importance of integrating ecological perspectives into MBD prediction due to their situation at the nexus between environmental change, ecosystems, and health (Gibb *et al.*, 2020b).

Knowledge on how different global change processes combine to alter MBD risk remains unclear (Chapter 2). Several studies have explored how climate and land-use may interact to influence MBD risk and have found that the combined effects of both pressures may lead to reduced predictability and increased potential for larger epidemics (Baeza *et al.*, 2011; Tompkins and Caporaso, 2016; Lowe *et al.*, 2021). Furthermore, the interactions of these processes with socioeconomic factors (e.g., poverty, human mobility, demographics, trade) adds another level of complexity which is difficult to assess but critical for understanding the impact of global change on MBD risk. Although poverty prevalence was found to be positively associated with JE outbreak occurrence in Chapters 4 and 5, the compound nature of the variable (i.e., it is mediated by several factors) makes interpretation of this relationship challenging. Understanding the influence of socioeconomic factors on MBD risk requires a sophisticated approach that considers how these effects might interact with climate and land-use. For example, a study investigating the relationship between malaria and socioeconomic conditions associated with land-use change (Baeza *et al.*, 2017) developed an epidemiological compartmental model of malaria transmission which included a subpopulation not at risk of contracting malaria due to improvement in

socioeconomic conditions. This model was then combined with a mosquito population dynamics model and an economic model which mimicked an agricultural, labour-intensive productive system that captured economic productivity and demographic changes. The study found an initial increase in malaria transmission due to relatively fast ecological changes associated with land-use conversion, followed by either a decline or a further increase in risk which related to the pace of investment in interventions. Therefore, although climate and land-use changes are predicted to have directional (i.e., positive, or negative) effects on MBD hazard and risk, approaches that consider how these processes might interact with socioeconomic factors are necessary to understand how these diseases may be affected by future environmental change.

In Chapter 5 I used a statistical model of outbreak risk to project the combined effects of future climatic, agricultural, and socioeconomic change on future populations at risk of JE. Despite the strong influence on population projections under different SSP scenarios, I also revealed the potential dampening effect that future environmental conditions may have on JE risk. This was especially evident for SSP1-RCP2.6 (i.e., 'sustainability' scenario) and SSP5-RCP8.5 (i.e., 'rapid growth' scenario) which are both projected dramatic reductions in populations at risk by 2070. Although SSP1-RCP2.6 and SSP5-RCP8.5 differ dramatically in their projected climatic conditions (van Vuuren *et al.*, 2011), they both represent high equity pathways whereby reductions in agriculture will occur either because of sustainable practices or technological advancement. These findings suggest that, irrespective of climatic or socioeconomic conditions, reducing rice cropland extent may be important in limiting the future impact of JE. However, the lack of inferred mechanistic relationships between covariates and risk may limit the model's ability to predict risk responses to novel settings (Getz *et al.*, 2018). Future research could extend this model to include mechanistic processes and therefore improve its potential predictive ability. For example, a recent VBD study combined an agent-based model with host species distribution modelling and models of climates and land-use change to look at the impact of various climate and socioeconomic scenarios on the spread of Lyme

disease in Europe (Li *et al.*, 2019). The study found that the projected impact of climate and land-use change of future disease risk were likely to be different, with climate warming projected to expand risk in northern Europe and agricultural land expansion projected to limit risk in southern Europe (Li *et al.*, 2019).

6.4 Policy implications

The importance of climate, land-use and agricultural practices on JE emphasises the need for increased adaptive, ecosystem-based interventions to help manage MBD hazards and risks across multiple areas of policy (i.e., public health, agricultural, environmental, and land management). As I have demonstrated in this thesis, evaluating how vector populations respond to agricultural expansion and climate changes can identify high risk areas for MBD transmission. This information can inform the design of agricultural landscapes and practices to regulate vector and host populations and their interactions, reducing pathogen availability and potential human exposure. An example of this approach is seen with the reintroduction of prawns to riverine ecosystems in Senegal to regulate snail host populations, reduce the prevalence of vector-borne human schistosomiasis, while also benefiting local food security (Sokolow *et al.*, 2015). In the context of JE ecology, adopting methods from high yield rice cultivation strategies that require less standing water (e.g., alternate wetting and drying irrigation methods, the development of drought-tolerant cultivars) (Singh *et al.*, 2021) could enable more efficient use of land and reduce wildlife-vector-human interfaces. This approach could have added benefits for biodiversity (Folberth *et al.*, 2020), food security by reducing crop losses due to climate change (IRRI, 2018; Oladosu *et al.*, 2019), could benefit biodiversity (Folberth *et al.*, 2020) and could improve water security due to the reduced demand for irrigation (Luo, 2010; Kayatz *et al.*, 2019). Indeed, there is scope to include MBDs such as JE within the "water-food-energy nexus" approach to sustainable development which acknowledges that actions in one of these domains commonly impacts the others (FAO, 2014; UNECE, 2021). This would enable

the identification and management of trade-offs across the different policy sectors of water, food, energy and public health, allowing for more integrated and cost-effective planning to safeguard ecosystem and human health.

The integration of ecological knowledge into modelling approaches for MBDs is fundamental to the understanding of these disease systems (Chapters 3 and 4). Under future global change, ecological knowledge will be increasingly important to support both short-term public health policy (e.g., early warning systems for prevention and targeting resources) and long-term decisions for adaptation to different scenarios (e.g., strengthening health systems and surveillance, improving diagnostic capacities, and targeting vaccinations) (Chapter 5). However, ecological perspectives are rarely factored into current and future public health policy (Gibb *et al.*, 2020b). Changing this '*status quo*' requires a transdisciplinary approach to public health policy involving the integration of knowledge, evidence, and research across ecological, social, and health domains (Grant *et al.*, 2016; Bedford *et al.*, 2019; Li *et al.*, 2019; Purse *et al.*, 2020; Burthe *et al.*, 2021). Furthermore, the sharing of data across these different disciplines via the development of open access platforms could help fill gaps in data and improve public health policy in the prevention and control of MBD. Planetary Health provides a framework for the necessary broadening of public health policy by promoting a systems approach to human health outcomes (Pongsiri *et al.*, 2017) whereby stakeholder objectives across domains can be matched and the challenges that society faces identified, studied, and addressed holistically.

The need for a holistic, systems-thinking approach to health is repeated in the research and policy contributions I made in other projects during my time as a PhD student. I co-authored a report for the World Wide Fund for Nature and the Smithsonian Institute which reviewed the links between environmental degradation and health outcomes in Africa to identify how efforts to preserve the natural environment and sustainably manage natural resources could have an impact on human and animal health (Hassell *et al.*, 2021a). The report highlighted major gaps in knowledge of the mechanisms by which environmental degradation endangers human health and

recommended the formation of interdisciplinary partnerships to advocate for nature to be at the centre of public health policy and to frame natural resource management as a form of preventative medicine. Similar themes emerged in my co-authored analysis piece for the British Medical Journal in which I highlighted the need for improved understanding of how environmental changes can affect zoonotic risk to help prevent and respond to outbreaks (Gibb *et al.*, 2020b). The paper outlined the socio-ecological challenges associated with managing zoonotic disease transmission and advocated for ecological perspectives to be integrated into public health policy to help evaluate disease-risk trade-offs, prioritise interventions, and build health resilience to global change. Moreover, during my policy fellowship at the House of Commons Environmental Audit Committee, I was able to further advocate the need for policymakers to consider the relationships between environmental and human health. During my placement I took a lead role in an inquiry highlighting the links between environmental and human health in relation to the COVID-19 pandemic. This culminated in a report to the government advocating for nature to be placed at the centre of the economic recovery (EAC, 2021).

In a perspective piece, I explored how predictive systems ecology models could be used to understand interactions between pathogens, hosts and the environment, transforming our understanding of disease ecology and identifying the best ways to manage emerging disease risk (Hassell *et al.*, 2021b). Furthermore, I held a transdisciplinary workshop that brought together experts from the United Nations, humanitarian non-governmental organisations, policy, and academia to develop a better understanding of how big data could be used to understand drivers of migration. The workshop highlighted the potential application of big data to understand environmental drivers of migration such as climate change and highlighted the benefit of transdisciplinary collaborations when addressing complex problems (Franklinos *et al.*, 2021).

6.5 Outstanding questions, limitations, and opportunities

As described in Chapter 2, enhanced surveillance is required to improve health data and define the factors that promote MBD risk. However, due to differences in capacity, resources and the need for integration into pre-existing systems, considerable variability exists in the approach, quality, and extent of JE surveillance (Heffelfinger *et al.*, 2017). The lack of JE surveillance data was a prevalent challenge for the quantitative parts of my thesis. Notably, the spatial and temporal biases of available vector and human surveillance data were significant limitations in Chapters 3 and 4 and hindered my ability to accurately describe important associations and to make predictions in data-poor regions. However, in both chapters, my analyses informed where future surveillance efforts could be targeted, principally to areas with high predicted hazard or risk that have low reporting effort. Like other understudied diseases, it is imperative to establish a broader surveillance system to better characterise the distribution of the disease rather than continue to target surveillance efforts in known endemic regions. Enhanced surveillance data could then be used to inform models and improve and update predictions and test and monitor interventions.

Owing to the dearth of available long term vector data needed to identify population trends (Rund *et al.*, 2019), several methods of vector surveillance have been developed that are less time-intensive and involve citizen scientists that do not require expertise. For example, citizen science projects that either involve visual surveys of breeding habitats (Palmer *et al.*, 2017; Low *et al.*, 2021; Pataki *et al.*, 2021; Sousa *et al.*, 2022) or acoustic surveillance (Mukundarajan *et al.*, 2017; Vasconcelos *et al.*, 2019; Sinka *et al.*, 2021) have the potential to vastly increase information on the spatiotemporal distribution of mosquito vectors and to evaluate the success of vector control measures. However, these data will be influenced by sampling bias (Palmer *et al.*, 2017) and biases caused by changes in the algorithms behind data collection platforms or the behaviour of the people interacting with the platforms (UN Global Pulse, 2012) which must be addressed. Furthermore, relatively low engagement reported for citizen

science projects in the Global South (Rathnayake, Joshi and Cerratto-Pargman, 2020) may mean these data also suffer from significant spatial biases.

Future JE research would benefit from targeted serosurveillance data to capture subclinical cases and reduce data biases associated with the effects of test cross-reactivity, variations in healthcare diagnostics and differences in reporting effort. These data would help address the poor baseline knowledge of current JE distribution and burden which is required to project and mitigate future changes in risk (Campbell-Lendrum *et al.*, 2015). Alternative surveillance data collection methods via the use of smartphones, wireless connectivity, and cloud-based technologies also have great potential to augment the amount, detail and type of disease data (Mtema *et al.*, 2016; Carrillo *et al.*, 2021; Pley *et al.*, 2021). However, these data will be biased towards populations that are able to access the technology (WHO, 2011) and may not be suitable for diseases without characteristic case definitions (Pley *et al.*, 2021) such as JE. Underreporting of JE cases also occurs due to difficulties in diagnosis (Vannice *et al.*, 2021) and so improved access to diagnostics and laboratory testing is needed to increase the quality and amount of surveillance data, especially in remote areas. Furthermore, there is a clear need to develop systematic surveillance programmes to better characterise JEV reservoir hosts (Lord, Gurley and Pulliam, 2015) and to understand seasonal and spatial dynamics in JE seroprevalence in these groups.

Although the results of my thesis highlight the importance of environmental factors on MBD risk, the observational datasets and correlative analytic methods used do not enable the identification of underlying causal mechanisms (Hernán, 2018; Kraemer, Reiner and Bhatt, 2019). This limits the generalisability of these ecological associations across time and space (Washburne *et al.*, 2019) and hinders the ability of models to investigate the effects of interventions, as has been performed for other VBDs (White *et al.*, 2017). Furthermore, there are likely to be unmeasured variables that have not been accounted for in the models that are also influencing risk. For

example, when considering the effect of land-use on JE risk, unmeasured abiotic (e.g., agrichemical use, method or irrigation) (Kibuthu *et al.*, 2016) and biotic factors (e.g., competition and predation) (Ohba, Matsuo and Takagi, 2013; Elphick, 2015; Lounibos and Juliano, 2018) may be influencing vector and host populations that are not accounted for in models. Indeed, a recent study revealed the importance of biotic interactions in shaping MBD dynamics by showing that vector predators can limit disease transmission via their effects on vector survival and size and by modifying vector oviposition behaviour (Russell *et al.*, 2022). Another study demonstrated the effect of competition in determining the geographic distribution of *Aedes* mosquitoes (Lounibos and Juliano, 2018), a factor that is often not considered when predicting the potential geographic distribution of these vectors (Kraemer *et al.*, 2015; Ryan *et al.*, 2019). Moreover, the influence of land-use practices on reservoir host ecology (Gibb *et al.*, 2020a) and the potential for hosts to disperse pathogens long distances (Peterson, 2008; Duggal *et al.*, 2019) are not well understood. Overall, further empirical research investigating underlying ecological processes that influence MBD risk is imperative to improve understanding and parameterisation of models (Lounibos and Juliano, 2018; Gibb *et al.*, 2020b).

Another significant limitation in my thesis related to insufficient understanding of the socioeconomic factors that drive exposure (Monroe *et al.*, 2020) and vulnerabilities to MBDs (Bardosh *et al.*, 2017) and how these aspects of MBD risk may be influenced by environmental conditions (Baeza *et al.*, 2017). Socioeconomic factors influence exposure to disease via their influence on population distribution, migration, and landscape use at various scales (Li *et al.*, 2019). Studies that include human demography and behaviour in MBD risk models are needed to further understand disease exposure and therefore target people at risk and raise public awareness. A recent study explored the projected *Aedes*-borne virus transmission risk by demographic group (e.g., age-sex-race/ethnicity cohorts) in the USA under different combinations of climate and socioeconomic change (Rohat *et al.*, 2020). The study found that projected disease exposure changes were mainly driven by changes in the population of vulnerable demographic groups. Future studies

on JE would benefit from including demographic data when predicting current and future disease impacts.

Lack of knowledge on the impact of global change drivers is further compounded by poor understanding of the scale at which these processes influence MBD risk and how different scales should be incorporated into risk models (Caminade *et al.*, 2014; Parham *et al.*, 2015; Booth, 2018). Despite the identification of causal relationships being the ultimate goal when understanding drivers of disease emergence (Kraemer, Reiner and Bhatt, 2019), the complexity, scale, and natural variability of the systems involved mean that this is likely to be impractical for MBDs (Plowright *et al.*, 2008). Instead, amassing sufficient evidence to implicate drivers of MBD risk to inform predictions and mitigation efforts is a more realistic and achievable objective.

6.6   Future directions and challenges

The classification of ardeid birds and pigs as reservoir hosts of JEV has its origins in the first investigations of JEV transmission ecology that were conducted in the 1950s in Japan (Scherer, Buescher and McClure, 1959; Buescher et al., 1959; Scherer *et al.*, 1959; Scherer and Buescher, 1959). The justification for focusing on these hosts was that their reproductive rate enabled them to have a high enough population turnover to enable the continuous supply of susceptible individuals needed for annual epidemics. Ardeid birds were selected as a wildlife study group because their size meant they were relatively easy to catch and large enough to enable repeated blood sampling, rather than imply that other wild birds were not potential hosts (Scherer and Buescher, 1959). Both pigs and ardeid birds are likely to be important JEV reservoir hosts due to the high level of viraemia they produce which is sufficient to infect mosquitoes. However, it is important to reconsider the transmission cycle for other JE endemic regions that might differ from that first described in Japan (Lord, Gurley and Pulliam, 2015). In particular, the role of domestic birds such as chickens and ducks remains unknown

despite evidence that they can produce high levels of JEV viraemia (Dhanda *et al.*, 1977; Cleton *et al.*, 2014; Kalaiyarasu *et al.*, 2016). Although I identified pig populations as important drivers of JE risk in northeast India (Chapter 4), knowledge on the relative contribution of pigs to JEV transmission compared to other hosts and how this may vary in space and time is deficient.

To address these knowledge gaps requires veterinary surveillance of wildlife and domestic animals within JE endemic areas. Targeted serological surveillance of wildlife and domestic animals will help determine the absence or geographic and temporal distributions in prevalence of JEV in different populations and therefore, the likelihood of their ability to act as reservoir hosts. Simultaneously, scanning surveillance of pigs could be undertaken at slaughter to assess the geographic and seasonal variation in their ability to transmit JEV and to understand their relative importance to JE transmission ecology. This is particularly important given their recently discovered ability to transmit JEV directly between pigs without a vector (Ricklin et al., 2016). Furthermore, mobile phone syndromic surveillance programmes could be employed to detect potential JE outbreaks in domestic animal populations in rural communities as has been performed for other zoonotic flaviviruses (Thumbi *et al.*, 2019). In addition, the development of the Global Virome in One Network (VIRION) (Carlson *et al.*, 2022), an open access database of vertebrate-virus species interactions, makes identifying potential JEV hosts easier. Defining the breadth of potential JEV host species and quantifying their relative contributions to JE risk, would help to characterise geographical and seasonal variations in host seroprevalence across Asia and the West Pacific, and how these may vary with important JE drivers identified in this thesis (i.e., climate, agricultural land cover, poverty). This knowledge would improve assessments of the ability for JEV to spread to new geographic regions (Mackenzie, Gubler and Petersen, 2004; van den Hurk, Ritchie and Mackenzie, 2009; Lord, 2021) and potential impact of global change processes such as climate and land-use change on disease risk (Gibb *et al.*, 2018; Gibb *et al.*, 2020b).

As seen with the recent emergence of JE in Australia (Commonwealth of Australia, 2022), JE epidemics can often occur without warning and overwhelm public health services (Kulkarni *et al.*, 2018). Therefore, the development of a short-term early warning system that combines seasonal environmental forecasts with surveillance data would be beneficial to help prepare mitigation efforts (e.g., targeting of vaccination effort, advance warning of high risk periods), and improve JE diagnosis and treatment outcomes (e.g., increased clinical suspicion during high risk periods) (Hussain-Alkhateeb *et al.*, 2021). The high out-of-sample predictive ability for the temporal model of JE incidence in Chapter 4 suggests that short-term forecasting of JE incidence in endemic areas to inform vaccination programmes may be possible with this model. However, the model requires further development and parametrisation with additional data reported since 2019 to accurately determine its potential as a tool for public health decision support (Ballester *et al.*, 2016). Host seroprevalence data and vector abundance predictions could also be explored as possible predictors in the model. Indeed, there is scope for developing the vector abundance model from Chapter 3 into a forecasting model of seasonal vector abundance which could in turn inform a JE outbreak early warning system.

Despite the increasing importance of early warning systems to disease outbreak prediction and control, there is relatively little data on their effectiveness or the feasibility of their integration into existing surveillance programmes (Hussain-Alkhateeb *et al.*, 2021). Therefore, it is imperative that the development of an early warning system for JE involves stakeholder perspectives to ensure its utility and effectiveness in controlling disease outbreaks. To operationalise and sustain an early warning tool for JE would require models to be developed via a process of co-production with stakeholders in which different forms of knowledge are integrated into decision-making (Purse *et al.*, 2020). Stakeholders would be selected due to their key roles in the understanding and management of JE across different sectors and geographic scales. These may include policymakers and actors from public health, veterinary and agricultural sectors at the scale of national decision-makers down to village communities. This process of co-production

would enable models to be parameterised with data and knowledge from the field and for the spatial grain of the models to be tailored to the scale of intervention and ecosystem use (Leach and Scoones, 2013). In addition, interpretation and validation of model outputs by stakeholders would likely increase the uptake of the early warning system for targeting surveillance and interventions. Furthermore, the early warning system would have to be simple, practical, and sustainable to guarantee that it would be useful to local decision makers over the long-term.

My findings throughout this thesis have revealed MBD as a nexus issue between the environment and human health, thus validating the application of the Planetary Health approach (Pongsiri *et al.*, 2017) in the understanding and mitigation of these diseases in the era of dramatic global change. In the context of JE, the importance of agricultural land management practices highlighted in this work has implications for the projected expansion of irrigated agricultural land (Keiser et al., 2005b; Alexandratos and Bruinsma, 2012) and intensification of rice production (Song *et al.*, 2018) needed to improve food security. Therefore, if we want to significantly expand rice paddy cultivation and at the same time work towards reducing MBD risk, we will need to develop ways to reconcile these two goals.

Modelling approaches such as those applied in Chapter 5, could support this work by evaluating the consequences of proposed future land-use changes for MBD risk to identify trade-offs across land-use, climate, food security and human health. Furthermore, such counterfactual analyses whereby different scenarios are evaluated, could be conducted for multiple MBDs to enhance policy decisions that benefit both public health and environmental sectors. Examples of potential counterfactual questions could include: '*If we alter different characteristics of rice cultivation (e.g., type of rice grown, size of irrigation schemes, and distance of rice-growing communities from their fields) how many JE infections could be averted*?' Or '*If we increase the availability of natural wetlands, do we reduce JE risk due to decreased contact between vectors and ardeid birds?*' In addition, which agricultural practices are best for ensuring food security and reducing MBD risk, while

accounting for the influence of predicted climate and socioeconomic change? These counterfactuals can be used to structure and manage agricultural landscapes to ensure food security, preserve ecosystem health and regulate vector and reservoir host populations across projected scenarios of global change.

6.7   Conclusions

Much of recent human development has come at the expense of the natural environment, leading to ecosystem degradation, biodiversity loss and increased exposure and vulnerability to infectious diseases such as MBDs. This has been emphasised by the SARS CoV2 pandemic which has increased global awareness of the need to expand and strengthen our understanding of the links between nature and human health (FAO *et al.*, 2021). Traditionally, public health interventions have been aimed at reducing the exposure and vulnerability of populations to disease (Gibb *et al.*, 2020b) by focusing on disease control and vaccination efforts. However, with future global change, broader perspectives that consider the combined influence of different socio-ecological pressures driving disease risk will be increasingly important to support both short-term public health policy and long-term decisions for adaptation to different scenarios. In this thesis, I have illustrated the importance of environmental and socioeconomic change to MBD risk, underlining the need to integrate socio-ecological perspectives into not only public health but environmental planning decisions, to help understand and predict disease risk and therefore build wider health resilience to global change.

Bibliography

Abajobir, A.A. et al. (2017) 'Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016', The Lancet, 390(10100), pp. 1151–1210. doi:10.1016/S0140-6736(17)32152-9.

Abatzoglou, J.T. et al. (2018) 'TerraClimate, a high-resolution global dataset of monthly climate and climatic water balance from 1958–2015', Scientific Data, 5(1), pp. 1–12. doi:10.1038/sdata.2017.191.

Abeysinghe, N. and Neuzil, K. (2018) Japanese encephalitis—no longer neglected: A model for other new vaccines, PATH. Available at: https://www.path.org/articles/japanese-encephalitis-no-longer-neglected-a-model-for-other-new-vaccines/ (Accessed: 3 March 2022).

Acharya, R. and Porwal, A. (2020) 'A vulnerability index for the management of and response to the COVID-19 epidemic in India: an ecological study', The Lancet Global Health, 8(9), pp. e1142–e1151. doi:10.1016/S2214-109X(20)30300-4.

Aerts, C. et al. (2020) 'Understanding the role of disease knowledge and risk perception in shaping preventive behavior for selected vector-borne diseases in Guyana', PLOS Neglected Tropical Diseases, 14(4), p. e0008149.

Aguirre, A. et al. (2019) 'Transdisciplinary and social-ecological health frameworks—Novel approaches to emerging parasitic and vector-borne diseases', Parasite Epidemiology and Control, 4, p. e00084. doi:10.1016/j.parepi.2019.e00084.

Ahmad, A. et al. (2015) 'Japanese Encephalitis in Assam, India: Need to Increase Healthcare Workers' Understanding to Improve Health Care', PLOS ONE, 10(8), p. e0135767. doi:10.1371/journal.pone.0135767.

Ahmad, A. et al. (2017) 'Community knowledge and attitude towards Japanese encephalitis in Darrang, India: a cross-sectional study', Annals of Tropical Medicine and Public Health, 10(2), pp. 377–377.

Albert, C.H. et al. (2017) 'Applying network theory to prioritize multispecies habitat networks that are robust to climate and land-use change', Conservation Biology: The Journal of the Society for Conservation Biology, 31(6), pp. 1383–1396. doi:10.1111/cobi.12943.

Alexandratos, N. and Bruinsma, J. (2012) World agriculture towards 2030/2050: the 2012 revision. ESA Working Paper No. 12-03. Rome: FAO, p. 160.

Ali, S. et al. (2017) 'Environmental and Social Change Drive the Explosive Emergence of Zika Virus in the Americas', PLoS Neglected Tropical Diseases, 11(2), pp. 1–16. doi:10.1371/journal.pntd.0005135.

Alkire, S., Oldiges, C. and Kanagaratnam, V. (2018) Multidimensional poverty reduction in India 2005/6–2015/16: Still a long way to go but the poorest are catching up. 54a OPHI Research in Progress. University of Oxford: Oxford Poverty and Human Development Initiative (OPHI). Available at: https://www.ophi.org.uk/wp-content/uploads/OPHIRP54a_vs2.pdf (Accessed: 15 November 2021).

Alkishe, A.A., Peterson, A.T. and Samy, A.M. (2017) 'Climate change influences on the potential geographic distribution of the disease vector tick Ixodes ricinus', PLoS ONE, 12(12). doi.org/10.1371/journal.pone.0189092.

Allen, T. et al. (2017) 'Global hotspots and correlates of emerging zoonotic diseases', Nature Communications, 8(1), pp. 1–10. doi:10.1038/s41467-017-00923-8.

Alley, W.M. (1984) 'The Palmer Drought Severity Index: Limitations and Assumptions', Journal of Applied Meteorology and Climatology, 23(7), pp. 1100–1109. doi:10.1175/1520-0450(1984)023<1100:TPDSIL>2.0.CO;2.

Alsan, M.M. et al. (2012) 'Poverty, global health and infectious disease: lessons from Haiti and Rwanda', infect Dis Clin North Am, 25(3), pp. 611–622. doi:10.1016/j.idc.2011.05.004.Poverty.

Amaku, M. et al. (2016) 'Magnitude and frequency variations of vector-borne infection outbreaks using the Ross–Macdonald model: explaining and predicting outbreaks of dengue fever', Epidemiology & Infection, 144(16), pp. 3435–3450. doi:10.1017/S0950268816001448.

Amoah, B., Diggle, P.J. and Giorgi, E. (2020) 'A geostatistical framework for combining spatially referenced disease prevalence data from multiple diagnostics', Biometrics, 76(1), pp. 158–170. doi:10.1111/biom.13142.

Anderson, E.P. et al. (2018) 'Fragmentation of Andes-to-Amazon connectivity by hydropower dams', Science Advances, 4, pp. 1–8. doi:10.1126/sciadv.aao1642.

Anyamba A., Chretien JP., Small J., Tucker CJ., F.P. (2009) 'Prediction of a Rift Valley fever outbreak', Procedure for National Academic Science, 106(3), pp. 955–959.

Arai, S. et al. (2008) 'Japanese encephalitis: Surveillance and elimination effort in Japan from 1982 to 2004', Japanese Journal of Infectious Diseases, 61(5), pp. 333–338.

Asare, E.O., Tompkins, A.M. and Bomblies, A. (2016) 'A Regional Model for Malaria Vector Developmental Habitats Evaluated Using Explicit, Pond-Resolving Surface Hydrology Simulations', PLOS ONE, 11(3), p. e0150626.

Athni, T.S. et al. (2021) 'The influence of vector-borne disease on human history: socio-ecological mechanisms', Ecology Letters, 24(4), pp. 829–846. doi:10.1111/ele.13675.

Badari, V. (1985) 'A socio-economic study of Japanese encephalitis in Kolar district of Karnataka during 1981', Health and Population—Perspectives & Issues, 8, pp. 29–49.

Baeza, A. et al. (2011) 'Climate forcing and desert malaria: the effect of irrigation', Malaria Journal, 10, p. 190. doi:10.1186/1475-2875-10-190.

Baeza, A. et al. (2017) 'The rise and fall of malaria under land-use change in frontier regions', Nature Ecology & Evolution, 1(5), p. 0108. doi:10.1038/s41559-017-0108.

Bagcchi, S. (2014) 'India intensifies Japanese encephalitis immunisation', The Lancet Infectious Diseases, 14(8), p. 682. doi:10.1016/S1473-3099(14)70862-X.

Bai, Y. et al. (2014) 'Regional Impact of Climate on Japanese Encephalitis in Areas Located near the Three Gorges Dam', PLoS ONE. Edited by M. Kirk, 9(1), p. e84326. doi:10.1371/journal.pone.0084326.

Baig, S. et al. (2013) 'Japanese Encephalitis Surveillance and Immunization — Asia and the Western Pacific, 2012', MMWR. Morbidity and Mortality Weekly Report, 62(33), pp. 658–662.

Baker, R.E. et al. (2021) 'Infectious disease in an era of global change', Nature Reviews Microbiology, pp. 1–13. doi:10.1038/s41579-021-00639-z.

Balakrishnan, A. et al. (2017) 'Seroprevalence of Japanese encephalitis virus & West Nile virus in Alappuzha district, Kerala', The Indian Journal of Medical Research, 146(Suppl 1), pp. S70–S76. doi.org/10.4103/ijmr.IJMR_1638_15.

Balasubramanian, R. and Nikhil, T.L. (2015) 'Effects of rainfall and salinity increase on prevalence of vector mosquitoes in coastal areas of Alappuzha district, Kerala', Journal of Environmental Biology, 36(6), pp. 1325–1328.

Ballester, J. et al. (2016) 'Seasonal forecasting and health impact models: challenges and opportunities', Annals of the New York Academy of Sciences, 1382(1), pp. 8–20. doi:10.1111/nyas.13129.

Bandyopadhyay, B. et al. (2013) 'Incidence of Japanese encephalitis among acute encephalitis syndrome cases in West Bengal, India', Biomed Res Int, 2013, p. 896749. doi:10.1155/2013/896749.

Barbazan, P. et al. (2010) 'Modelling the effect of temperature on transmission of dengue', Medical and Veterinary Entomology, 24(1), pp. 66–73. doi:10.1111/j.1365-2915.2009.00848.x.

Bardosh, K.L. et al. (2017) 'Addressing vulnerability, building resilience: community-based adaptation to vector-borne diseases in the context of global change', Infectious Diseases of Poverty, 6(1), p. 166. doi:10.1186/s40249-017-0375-2.

Barnagaud, J.Y. et al. (2012) 'Relating Habitat and Climatic Niches in Birds', PLoS ONE, 7(3), p. e32819. doi:10.1371/journal.pone.0032819.

Baruah, A. et al. (2018) 'Mosquito abundance and pig seropositivity as a correlate of Japanese encephalitis in human population in Assam, India', Journal of Vector Borne Diseases, 55(4), p. 291. doi:10.4103/0972-9062.256564.

Bashar, K. et al. (2016) 'Species composition and habitat characterization of mosquito (Diptera: Culicidae) larvae in semi-urban areas of Dhaka, Bangladesh', Pathogens and Global Health, 110(2), pp. 48–61. doi:10.1080/20477724.2016.1179862.

Baston, D. (2021) exactextractr: Fast Extraction from Raster Datasets using Polygons. ISciences, LLC. Available at: https://CRAN.R-project.org/package=exactextractr (Accessed: 13 October 2021).

Bates, M. (1949) The natural history of mosquitoes. New York: Harper and Row Publishers.

Baylis, M. et al. (2016) 'Emergence or improved detection of Japanese encephalitis virus in the Himalayan highlands?', Transactions of The Royal Society of Tropical Medicine and Hygiene, 110(4), pp. 209–211. doi:10.1093/trstmh/trw012.

Beck, H.E. et al. (2018) 'Present and future Köppen-Geiger climate classification maps at 1-km resolution', Scientific Data, 5(1), pp. 1–12. doi:10.1038/sdata.2018.214.

Becker, N. et al. (2010) 'Biology of mosquitoes', in Mosquitoes and Their Control. 2nd edn. London: Springer-Verlag Berlin Heidelberg, pp. 9–24. doi:10.1007/978-3-540-92874-4.

Bedford, J. et al. (2019) 'A new twenty-first century science for effective epidemic response', Nature, 575(7781), pp. 130–136. doi:10.1038/s41586-019-1717-y.

Béguin, A. et al. (2011) 'The opposing effects of climate change and socio-economic development on the global distribution of malaria', Global Environmental Change, 21(4), pp. 1209–1214. doi:10.1016/j.gloenvcha.2011.06.001.

Bergquist, R., Stensgaard, A.S. and Rinaldi, L. (2018) 'Vector-borne diseases in a warmer world: Will they stay or will they go?', Geospatial Health, 13, p. 699. doi:10.4081/ejh.2013.e2.

Besag, J., York, J. and Mollié, A. (1991) 'Bayesian image restoration, with two applications in spatial statistics', Annals of the Institute of Statistical Mathematics, 43(1), pp. 1–20. doi:10.1007/BF00116466.

Bhatt, S. et al. (2013) 'The global distribution and burden of dengue', Nature, 496(7446), pp. 504–507.

Bhattacharyya, D.R. et al. (1994) 'Host feeding patterns of Culex vishnui sub group of mosquitoes in Dibrugarh district of Assam.', Journal of Communicable Diseases, 26(3), pp. 133–138.

Bi, P. et al. (2003) 'Climate variability and transmission of Japanese encephalitis in eastern China', Vector Borne and Zoonotic Diseases (Larchmont, N.Y.), 3(3), pp. 111–115. doi:10.1089/153036603768395807.

Bista, M.B. and Shrestha, J.M. (2005) 'Epidemiological situation of Japanese encephalitis in Nepal', Journal of Nepal Medical Association, 44.

Bloom, D.E., Canning, D. and Sevilla, J. (2004) 'The effect of health on economic growth: A production function approach', World Development, 32(1), pp. 1–13. doi:10.1016/j.worlddev.2003.07.002.

Bonds, M.H. et al. (2010) 'Poverty trap formed by the ecology of infectious diseases', Proceedings of the Royal Society B: Biological Sciences, 277(1685), pp. 1185–1192. doi:10.1098/rspb.2009.1778.

Booth, M. (2018) Climate Change and the Neglected Tropical Diseases. 1st edn, Advances in Parasitology. 1st edn. Elsevier Ltd. doi:10.1016/bs.apar.2018.02.001.

Borah, J. et al. (2013) 'Association of weather and anthropogenic factors for transmission of Japanese encephalitis in an endemic area of India', EcoHealth, 10(2), pp. 129–136. doi:10.1007/s10393-013-0849-z.

Bouzid, M. et al. (2014) 'Climate change and the emergence of vector-borne diseases in Europe: case study of dengue fever', BMC Public Health, 14(1), p. 781. doi:10.1186/1471-2458-14-781.

Bowles, S., Durlauf, S. and Hoff, K. (eds) (2006) Poverty Traps. Princeton: Princeton University Press.

Brady, O.J. et al. (2014) 'Global temperature constraints on Aedes aegypti and Ae . albopictus persistence and competence for dengue virus transmission', Parasites & Vectors, 7, p. 338.

Brier, G. (1950) 'Verification of forecasts expressed in terms of probability', Monthly Weather Review, 78, pp. 1–3.

Britch, S.C. et al. (2013) 'Rift Valley Fever Risk Map Model and Seroprevalence in Selected Wild Ungulates and Camels from Kenya', PLOS ONE, 8(6), p. e66626. doi:10.1371/journal.pone.0066626.

Brock, P.M. et al. (2016) 'Plasmodium knowlesi transmission: integrating quantitative approaches from epidemiology and ecology to understand malaria as a zoonosis', Parasitology, 143(4), pp. 389–400. doi:10.1017/S0031182015001821.

Brock, P.M. et al. (2019) 'Predictive analysis across spatial scales links zoonotic malaria to deforestation', Proceedings of the Royal Society B: Biological Sciences, 286(1894), p. 20182351. doi:10.1098/rspb.2018.2351.

Bron, G.M. et al. (2020) 'Context matters: Contrasting behavioral and residential risk factors for Lyme disease between high-incidence states in the Northeastern and Midwestern United

States', Ticks and Tick-borne Diseases, 11(6), p. 101515.
doi.org/10.1016/j.ttbdis.2020.101515.

Brouard, O. et al. (2011) 'Are Algae Relevant to the Detritus-Based Food Web in Tank-Bromeliads?', PLOS ONE, 6(5), p. e20129.

Brown, H.E. et al. (2015) 'Projection of Climate Change Influences on U.S. West Nile Virus Vectors', Earth Interactions, 19(18), pp. 1–18. doi:10.1175/EI-D-15-0008.1.

Brown, J.E. et al. (2011) 'Worldwide patterns of genetic differentiation imply multiple "domestications" of Aedes aegypti, a major vector of human diseases', Proceedings. Biological Sciences, 278(1717), pp. 2446–2454. doi:10.1098/rspb.2010.2469.

Buescher, E.L., et al. (1959) 'Ecologic Studies of Japanese Encephalitis Virus in Japan IV. Avian Infection', The American Society of Tropical Medicine and Hygiene, 8, pp. 678–688.

Buonsenso, D. et al. (2014) 'The re-emergence of dengue virus in non-endemic countries: a case series', BMC Research Notes, 7(1), p. 596. doi:10.1186/1756-0500-7-596.

Burkett-Cadena, N.D. and Vittor, A.Y. (2017) 'Deforestation and vector-borne disease: Forest conversion favors important mosquito vectors of human pathogens', Basic and Applied Ecology, 26, pp. 101–10. doi:10.1016/j.baae.2017.09.012.

Burthe, S.J. et al. (2021) 'Reviewing the ecological evidence base for management of emerging tropical zoonoses: Kyasanur Forest Disease in India as a case study', PLOS Neglected Tropical Diseases, 15(4), p. e0009243. doi:10.1371/journal.pntd.0009243.

Butterworth, M.K., Morin, C.W. and Comrie, A.C. (2017) 'An analysis of the potential impact of climate change on dengue transmission in the southeastern United States', Environmental Health Perspectives, 125(4), pp. 579–585. doi:10.1289/EHP218.

Caminade, C. et al. (2014) 'Impact of climate change on global malaria distribution', Proceedings of the National Academy of Sciences, 111(9), pp. 3286–3291. doi:10.1073/pnas.1302089111.

Caminade, C. et al. (2017) 'Global risk model for vector-borne transmission of Zika virus reveals the role of El Niño 2015', Proceedings of the National Academy of Sciences, 114(1), pp. 119–124. doi:10.1073/pnas.1614303114.

Campbell, G.L. et al. (2011) 'Estimated global incidence of Japanese encephalitis: a systematic review', Bulletin of the World Health Organization, 89(10), pp. 766–774, 774A-774E. doi:10.2471/BLT.10.085233.

Campbell, L.P. et al. (2015) 'Climate change influences on global distributions of dengue and chikungunya virus vectors', Philosophical Transactions of the Royal Society B: Biological Sciences, 370(1665), pp. 20140135–20140135. doi:10.1098/rstb.2014.0135.

Campbell-Lendrum, D. et al. (2015) 'Climate change and vector-borne diseases: what are the implications for public health research and policy?', Philosophical Transactions of the Royal Society of London, 370(20130552).

Cao, M. et al. (2010) 'Contextual risk factors for regional distribution of Japanese encephalitis in the People's Republic of China', Tropical medicine & international health: TM & IH, 15(8), pp. 918–923. doi:10.1111/j.1365-3156.2010.02563.x.

Capinha, C., Rocha, J. Sousa, C.A. (2014) 'Macroclimate Determines the Global Range Limit of Aedes aegypti', EcoHealth, 11, pp. 420–428.

Cardona, O.-D. et al. (2012) 'Determinants of Risk: Exposure and Vulnerability', in Field, C.B. et al. (eds) Managing the Risks of Extreme Events and Disasters to Advance Climate Change Adaptation: Special Report of the Intergovernmental Panel on Climate Change. Cambridge: Cambridge University Press, pp. 65–108. doi:10.1017/CBO9781139177245.005.

Cardoso-Leite, R. et al. (2014) 'Recent and future environmental suitability to dengue fever in Brazil using species distribution model', Transactions of The Royal Society of Tropical Medicine and Hygiene, 108(2), pp. 99–104. doi:10.1093/trstmh/trt115.

Carlson, C.J. (2020) 'embarcadero: Species distribution modelling with Bayesian additive regression trees in R', Methods in Ecology and Evolution [Preprint]. doi:10.1111/2041-210X.13389.

Carlson, C.J. (2021) embarcadero. Available at: https://github.com/cjcarlson/embarcadero (Accessed: 18 January 2022).

Carlson, C.J. et al. (2022) 'The Global Virome in One Network (VIRION): an Atlas of Vertebrate-Virus Associations', mBio, p. e0298521. doi:10.1128/mbio.02985-21.

Carlson, C.J., Dougherty, E.R. and Getz, W. (2016) 'An Ecological Assessment of the Pandemic Threat of Zika Virus', PLOS Neglected Tropical Diseases, 10(8), pp. 1–18. doi:10.1371/journal.pntd.0004968.

Carrillo, M.A. et al. (2021) 'The use of mobile phones for the prevention and control of arboviral diseases: a scoping review', BMC Public Health, 21, p. 110. doi:10.1186/s12889-020-10126-4.

Carrington, L.B. et al. (2013) 'Fluctuations at a Low Mean Temperature Accelerate Dengue Virus Transmission by Aedes aegypti', PLOS Neglected Tropical Diseases, 7(4), p. e2190.

CDC (2017) One Health: Zoonotic Diseases, Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/onehealth/basics/zoonotic-diseases.html (Accessed: 30 March 2020).

CDC (2020) Culex Mosquito Life Cycle, Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/mosquitoes/about/life-cycles/culex.html (Accessed: 24 February 2022).

Chareonviriyaphap, T. et al. (2003) 'Larval habitats and distribution patterns of Aedes aegypti (Linnaeus) and Aedes albopictus (Skuse), in Thailand', The Southeast Asian Journal of Tropical Medicine and Public Health, 34(3), pp. 529–535.

Chase, J.M. and Knight, T.M. (2003) 'Drought-induced mosquito outbreaks in wetlands', Ecology Letters, 6(11), pp. 1017–1024. doi:10.1046/j.1461-0248.2003.00533.x.

Chastonay, A.H.M. and Chastonay, O.J. (2022) 'Housing Risk Factors of Four Tropical Neglected Diseases: A Brief Review of the Recent Literature', Tropical Medicine and Infectious Disease, 7(7), p. 143. doi.org/10.3390/tropicalmed7070143.

Chatterjee, S. et al. (2004) 'Serosurveillance for Japanese encephalitis in children in several districts of West Bengal, India', Acta Paediatrica, 93(3), pp. 390–393. doi:10.1111/j.1651-2227.2004.tb02967.x.

Chaves, L.F. et al. (2012) 'Nonlinear impacts of climatic variability on the density-dependent regulation of an insect vector of disease', Global Change Biology, 18(2), pp. 457–468. doi:10.1111/j.1365-2486.2011.02522.x.

Chaves, L.S.M. et al. (2018) 'Abundance of impacted forest patches less than 5 km2is a key driver of the incidence of malaria in Amazonian Brazil', Scientific Reports, 8(1), pp. 1–11. doi:10.1038/s41598-018-25344-5.

Chaves, L.S.M. et al. (2020) 'Global consumption and international trade in deforestation-associated commodities could influence malaria risk', Nature Communications, 11, p. 1258. doi:10.1038/s41467-020-14954-1.

Chen, M. et al. (2020) 'Global land use for 2015–2100 at 0.05° resolution under diverse socioeconomic and climate scenarios', Scientific Data, 7(1), p. 320. doi:10.1038/s41597-020-00669-x.

Chen, M.J. et al. (2012) 'Effects of Extreme Precipitation to the Distribution of Infectious Diseases in Taiwan, 1994–2008', PLOS ONE, 7(6), p. e34651. doi:10.1371/journal.pone.0034651.

Childs, M.L. et al. (2019) 'Mosquito and primate ecology predict human risk of yellow fever virus spillover in Brazil', Philosophical Transactions of the Royal Society B: Biological Sciences, 374(1782), p. 20180335. doi:10.1098/rstb.2018.0335.

Chowdhury, P. et al. (2014) 'Characterization of West Nile virus (WNV) isolates from Assam, India: Insights into the circulating WNV in northeastern India', Comparative Immunology, Microbiology and Infectious Diseases, 37(1), pp. 39–47. doi:10.1016/j.cimid.2013.10.006.

Christiansen-Jucht, C. et al. (2014) 'Temperature during larval development and adult maintenance influences the survival of Anopheles gambiae s.s.', Parasites {&} Vectors, 7(1), p. 489. doi:10.1186/s13071-014-0489-3.

Ciota, A.T. et al. (2014) 'The effect of temperature on life history traits of Culex mosquitoes', J Med Entomol, 51. doi:10.1603/ME13003.

Civitello, D.J. et al. (2015) 'Biodiversity inhibits parasites: Broad evidence for the dilution effect', Proceedings of the National Academy of Sciences, 112(28), pp. 8667–8671. doi:10.1073/pnas.1506279112.

Cleton, N.B. et al. (2014) 'Age-related susceptibility to Japanese encephalitis virus in domestic ducklings and chicks', The American Journal of Tropical Medicine and Hygiene, 90(2), pp. 242–246. doi:10.4269/ajtmh.13-0161.

Cliff, A. and Ord, J.K. (1973) Spatial Autocorrelation. London: Pion.

Colón-González, F.J. et al. (2018) 'Limiting global-mean temperature increase to 1.5–2 °C could reduce the incidence and spatial spread of dengue fever in Latin America', Proceedings of the National Academy of Sciences, 115(24), pp. 6243–6248. doi:10.1073/pnas.1718945115.

Colón-González, F.J. et al. (2021a) 'Projecting the risk of mosquito-borne diseases in a warmer and more populated world: a multi-model, multi-scenario intercomparison modelling study', The Lancet Planetary Health, 5(7), pp. e404–e414. doi:10.1016/S2542-5196(21)00132-7.

Colón-González, F.J. et al. (2021b) 'Probabilistic seasonal dengue forecasting in Vietnam: A modelling study using superensembles', PLoS Medicine, 18(3), p. e1003542. doi:10.1371/journal.pmed.1003542.

Commonwealth of Australia (2022) Japanese encephalitis, National pest & disease outbreaks. Available at: https://www.outbreak.gov.au/current-responses-to-outbreaks/japanese-encephalitis (Accessed: 10 March 2022).

Cunze, S., Koch, L.K., et al. (2016) 'Aedes albopictus and Aedes japonicus - two invasive mosquito species with different temperature niches in Europe', Parasites & Vectors, 9(1), p. 573. doi:10.1186/s13071-016-1853-2.

Czech, H.A. and Parsons, K.C. (2002) 'Agricultural Wetlands and Waterbirds: A Review', Waterbirds: The International Journal of Waterbird Biology, 25, pp. 56–65.

Dahlgren, F.S. et al. (2016) 'Expanding Range of Amblyomma americanum and Simultaneous Changes in the Epidemiology of Spotted Fever Group Rickettsiosis in the United States', American Journal of Tropical Medicine and Hygiene. 2015/10/26 edn, 94(1), pp. 35–42. doi:10.4269/ajtmh.15-0580.

Das Bhowmik, R., Suchetana, B. and Lu, M. (2019) 'Shower effect of a rainfall onset on the heat accumulated during a preceding dry spell', Scientific Reports, 9. doi:10.1038/s41598-019-43437-7.

Das, B.P., Lal, S. and Saxena, V.K. (2004) 'Outdoor resting preference of Culex tritaeniorhynchus, the vector of Japanese encephalitis in Warangal and Karim Nagar districts, Andhra Pradesh', Journal of Vector Borne Diseases, 41(1–2), pp. 32–36.

Das, D. et al. (2016) 'A change in epidemiology of Japanese encephalitis in Bankura and Purulia districts of West Bengal', Journal of Evolution of Medical and Dental Sciences, 5(78), pp. 5796–5799. doi:10.14260/jemds/2016/1308.

Dash, A.P. et al. (2001) 'Retrospective analysis of epidemiological investigation of Japanese encephalitis outbreak occurred in Rourkela, Orissa, India', Southeast Asian Journal of Tropical Medicine and Public Health, 32(1), pp. 137–139.

Datey, A. et al. (2020) 'Molecular epidemiology of Japanese encephalitis virus in pig population of Odisha, Assam and Manipur states of India', Infection, Genetics and Evolution, 83, p. 104325. doi:10.1016/j.meegid.2020.104325.

Davis, J.K. et al. (2017) 'Integrating Environmental Monitoring and Mosquito Surveillance to Predict Vector-borne Disease: Prospective Forecasts of a West Nile Virus Outbreak', PLoS currents, 9, p. ecurrents.outbreaks.90e80717c4e67e1a830f17feeaaf85de. doi:10.1371/currents.outbreaks.90e80717c4e67e1a830f17feeaaf85de.

Day, J.F. and Shaman, J. (2008) 'Using hydrologic conditions to forecast the risk of focal and epidemic arboviral transmission in peninsular Florida.', Journal of medical entomology, 45(3), pp. 458–465.

DeCarlo, C. et al. (2017) 'Potential Reservoir and Associated Factors for West Nile Virus in Three Distinct Climatological Zones', Vector Borne and Zoonotic Diseases (Larchmont, N.Y.), 17(10), pp. 709–713. doi:10.1089/vbz.2016.2098.

Desingu, P.A. et al. (2016) 'Pathogenic and Genotypic Characterization of a Japanese Encephalitis Virus Isolate Associated with Reproductive Failure in an Indian Pig Herd', PLOS ONE, 11(2), p. e0147611. doi:10.1371/journal.pone.0147611.

Despommier, D., Ellis, B.R. and Wilcox, B.A. (2006) 'The role of ecotones in emerging infectious diseases', EcoHealth, 3(4), pp. 281–289. doi:10.1007/s10393-006-0063-3.

Dev, V., Sharma, V. and Barman, K. (2015) 'Mosquito-borne diseases in Assam, north-east India: current status and key challenges', WHO South-East Asia Journal of Public Health, 4(1), p. 20. doi:10.4103/2224-3151.206616.

Devi, N.P. and Jauhari, R.K. (2004) 'Altitudinal distribution of mosquitoes in mountainous area of Garhwal region : Part–I', Journal of Vector Borne Diseases, 41, pp. 17–26.

Deville, P. et al. (2014) 'Dynamic population mapping using mobile phone data', PNAS, 111(45), pp. 15888–15893. doi:10.1073/pnas.1408439111.

Dhanda, V. et al. (1977) 'Experimental viraemia and transmission of Japanese encephalitis virus by mosquitoes in domestic ducks.', The Indian Journal of Medical Research, 66(6), pp. 881–888.

Dhiman, R.C. (2014) 'Emerging Vector-Borne Zoonoses: Eco-Epidemiology and Public Health Implications in India', Frontiers in Public Health, 2, p. 168. doi:10.3389/fpubh.2014.00168.

Dhiman, S. et al. (2013) 'DDT & deltamethrin resistance status of known Japanese encephalitis vectors in Assam, India', The Indian Journal of Medical Research, 138(6), pp. 988–994.

Didan, K. (2015) 'MOD13C2 MODIS/Terra Vegetation Indices Monthly L3 Global 0.05Deg CMG V006'. NASA EOSDIS Land Processes DAAC. doi:10.5067/MODIS/MOD13C2.006.

Diuk-Wasser, M.A., VanAcker, M.C. and Fernandez, M.P. (2021) 'Impact of Land Use Changes and Habitat Fragmentation on the Eco-epidemiology of Tick-Borne Diseases', Journal of Medical Entomology, 58(4), pp. 1546–1564. doi.org/10.1093/jme/tjaa209.

Dobson, A. (2009) 'Climate variability, global change, immunity, and the dynamics of infectious diseases', Ecology, 90(4), pp. 920–927. doi:10.1890/08-0736.1.

Drake, J.M. and Beier, J.C. (2014) 'Ecological niche and potential distribution of Anopheles arabiensis in Africa in 2050', Malaria Journal, 13(1), p. 213. doi:10.1186/1475-2875-13-213.

Duggal, N.K. et al. (2019) 'On the Fly: Interactions Between Birds, Mosquitoes, and Environment That Have Molded West Nile Virus Genomic Structure Over Two Decades', Journal of Medical Entomology, 56(6), pp. 1467–1474. doi:10.1093/jme/tjz112.

Dutta, P. et al. (2011) 'The Effect of Insecticide-Treated Mosquito Nets (ITMNs) on Japanese Encephalitis Virus Seroconversion in Pigs and Humans', The American Journal of Tropical Medicine and Hygiene, 84(3), pp. 466–472. doi.org/10.4269/ajtmh.2011.10-0270.

Dutta, R. (2014) 'Climate change and its impact on tea in Northeast India', Journal of Water and Climate Change, 5(4), pp. 625–632. doi:10.2166/wcc.2014.143.

EAC (2021) Growing back better: putting nature and net zero at the heart of the economic recovery. House of Commons Environmental Audit Committee. Available at: https://committees.parliament.uk/publications/4712/documents/47430/default/.

Ebi, K.L. and Nealon, J. (2016) 'Dengue in a changing climate', Environmental Research, 151, pp. 115–123. doi:10.1016/j.envres.2016.07.026.

eBird (2021) eBird Basic Dataset. Version: EBD_relMar-2021. Ithaca, New York: Cornell Lab of Ornithology.

Elith, J., Burgman, M.A. and Regan, H.M. (2002) 'Mapping epistemic uncertainties and vague concepts in predictions of species distribution', Ecological Modelling, 157(2), pp. 313–329. doi:10.1016/S0304-3800(02)00202-8.

Elith, J. and Leathwick, J.R. (2009) 'Species Distribution Models: Ecological Explanation and Prediction Across Space and Time', Annual Review of Ecology, Evolution, and Systematics, 40(1), pp. 677–697. doi:10.1146/annurev.ecolsys.110308.120159.

Elphick, C.S. et al. (2010) 'The Future for Research on Waterbirds in Rice Fields', Waterbirds, 33(sp1), pp. 231–243. doi:10.1675/063.033.s117.

Elphick, C.S. (2015) 'A history of ecological studies of birds in rice fields', Journal of Ornithology, 156(1), pp. 239–245. doi:10.1007/s10336-015-1194-5.

Endo, N. and Eltahir, E.A.B. (2020) 'Increased risk of malaria transmission with warming temperature in the Ethiopian Highlands', Environmental Research Letters, 15(5), p. 054006. doi:10.1088/1748-9326/ab7520.

Engebretsen, S. et al. (2020) 'Time-aggregated mobile phone mobility data are sufficient for modelling influenza spread: the case of Bangladesh', Journal of The Royal Society Interface, 17(167), p. 20190809. doi.org/10.1098/rsif.2019.0809.

Equihua, M. et al. (2017) 'Establishment of Aedes aegypti (L.) in mountainous regions in Mexico: Increasing number of population at risk of mosquito-borne disease and future climate conditions', Acta Tropica, 166, pp. 316–327. doi:10.1016/j.actatropica.2016.11.014.

Erlanger, T.E. et al. (2005) 'Effect of water resource development and management on lymphatic filariasis, and estimates of populations at risk.', The American journal of tropical medicine and hygiene, 73(3), pp. 523–533. doi:10.4269/ajtmh.2005.73.523.

Erlanger, T.E. et al. (2009) 'Past, present, and future of Japanese encephalitis', Emerging Infectious Diseases, 15(1), pp. 1–7. doi:10.3201/eid1501.080311.

ECDC and EFSA (2018) The importance of vector abundance and seasonality - Results from an expert consultation. Stockholm and Parma: European Centre for Disease Prevention and Control and European Food Safety Authority.

European Space Agency (2022) ESA WorldCover 2021. Available at: https://worldcover2021.esa.int/ (Accessed: 19 January 2023)..

Ewing, D.A. et al. (2016) 'Modelling the effect of temperature on the seasonal population dynamics of temperate mosquitoes', Journal of Theoretical Biology, 400, pp. 65–79. doi:10.1016/j.jtbi.2016.04.008.

Ewing, D.A. et al. (2019) 'Uncovering mechanisms behind mosquito seasonality by integrating mathematical models and daily empirical population data: Culex pipiens in the UK', Parasites & Vectors, 12(1), p. 74. doi:10.1186/s13071-019-3321-2.

Falzon, L.C. et al. (2018) 'Quantitative Outcomes of a One Health approach to Study Global Health Challenges', EcoHealth, 15(1), pp. 209–227. doi:10.1007/s10393-017-1310-5.

Fang, Y. et al. (2019) 'New strains of Japanese encephalitis virus circulating in Shanghai, China after a ten-year hiatus in local mosquito surveillance', Parasites & Vectors, 12(1), p. 22. doi:10.1186/s13071-018-3267-9.

FAO (2014) The Water-Energy-Food Nexus: A new approach in support of food security and sustainable agriculture. Rome: Food and Agriculture Organization of the United Nations.

FAO (2020) FAOSTAT: FAO Statistical Databases (Food and Agriculture Organization of the United Nations). Available at: https://www.fao.org/faostat/en/#data (Accessed: 18 January 2022).

FAO et al. (2021) 'Tripartite and UNEP support OHHLEP's definition of "One Health"', OIE - World Organisation for Animal Health, 1 December. Available at: https://www.oie.int/en/tripartite-and-unep-support-ohhleps-definition-of-one-health/ (Accessed: 31 March 2022).

Faust, C.L. et al. (2017) 'Null expectations for disease dynamics in shrinking habitat: dilution or amplification?', Philosophical Transactions of the Royal Society B: Biological Sciences, 372(1722), p. 20160173. doi:10.1098/rstb.2016.0173.

Feachem, R.G.A. et al. (2019) 'Malaria eradication within a generation: ambitious, achievable, and necessary', The Lancet, 394 (10203), pp. 1056–1112. doi:10.1016/S0140-6736(19)31139-0.

Feng, C.X. (2021) 'A comparison of zero-inflated and hurdle models for modeling zero-inflated count data', Journal of Statistical Distributions and Applications, 8(1), p. 8. doi.org/10.1186/s40488-021-00121-4.

Fischer, M. et al. (2008) 'Japanese Encephalitis Prevention and Control: Advances, Challenges, and New Initiatives', in Emerging Infections 8. John Wiley & Sons, Ltd, pp. 93–124. doi.org/10.1128/9781555815592.ch6.

Fleming, L. et al. (2017) 'Big Data in Environment and Human Health', Oxford Research Encyclopedia of Environmental Science, July, pp. 1–27. doi:10.1093/acrefore/9780199389414.013.541.

Fletcher, I.K. et al. (2019) 'Environmental change and malaria risk in El Oro Province, Ecuador', International Journal of Infectious Diseases, 79, pp. 28–29. doi:10.1016/j.ijid.2018.11.084.

Folberth, C. et al. (2020) 'The global cropland-sparing potential of high-yield farming', Nature Sustainability, 3(4), pp. 281–289. doi:10.1038/s41893-020-0505-x.

Folly, A.J. et al. (2021) 'Temperate conditions restrict Japanese encephalitis virus infection to the mid-gut and prevents systemic dissemination in Culex pipiens mosquitoes', Scientific Reports, 11(1), p. 6133. doi:10.1038/s41598-021-85411-2.

Fornace, K.M. et al. (2016) 'Association between Landscape Factors and Spatial Patterns of Plasmodium knowlesi Infections in Sabah, Malaysia', Emerging Infectious Disease journal, 22(2), p. 201. doi:10.3201/eid2202.150656.

Fornace, K.M. et al. (2018) 'Exposure and infection to Plasmodium knowlesi in case study communities in Northern Sabah, Malaysia and Palawan, The Philippines', PLOS Neglected Tropical Diseases, 12(6), p. e0006432. doi:10.1371/journal.pntd.0006432.

Franklinos, L.H.V., Jones, Kate E., et al. (2019) 'The effect of global change on mosquito-borne disease', The Lancet Infectious Diseases, 19(9), pp. e302–e312. doi:10.1016/S1473-3099(19)30161-6.

Franklinos, L.H.V. et al. (2021) 'Key opportunities and challenges for the use of big data in migration research and policy', UCL Open Environment [Preprint]. doi:10.14324/111.444/ucloe.000027.

Fuller, D.O. et al. (2012) 'Linking land cover and species distribution models to project potential ranges of malaria vectors: an example using Anopheles arabiensis in Sudan and Upper Egypt', Malaria Journal, 11, p. 264. doi:10.1186/1475-2875-11-264.

Funk, S., Salathé, M. and Jansen, V.A.A. (2010) 'Modelling the influence of human behaviour on the spread of infectious diseases: a review', Journal of The Royal Society Interface, 7(50), pp. 1247–1256. doi.org/10.1098/rsif.2010.0142.

Fustec, B. et al. (2021) 'Serological biomarker for assessing human exposure to Aedes mosquito bites during a randomized vector control intervention trial in northeastern Thailand', PLOS Neglected Tropical Diseases, 15(5), p. e0009440. doi:10.1371/journal.pntd.0009440.

Gajanana, A. et al. (1997) 'Japanese encephalitis in south Arcot district, Tamil Nadu, India: a three-year longitudinal study of vector abundance and infection frequency', Journal of Medical Entomology, 34(6), pp. 651–659. doi:10.1093/jmedent/34.6.651.

Galaz, V. et al. (2015) The political economy of One Health research and policy. STEPS Working Paper 81. Brighton: STEPS Centre. Available at: https://steps-centre.org/wp-content/uploads/One-Health-wp3.pdf (Accessed: 30 December 2021).

Gallup, J.L. and Sachs, J.D. (2001) 'The economic burden of malaria', Am J Trop Med Hyg, 64, pp. 85–96. doi:11425181.

GBIF (2021a) GBIF occurrence download: Ardeola grayii - Bangladesh, Bhutan. Available at: https://doi.org/10.15468/dl.nhdz47 (Accessed: 24 November 2021).

GBIF (2021b) GBIF occurrence download: Ardeola grayii - India. Available at: https://doi.org/10.15468/dl.sjf5xc (Accessed: 22 November 2021).

GBIF (2021c) GBIF occurrence download: Bubulcus ibis - Bangladesh, Bhutan. Available at: https://doi.org/10.15468/dl.s3efhx (Accessed: 24 November 2021).

GBIF (2021d) GBIF occurrence download: Bubulcus ibis - India. Available at: https://doi.org/10.15468/dl.s2hh9n (Accessed: 22 November 2021).

GBIF (2021e) GBIF occurrence download: Egretta garzetta - Bangladesh, Bhutan. Available at: https://doi.org/10.15468/dl.59x8te (Accessed: 24 November 2021).

GBIF (2021f) GBIF occurrence download: Egretta intermedia - Bangladesh, Bhutan. Available at: https://doi.org/10.15468/dl.xyknvk (Accessed: 24 November 2021).

GBIF (2021g) GBIF occurrence download: Egretta intermedia - India. Available at: https://10.15468/dl.6wsygw (Accessed: 29 April 2021).

GBIF (2021h) GBIF occurrence download: Nycticorax nycticorax - Bangladesh, Bhutan. Available at: https://doi.org/10.15468/dl.upkgth (Accessed: 24 November 2021).

GBIF (2021i) GBIF occurrence download: Nycticorax nycticorax - India. Available at: https://doi.org/10.15468/dl.rwfsjm (Accessed: 22 November 2021).

Gething, P.W. et al. (2010) 'Climate change and the global malaria recession', Nature, 465(7296), pp. 342–345.

Getz, W.M. et al. (2018) 'Making ecological models adequate', Ecology Letters, 21(2), pp. 153–166. doi:10.1111/ele.12893.

Ghosh, R.S., Haldar, P. and Jacobson, J. (2022) 'Lessons Learned from the Japanese Encephalitis Vaccine Introduction in India That Supported the Introduction of Ivermectin–Diethylcarbamazine–Albendazole for Lymphatic Filariasis Elimination', The American Journal of Tropical Medicine and Hygiene, 106(5 Suppl), pp. 48–55. doi.org/10.4269/ajtmh.21-1168.

Gibb, R. et al. (2017) 'Understanding the cryptic nature of Lassa fever in West Africa', Pathogens and Global Health, 111(6), pp. 276–288. doi:10.1080/20477724.2017.1369643.

Gibb, R. et al. (2018) 'Effects of land use on zoonotic host communities: a global correlative analysis', The Lancet Planetary Health, 2, p. S2. doi:10.1016/S2542-5196(18)30087-1.

Gibb, R. et al. (2020a) 'Zoonotic host diversity increases in human-dominated ecosystems', Nature, 584(7821), pp. 398–402. doi:10.1038/s41586-020-2562-8.

Gibb, R. et al. (2020b) 'Ecosystem perspectives are needed to manage zoonotic risks in a changing climate', BMJ, 371, p. m3389. doi:10.1136/bmj.m3389.

Gilbert, M. et al. (2018) 'Global distribution data for cattle, buffaloes, horses, sheep, goats, pigs, chickens and ducks in 2010', Scientific Data, 5(1), p. 180227. doi:10.1038/sdata.2018.227.

Githeko, A.K. et al. (2000) 'Climate change and vector-borne diseases: a regional analysis', World Health Organization, 78(9), pp. 1136–1147.

Gneiting, T. and Raftery, A.E. (2007) 'Strictly Proper Scoring Rules, Prediction, and Estimation', Journal of the American Statistical Association, 102(477), pp. 359–378. doi:10.1198/016214506000001437.

Godfrey, E.R. and Randolph, S.E. (2011) 'Economic downturn results in tick-borne disease upsurge', Parasites & Vectors, 4(1), p. 35. doi.org/10.1186/1756-3305-4-35.

Golding, N. and Purse, B.V. (2016) 'Fast and flexible Bayesian species distribution modelling using Gaussian processes', Methods in Ecology and Evolution, 7(5), pp. 598–608. doi:10.1111/2041-210X.12523.

González, C. et al. (2010) 'Climate Change and Risk of Leishmaniasis in North America: Predictions from Ecological Niche Models of Vector and Reservoir Species', PLOS Neglected Tropical Diseases, 4(1), p. e585. doi.org/10.1371/journal.pntd.0000585.

Gottdenker, N.L. et al. (2014) 'Anthropogenic Land Use Change and Infectious Diseases: A Review of the Evidence', EcoHealth, 11(4), pp. 619–632. doi:10.1007/s10393-014-0941-z.

Gould, E.A. and Solomon, T. (2008) 'Pathogenic flaviviruses', Lancet (London, England), 371(9611), pp. 500–509. doi:10.1016/S0140-6736(08)60238-X.

Government of India (2011) Census of India 2011 - Report on Post-Enumeration Survey. Delhi, India: Ministry of Home Affairs, Government of India. Available at: https://censusindia.gov.in/2011Census/pes/Pesreport.pdf.

Government of India (2014) Operational Guidelines: National Programme for Prevention and Control of Japanese Encephalitis/Acute Encephalitis Syndrome. Delhi: Government of India Ministry of Health & Family Welfare Directorate General of Health Services National Vector Borne Disease Control Programme, p. 114.

Government of India (2021a) HMIS-Health Management Information System. Available at: https://hmis.nhp.gov.in/#!/aboutus (Accessed: 18 January 2022).

Government of India (2021b) Integrated Disease Surveillance Programme (IDSP), Ministry of Health & Family Welfare. Available at: https://idsp.nic.in/ (Accessed: 1 September 2021).

Government of India (2022) Data Management, Integrated Disease Surveillance Programme (IDSP). Available at: https://idsp.nic.in/index4.php?lang=1&level=0&linkid=412&lid=3695 (Accessed: 6 February 2022).

Grace, D., Gilbert, J., et al. (2012a) 'The multiple burdens of zoonotic disease and an ecohealth approach to their assessment', Tropical Animal Health and Production, 44(1), pp. 67–73. doi:10.1007/s11250-012-0209-y.

Grace, D., Mutua, F., et al. (2012b) Mapping of poverty and likely zoonoses hotspots: Report to Department for International Development, UK. Zoonoses Project 4. London: Department for International Development, UK. Available at: https://cgspace.cgiar.org/bitstream/handle/10568/21161/ZooMap_July2012_final.pdf?sequence=4 (Accessed: 18 December 2019).

Graham, N.T. et al. (2018) 'Water Sector Assumptions for the Shared Socioeconomic Pathways in an Integrated Modeling Framework', Water Resources Research, 54(9). doi:10.1029/2018WR023452.

Graham, N.T. et al. (2020) 'Humans drive future water scarcity changes across all Shared Socioeconomic Pathways', Environmental Research Letters, 15(1), p. 014007. doi:10.1088/1748-9326/ab639b.

Grant, C. et al. (2016) Moving interdisciplinary science forward: Integrating participatory modelling with mathematical modelling of zoonotic disease in Africa, Infectious Diseases of Poverty. (1). doi:10.1186/s40249-016-0110-4.

Grobbelaar, A.A. et al. (2016) 'Resurgence of yellow fever in Angola, 2015–2016', Emerging Infectious Diseases, 22(10), pp. 1854–1855. doi:10.3201/eid2210.160818.

Gubler, D.J. (2011) 'Dengue, Urbanization and Globalization: The Unholy Trinity of the 21st Century', Tropical Medicine and Health, 39(4 Suppl), pp. 3–11. doi:10.2149/tmh.2011-S05.

Guhathakurta, P. and Rajeevan, M. (2008) 'Trends in the rainfall pattern over India', International Journal of Climatology, 28(11), pp. 1453–1469. doi:10.1002/joc.1640.

Gupta, I. and Guin, P. (2010) 'Communicable diseases in the South-East Asia Region of the World Health Organization: towards a more effective response', Bulletin of the World Health Organization, 88, pp. 199–205. doi:10.2471/BLT.09.065540.

Gurav, Y.K. et al. (2016) 'A large outbreak of Japanese encephalitis predominantly among adults in northern region of West Bengal, India', Journal of Medical Virology, 88(11), pp. 2004–2011. doi.org/10.1002/jmv.24556.

Guzman, M.G. and Harris, E. (2015) 'Dengue', The Lancet, 385(9966), pp. 453–465. doi:10.1016/S0140-6736(14)60572-9.

Hafner, H. (1997) 'Ecology of Wading Birds', Colonial Waterbirds, 20(1), pp. 115–120. doi:10.2307/1521773.

Hahn, M.B. et al. (2014) 'Influence of Deforestation, Logging, and Fire on Malaria in the Brazilian Amazon', PLOS ONE, 9(1), p. e85725.

Halstead, S.B. and Jacobson, J. (2003) 'Japanese encephalitis', Advances in Virus Research, 61, pp. 103–138. doi:10.1016/s0065-3527(03)61003-1.

Harris, R.M.B. et al. (2014) 'Climate projections for ecologists', Wiley Interdisciplinary Reviews: Climate Change, 5(5), pp. 621–637. doi:10.1002/wcc.291.

Hassell, James M et al. (2017) 'Urbanization and Disease Emergence: Dynamics at the Wildlife–Livestock–Human Interface', Trends in Ecology & Evolution, 32, pp. 1–13. doi:10.1016/j.tree.2016.09.012.

Hassell, J.M. et al. (2021a) The Natural Environment & Health in Africa. WWF and Smithsonian Conservation Biology Institute. Available at: https://repository.si.edu/handle/10088/111281 (Accessed: 18 October 2021).

Hassell, J.M. et al. (2021b) 'Towards an ecosystem model of infectious disease', Nature Ecology & Evolution, pp. 1–12. doi:10.1038/s41559-021-01454-8.

Hay, S.I. et al. (2013) 'Big Data Opportunities for Global Infectious Disease Surveillance', PLoS Medicine, 10(4), pp. 2–5. doi:10.1371/journal.pmed.1001413.

Heffelfinger, J.D. et al. (2017) 'Japanese Encephalitis Surveillance and Immunization — Asia and Western Pacific Regions, 2016', MMWR. Morbidity and Mortality Weekly Report, 66(22), pp. 579–583. doi:10.15585/mmwr.mm6622a3.

Hennessy, S. et al. (1996) 'Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): a case-control study', The Lancet, 347(9015), pp. 1583–1586. doi.org/10.1016/S0140-6736(96)91075-2.

Hernán, M.A. (2018) 'The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data', American Journal of Public Health, 108(5), pp. 616–619. doi.org/10.2105/AJPH.2018.304337.

Heymann, D.L. et al. (2015) 'Global health security: the wider lessons from the west African Ebola virus disease epidemic', Lancet (London, England), 385(9980), pp. 1884–1901. doi:10.1016/S0140-6736(15)60858-3.

Hijmans, R.J. et al. (2020) raster: Geographic Data Analysis and Modeling. Available at: https://CRAN.R-project.org/package=raster (Accessed: 27 April 2021).

Hijmans, R.J. and van Etten, J. (2014) raster: Geographic data analysis and modeling (R package). Available at: https://cran.r-project.org/package=raster.

Hill, M.P., Axford, J.K. and Hoffmann, A.A. (2014) 'Predicting the spread of Aedes albopictus in Australia under current and future climates: Multiple approaches and datasets to incorporate potential evolutionary divergence', Austral Ecology, 39(4), pp. 469–478. doi:10.1111/aec.12105.

Hinz, R. et al. (2020) 'Agricultural Development and Land Use Change in India: A Scenario Analysis of Trade-Offs Between UN Sustainable Development Goals (SDGs)', Earth's Future, 8(2), p. e2019EF001287. doi:10.1029/2019EF001287.

Ho, S.H., Speldewinde, P. and Cook, A. (2016) 'A Bayesian Belief Network for Murray Valley encephalitis virus risk assessment in Western Australia', International Journal of Health Geographics, 15(1), p. 6. doi:10.1186/s12942-016-0036-x.

Hofman, J.M. et al. (2021) 'Integrating explanation and prediction in computational social science', Nature, 595(7866), pp. 181–188. doi:10.1038/s41586-021-03659-0.

Hombach, J. et al. (2005) 'Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2-3 September, 2004', Vaccine, 23(45), pp. 5205–5211. doi.org/10.1016/j.vaccine.2005.07.002.

Hooten, M.B. and Hobbs, N.T. (2015) 'A guide to Bayesian model selection for ecologists', Ecological Monographs, 85(1), pp. 3–28.

Hossain, M.J. et al. (2010) 'Hospital-based surveillance for Japanese encephalitis at four sites in Bangladesh, 2003-2005', American Journal of Tropical Medicine and Hygiene, 82(2), pp. 344–349. doi:10.4269/ajtmh.2010.09-0125.

Hosseini, P.R. et al. (2017) 'Does the impact of biodiversity differ between emerging and endemic pathogens? The need to separate the concepts of hazard and risk', Philosophical Transactions of the Royal Society B: Biological Sciences, 372(1722), p. 20160129. doi:10.1098/rstb.2016.0129.

Hotez, P.J. et al. (2009) 'Rescuing the bottom billion through control of neglected tropical diseases', The Lancet, 373(9674), pp. 1570–1575. doi:10.1016/S0140-6736(09)60233-6.

Hotez, P.J. (2013) 'NTDs V.2.0: "Blue Marble Health"—Neglected Tropical Disease Control and Elimination in a Shifting Health Policy Landscape', PLOS Neglected Tropical Diseases, 7(11), p. e2570. doi:10.1371/journal.pntd.0002570.

Hotez, P.J. (2016) 'Neglected Tropical Diseases in the Anthropocene: The Cases of Zika, Ebola, and Other Infections', PLOS Neglected Tropical Diseases, 10(4), p. e0004648. doi:10.1371/journal.pntd.0004648.

Hotez, P.J. (2017) 'Global urbanization and the neglected tropical diseases', PLoS Neglected Tropical Diseases, 11(2), pp. 1–5. doi:10.1371/journal.pntd.0005308.

Hrudya, P.H., Varikoden, H. and Vishnu, R. (2021) 'A review on the Indian summer monsoon rainfall, variability and its association with ENSO and IOD', Meteorology and Atmospheric Physics, 133(1), pp. 1–14. doi.org/10.1007/s00703-020-00734-5.

Hsu, L.-C. et al. (2014) 'The Incidence of Japanese Encephalitis in Taiwan—A Population-Based Study', PLOS Neglected Tropical Diseases, 8(7), p. e3030. doi.org/10.1371/journal.pntd.0003030.

Huang, J. et al. (2014) 'Analysis of NDVI Data for Crop Identification and Yield Estimation', IEEE Journal of Selected Topics in Applied Earth Observations and Remote Sensing, 7(11), pp. 4374–4384. doi:10.1109/JSTARS.2014.2334332.

Hudson, L.N. et al. (2014) 'The PREDICTS database : a global database of how local terrestrial biodiversity responds to human impacts', pp. 1–35.

Humphreys, J.M. et al. (2019) 'Seasonal occurrence and abundance of dabbling ducks across the continental United States: Joint spatio-temporal modelling for the Genus Anas', Diversity and Distributions, 25(9), pp. 1497–1508. doi:10.1111/ddi.12960.

van den Hurk, A.F., Ritchie, S.A. and Mackenzie, J.S. (2009) 'Ecology and geographical expansion of Japanese encephalitis virus', Annual Review of Entomology, 54, pp. 17–35. doi:10.1146/annurev.ento.54.110807.090510.

Hurtt, G.C. et al. (2011) 'Harmonization of land-use scenarios for the period 1500-2100: 600 years of global gridded annual land-use transitions, wood harvest, and resulting secondary lands', Climatic Change, 109(1), pp. 117–161. doi:10.1007/s10584-011-0153-2.

Hussain-Alkhateeb, L. et al. (2021) 'Early warning systems (EWSs) for chikungunya, dengue, malaria, yellow fever, and Zika outbreaks: What is the evidence? A scoping review', PLOS Neglected Tropical Diseases, 15(9), p. e0009686. doi:10.1371/journal.pntd.0009686.

Iacono, G.L. et al. (2018) 'Environmental limits of Rift Valley fever revealed using ecoepidemiological mechanistic models', Proceedings of the National Academy of Sciences of the United States of America, 115(31), pp. E7448–E7456. doi:10.1073/pnas.1803264115.

ICMR (2001) Centre for Research in Medical Entomology Annual Report 2000-2001. Madurai, India.

Ijumba, J.N. and Lindsay, S.W. (2001) 'Impact of irrigation on malaria in Africa: Paddies paradox', Medical and Veterinary Entomology, 15(1), pp. 1–11. doi:10.1046/j.1365-2915.2001.00279.x.

Imhoff, M.L. et al. (2010) 'Remote sensing of the urban heat island effect across biomes in the continental USA', Remote Sensing of Environment, 114(3), pp. 504–513. doi:https://doi.org/10.1016/j.rse.2009.10.008.

Immerzeel, W.W., van Beek, L.P.H. and Bierkens, M.F.P. (2010) 'Climate Change Will Affect the Asian Water Towers', Science, 328(5984), pp. 1382–1385. doi:10.1126/science.1183188.

Impoinvil, D.E. et al. (2011) 'The Spatial Heterogeneity between Japanese Encephalitis Incidence Distribution and Environmental Variables in Nepal', PLOS ONE, 6(7), p. e22192. doi:10.1371/journal.pone.0022192.

Institute for Health Metrics and Evaluation (2021) India Health Management Information System (HMIS), Global Health Data Exchange. Available at: http://ghdx.healthdata.org/series/india-health-management-information-system-hmis (Accessed: 1 September 2021).

International Society for Infectious Diseases (2021) ProMED, ProMED-mail. Available at: https://promedmail.org/ (Accessed: 1 September 2021).

IOM (2008) 'Summary and Assessment', in Vector-Borne Diseases: Understanding the Environmental, Human Health, and Ecological Connections, Workshop Summary. Washington (DC): National Academies Press (US). Available at: https://www.ncbi.nlm.nih.gov/books/NBK52939/.

IPBES (2019) Global assessment report on biodiversity and ecosystem services of the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services. Bonn, Germany: IPBES secretariat, p. 1148. Available at: https://doi.org/10.5281/zenodo.3831673.

IPCC (2013) 'Summary for Policymakers', Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change, p. 33. doi:10.1017/CBO9781107415324.

IPCC (2014a) Climate Change 2014: Impacts, Adaptation, and Vulnerability. Part A: Global and Sectoral Aspects. Contribution of Working Group II to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. Edited by C. Field et al. Cambridge, United Kingdom and New York, NY, USA: Cambridge University Press.

IPCC (2014b) 'Summary for policymakers.', in Field, C.B., V.R. Barros, D.J. Dokken, K.J. Mach, M.D. Mastrandrea, T.E. Bilir, M. Chatterjee, K.L. Ebi, Y.O. Estrada, R.C. Genova, B. Girma, E.S. Kissel, A.N. Levy, S. MacCracken, P.R. Mastrandrea, and L.L.W. (ed.) Climate Change 2014: Impacts, Adaptation, and Vulnerability. Part A: Global and Sectoral Aspects. Contribution of Working Group II to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge, United Kingdom and New York, NY, USA: Cambridge University Press, pp. 1–32. doi:10.1016/j.renene.2009.11.012.

IPCC (2022) Climate Change 2022: Impacts, Adaptation, and Vulnerability. Contribution of Working Group II to the Sixth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge University Press. Available at: https://report.ipcc.ch/ar6wg2/pdf/IPCC_AR6_WGII_FinalDraft_FullReport.pdf (Accessed: 2 March 2022).

IRRI (1988) Vector-borne disease control in humans through rice agroecosystem management. Los Baños (Philippines). doi:10.1016/0169-4758(89)90277-9.

IRRI (2018) Climate change - ready rice, International Rice Research Institute. Available at: https://www.irri.org/climate-change-ready-rice (Accessed: 8 March 2022).

Iwamura, T., Guzman-Holst, A. and Murray, K.A. (2020) 'Accelerating invasion potential of disease vector Aedes aegypti under climate change', Nature Communications, 11(1), p. 2130. doi:10.1038/s41467-020-16010-4.

Jaleta, K.T. et al. (2013) 'Agro-ecosystems impact malaria prevalence: large-scale irrigation drives vector population in western Ethiopia', Malaria Journal, 12(1), p. 350. doi:10.1186/1475-2875-12-350.

James, S.L. et al. (2018) 'Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017', The Lancet, 392(10159), pp. 1789–1858. doi:10.1016/S0140-6736(18)32279-7.

Jia, P. et al. (2017) 'How does the dengue vector mosquito Aedes albopictus respond to global warming?', Parasites & Vectors, 10(1), p. 140. doi:10.1186/s13071-017-2071-2.

Jian, Y. et al. (2014) 'Environmental forcing and density-dependent controls of Culex pipiens abundance in a temperate climate (Northeastern Italy)', Ecological Modelling, 272, pp. 301–310. doi:10.1016/j.ecolmodel.2013.10.019.

Johnson, E.E., Escobar, L.E. and Zambrana-Torrelio, C. (2019) 'An Ecological Framework for Modeling the Geography of Disease Transmission', Trends in Ecology & Evolution, 34(7), pp. 655–668. doi:10.1016/j.tree.2019.03.004.

Johnson, P.T.J., de Roode, J.C. and Fenton, A. (2015) 'Why infectious disease research needs community ecology', Science, 349, p. 1259504. doi:10.1126/science.1259504.

Jones, B. and O'Neill, B.C. (2016) 'Spatially explicit global population scenarios consistent with the Shared Socioeconomic Pathways', Environmental Research Letters, 11(8), p. 084003. doi:10.1088/1748-9326/11/8/084003.

Jones, K.E. et al. (2008) 'Global trends in emerging infectious diseases', Nature Letters, 451(February), pp. 990–994. doi:10.1038/nature06536.

Kakoti, G. et al. (2013) 'Clinical Profile and Outcome of Japanese Encephalitis in Children Admitted with Acute Encephalitis Syndrome', BioMed Research International, 2013. doi:10.1155/2013/152656.

Kalaiyarasu, S. et al. (2016) 'Serological evidence of widespread West Nile virus and Japanese encephalitis virus infection in native domestic ducks (Anas platyrhynchos var domesticus) in Kuttanad region, Kerala, India', Comparative Immunology, Microbiology and Infectious Diseases, 48, pp. 61–68. doi:10.1016/j.cimid.2016.08.002.

Kampen, H. et al. (2016) 'Indoor development of Aedes aegypti in Germany, 2016', Eurosurveillance, 21(47), pp. 2–4. doi:10.2807/1560-7917.ES.2016.21.47.30407.

Kanojia, P. C. et al. (2010) 'Morphometric and allozyme variation in Culex tritaeniorhynchus mosquito populations from India.', Journal of insect science (Online), 10(138), p. 138. doi:10.1673/031.010.13801.

Kanojia, P.C. and Geevarghese, G. (2004) 'First Report on High-Degree Endophilism in Culex tritaeniorhynchus (Diptera: Culicidae) in an Area Endemic for Japanese Encephalitis', Journal of Medical Entomology, 41(5), pp. 994–996. doi:10.1603/0022-2585-41.5.994.

Kanojia, P.C. and Geevarghese, G. (2005) 'New mosquito records of an area known for Japanese encephalitis hyperendemicity, Gorakhpur District, Uttar Pradesh, India', Journal of the American Mosquito Control Association, 21(1), pp. 1–4. doi:10.2987/8756-971X(2005)21[1:NMROAA]2.0.CO;2.

Kanojia, P.C., Shetty, P.S. and Geevarghese, G. (2003) 'A long-term study on vector abundance & seasonal prevalence in relation to the occurrence of Japanese encephalitis in Gorakhpur district, Uttar Pradesh', The Indian Journal of Medical Research, 117, pp. 104–110.

Kari, K. et al. (2006) 'A hospital-based surveillance for Japanese encephalitis in Bali, Indonesia', BMC medicine, 4, p. 8. doi.org/10.1186/1741-7015-4-8.

Kayatz, B. et al. (2019) '"More crop per drop": Exploring India's cereal water use since 2005', Science of The Total Environment, 673, pp. 207–217. doi:10.1016/j.scitotenv.2019.03.304.

Kehoe, L. et al. (2015) 'Global patterns of agricultural land-use intensity and vertebrate diversity', Diversity and Distributions. Edited by F. Essl, 21(11), pp. 1308–1318. doi:10.1111/ddi.12359.

Keiser, J. et al. (2005a) 'Effect of irrigation and large dams on the burden of malaria on a global and regional scale', American Journal of Tropical Medicine and Hygiene, 72(4), pp. 392-406. doi.org/10.4269/ajtmh.2005.72.392.

Keiser, J. et al. (2005b) 'Effect of irrigated rice agriculture on Japanese encephalitis, including challenges and opportunities for integrated vector management', Acta Tropica, 95(1), pp. 40–57. doi:10.1016/j.actatropica.2005.04.012.

Khan, S.A. et al. (2011) 'West Nile Virus Infection, Assam, India', Emerging Infectious Diseases, 17(5), pp. 947–948. doi:10.3201/eid1705.100479.

Khan, S.U. et al. (2014) 'Dynamics of Japanese Encephalitis Virus Transmission among Pigs in Northwest Bangladesh and the Potential Impact of Pig Vaccination', PLOS Neglected Tropical Diseases, 8(9), p. e3166. doi:10.1371/journal.pntd.0003166.

Khormi, H.M. and Kumar, L. (2016) 'Future malaria spatial pattern based on the potential global warming impact in South and Southeast Asia', Geospatial Health, 11(3), pp. 290–298. doi:10.4081/gh.2016.416.

Kibret, S. et al. (2016) 'Malaria and large dams in sub-Saharan Africa: future impacts in a changing climate', Malaria Journal, 15(1), p. 448. doi:10.1186/s12936-016-1498-9.

Kibuthu, T.W. et al. (2016) 'Agricultural chemicals: life changer for mosquito vectors in agricultural landscapes?', Parasites & Vectors, 9(1), p. 500. doi:10.1186/s13071-016-1788-7.

Kilpatrick, A.M. and Pape, W.J. (2013) 'Predicting human West Nile virus infections with mosquito surveillance data', Am J Epidemiol, 178. doi:10.1093/aje/kwt046.

Kilpatrick, A.M. and Randolph, S.E. (2012) 'Drivers, dynamics, and control of emerging vector-borne zoonotic diseases', The Lancet, 380(9857), pp. 1946–1955. doi:10.1016/S0140-6736(12)61151-9.

Kim, N.-H. et al. (2014) 'Prediction Forecast for Culex tritaeniorhynchus Populations in Korea', Osong Public Health and Research Perspectives, 5(3), pp. 131–137. doi:10.1016/j.phrp.2014.04.004.

Kingwell-Banham, E. (2019) 'Dry, rainfed or irrigated? Reevaluating the role and development of rice agriculture in Iron Age-Early Historic South India using archaeobotanical approaches', Archaeological and Anthropological Sciences, 11(12), pp. 6485–6500. doi:10.1007/s12520-019-00795-7.

Kishore, P. et al. (2016) 'Precipitation climatology over India: validation with observations and reanalysis datasets and spatial trends', Climate Dynamics, 46(1), pp. 541–556. doi.org/10.1007/s00382-015-2597-y.

Koch, L.K. et al. (2016) 'Modeling the habitat suitability for the arbovirus vector Aedes albopictus (Diptera: Culicidae) in Germany', Parasitology Research, 115(3), pp. 957–964. doi:10.1007/s00436-015-4822-3.

Korgaonkar, N.S. et al. (2012) 'Mosquito biting activity on humans & detection of Plasmodium falciparum infection in Anopheles stephensi in Goa, India', The Indian Journal of Medical Research, 135, pp. 120–126. doi:10.4103/0971-5916.93434.

Kraemer, M.U.G. et al. (2015) 'The global distribution of the arbovirus vectors Aedes aegypti and Ae. Albopictus', eLife, 4(JUNE2015), pp. 1–18. doi:10.7554/eLife.08347.

Kraemer, M.U.G. et al. (2016) 'Progress and Challenges in Infectious Disease Cartography', Trends in Parasitology, 32(1), pp. 19–29. doi:10.1016/j.pt.2015.09.006.

Kraemer, M.U.G. et al. (2019a) 'Past and future spread of the arbovirus vectors Aedes aegypti and Aedes albopictus', Nature Microbiology, 4(5), pp. 854–863. doi:10.1038/s41564-019-0376-y.

Kraemer, M.U.G. et al. (2019b) 'Utilizing general human movement models to predict the spread of emerging infectious diseases in resource poor settings', Scientific Reports, 9(1), p. 5151. doi.org/10.1038/s41598-019-41192-3.

Kraemer, M.U.G., Reiner, R.C. and Bhatt, S. (2019) 'Causal Inference in Spatial Mapping', Trends in Parasitology, 35(10), pp. 743–746. doi:10.1016/j.pt.2019.06.005.

Kugeler, K.J. et al. (2022) 'Changing Trends in Age and Sex Distributions of Lyme Disease-United States, 1992-2016', Public Health Reports (Washington, D.C.: 1974), 137(4), pp. 655–659. doi.org/10.1177/00333549211026777.

Kulkarni, R. et al. (2018) 'Japanese Encephalitis: A Brief Review on Indian Perspectives', The Open Virology Journal, 12, pp. 121–130. doi:10.2174/1874357901812010121.

Kumari, R. et al. (2013) 'First indigenous transmission of Japanese Encephalitis in urban areas of National Capital Territory of Delhi, India', Tropical medicine & international health: TM & IH, 18(6), pp. 743–749. doi:10.1111/tmi.12104.

Kumari, R. and Joshi, P.L. (2012) 'A review of Japanese encephalitis in Uttar Pradesh, India', WHO South-East Asia Journal of Public Health, 1(4), p. 374. doi:10.4103/2224-3151.207040.

Kwa, B.H. (2008) 'Environmental change, development and vectorborne disease: Malaysia's experience with filariasis, scrub typhus and dengue', Environment, Development and Sustainability, 10(2), pp. 209–217. doi:10.1007/s10668-006-9060-5.

Kwak, B.O., Hong, Y.J. and Kim, D.H. (2021) 'Changes in age-specific seroprevalence of Japanese encephalitis virus and impact of Japanese encephalitis vaccine in Korea', Clinical and Experimental Pediatrics, 65(3), pp. 108–114. doi.org/10.3345/cep.2020.01984.

LaBeaud, A.D. (2008) 'Why Arboviruses Can Be Neglected Tropical Diseases', PLoS Neglected Tropical Diseases, 2(6). doi:10.1371/journal.pntd.0000247.

Laborte, A.G. et al. (2017) 'Data Descriptor: RiceAtlas , a spatial database of global rice calendars and production', Scientific Data, 4, pp. 1–10.

Ladeau, S.L. et al. (2015) 'The ecological foundations of transmission potential and vector-borne disease in urban landscapes', Functional Ecology, pp. 889–901. doi:10.1111/1365-2435.12487.The.

Lafferty, K.D. (2009) 'The ecology of climate change and infectious diseases', Ecology, 90(4), pp. 888–900.

Lai, S. et al. (2019) 'Exploring the use of mobile phone data for national migration statistics', Palgrave Communications, 5(1), pp. 1–10. doi.org/10.1057/s41599-019-0242-9.

Lambin, E.F. et al. (2010) 'Pathogenic landscapes: interactions between land, people, disease vectors, and their animal hosts.', International journal of health geographics, 9(5), p. 54. doi:10.1186/1476-072X-9-54.

Lambrechts, L. et al. (2011) 'Impact of daily temperature fluctuations on dengue virus transmission by Aedes aegypti', Proceedings of the National Academy of Sciences, 108(18), p. 7460 LP – 7465.

Laneri, K. et al. (2015) 'Dynamical malaria models reveal how immunity buffers effect of climate variability', Proceedings of the National Academy of Sciences, 112(28), pp. 8786–8791. doi:10.1073/pnas.1419047112.

Laporta, G.Z. et al. (2015) 'Malaria vectors in South America: current and future scenarios', Parasites & Vectors, 8(1), p. 426. doi:10.1186/s13071-015-1038-4.

Leach, M. and Scoones, I. (2013) 'The social and political lives of zoonotic disease models: Narratives, science and policy', Social Science & Medicine, 88, pp. 10–17. doi.org/10.1016/j.socscimed.2013.03.017.

Lee, D.-W. et al. (2012) 'Epidemiology of Japanese encephalitis in South Korea, 2007-2010', International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases, 16(6), pp. e448-452. doi.org/10.1016/j.ijid.2012.02.006.

Le Flohic, G. et al. (2013) 'Review of Climate, Landscape, and Viral Genetics as Drivers of the Japanese Encephalitis Virus Ecology', PLoS Neglected Tropical Diseases, 7(9), pp. 5–11. doi:10.1371/journal.pntd.0002208.

Lequime, S., Paul, R.E. and Lambrechts, L. (2016) 'Determinants of Arbovirus Vertical Transmission in Mosquitoes', PLOS Pathogens, 12(5), p. e1005548. doi:10.1371/journal.ppat.1005548.

Lerner, H. and Berg, C. (2015) 'The concept of health in One Health and some practical implications for research and education: what is One Health?', Infection ecology & epidemiology, 5(1), p. 25300.

Leta, S. et al. (2019) 'Modeling the global distribution of Culicoides imicola: an Ensemble approach', Scientific Reports, 9(1), p. 14187. doi.org/10.1038/s41598-019-50765-1.

Li, S. et al. (2019) 'Lyme Disease Risks in Europe under Multiple Uncertain Drivers of Change', Environmental Health Perspectives, 127(6), p. 067010. doi.org/10.1289/EHP4615.

Li, Y. et al. (2014) 'Urbanization Increases Aedes albopictus Larval Habitats and Accelerates Mosquito Development and Survivorship', PLoS Neglected Tropical Diseases, 8(11). doi:10.1371/journal.pntd.0003301.

Li, X. et al. (2016) 'The Spatio-temporal Distribution of Japanese Encephalitis Cases in Different Age Groups in Mainland China, 2004 – 2014', PLOS Neglected Tropical Diseases, 10(4), p. e0004611. doi.org/10.1371/journal.pntd.0004611.

Lin, C.-L. et al. (2017) 'Seasonal Patterns of Japanese Encephalitis and Associated Meteorological Factors in Taiwan', International Journal of Environmental Research and Public Health, 14(11), p. 1317. doi:10.3390/ijerph14111317.

Lindblade, K.A. et al. (2000) 'Land use change alters malaria transmission parameters by modifying temperature in a highland area of Uganda', Tropical Medicine and International Health, 5(4), pp. 263–274. doi:10.1046/j.1365-3156.2000.00551.x.

Lindgren, F. and Rue, H. (2015) 'Bayesian Spatial Modelling with R-INLA', Journal of Statistical Software, 63(19). Available at: https://www.jstatsoft.org/article/view/v063i19 (Accessed: 8 February 2021).

Lindquist, L. (2018) 'Recent and historical trends in the epidemiology of Japanese encephalitis and its implication for risk assessment in travellers', Journal of Travel Medicine, 25(suppl_1), pp. S3–S9. doi:10.1093/jtm/tay006.

Linthicum, K.J. et al. (2014) 'Association of Temperature and Historical Dynamics of Malaria in the Republic of Korea, Including Reemergence in 1993', Military Medicine, 179(7), pp. 806–814. doi:10.7205/MILMED-D-13-00545.

Liu, Z. et al. (2020) 'Nonlinear and Threshold Effect of Meteorological Factors on Japanese Encephalitis Transmission in Southwestern China', The American Journal of Tropical Medicine and Hygiene, 103(6), pp. 2442–2449. doi:10.4269/ajtmh.20-0040.

Liu-Helmersson, J. et al. (2014) 'Vectorial Capacity of Aedes aegypti: Effects of Temperature and Implications for Global Dengue Epidemic Potential', PLOS ONE, 9(3), p. e89783.

Liu-Helmersson, J. et al. (2016) 'Climate Change and Aedes Vectors: 21st Century Projections for Dengue Transmission in Europe', EBioMedicine, pp. 267–277. doi:10.1016/j.ebiom.2016.03.046.

Liu-Helmersson, J. et al. (2019) 'Estimating Past, Present, and Future Trends in the Global Distribution and Abundance of the Arbovirus Vector Aedes aegypti Under Climate Change Scenarios', Frontiers in Public Health, 7(148). doi:10.3389/fpubh.2019.00148.

Loaiza, J.R. et al. (2017) 'Disturbance and mosquito diversity in the lowland tropical rainforest of central Panama', Scientific Reports, 7(1), pp. 1–13. doi:10.1038/s41598-017-07476-2.

Longbottom, J. et al. (2017) 'Mapping the spatial distribution of the Japanese encephalitis vector, Culex tritaeniorhynchus Giles, 1901 (Diptera: Culicidae) within areas of Japanese encephalitis risk', Parasites & Vectors, 10(1), p. 148. doi:10.1186/s13071-017-2086-8.

Lord, C.C. (2004) 'Seasonal population dynamics and behaviour of insects in models of vector-borne pathogens', Physiological Entomology, 29(3), pp. 214–222. doi:10.1111/j.0307-6962.2004.00411.x.Seasonal.

Lord, J.S., Gurley, E.S. and Pulliam, J.R.C. (2015) 'Rethinking Japanese Encephalitis Virus Transmission: A Framework for Implicating Host and Vector Species', PLoS Neglected Tropical Diseases, 9(12), pp. 1–7. doi:10.1371/journal.pntd.0004074.

Lord, J.S. (2021) 'Changes in Rice and Livestock Production and the Potential Emergence of Japanese Encephalitis in Africa', Pathogens, 10(3), p. 294. doi:10.3390/pathogens10030294.

Lounibos, L.P. and Juliano, S.A. (2018) 'Where vectors collide: the importance of mechanisms shaping the realized niche for modeling ranges of invasive Aedes mosquitoes', Biological Invasions, pp. 1–17. doi:10.1007/s10530-018-1674-7.

Low, R. et al. (2021) 'GLOBE Mosquito Habitat Mapper Citizen Science Data 2017–2020', GeoHealth, 5(10), p. e2021GH000436. doi:10.1029/2021GH000436.

Lowe, R. et al. (2016) 'Evaluating probabilistic dengue risk forecasts from a prototype early warning system for Brazil', eLife, 5(FEBRUARY2016), pp. 1–18. doi:10.7554/eLife.11285.

Lowe, R. et al. (2017) 'Climate services for health: predicting the evolution of the 2016 dengue season in Machala , Ecuador', Lancet Planetary Health, 1(4), pp. e142-51. doi:10.1016/S2542-5196(17)30064-5.

Lowe, R. et al. (2020) 'Emerging arboviruses in the urbanized Amazon rainforest', BMJ, 371, p. m4385. doi:10.1136/bmj.m4385.

Lowe, R. et al. (2021) 'Combined effects of hydrometeorological hazards and urbanisation on dengue risk in Brazil: a spatiotemporal modelling study', The Lancet Planetary Health, 5(4), pp. e209–e219. doi:10.1016/S2542-5196(20)30292-8.

Lucas, T.C.D. et al. (2021) 'Mapping malaria by sharing spatial information between incidence and prevalence data sets', Journal of the Royal Statistical Society: Series C (Applied Statistics) [Preprint]. doi:https://doi.org/10.1111/rssc.12484.

Luis, A.D., Kuenzi, A.J. and Mills, J.N. (2018) 'Species diversity concurrently dilutes and amplifies transmission in a zoonotic host–pathogen system through competing mechanisms',

Proceedings of the National Academy of Sciences, p. 201807106. doi:10.1073/pnas.1807106115.

Lule, S.A. et al. (2022) 'Widespread exposure to Crimean-Congo haemorrhagic fever in Uganda might be driven by transmission from Rhipicephalus ticks: Evidence from cross-sectional and modelling studies', Journal of Infection, 85(6), pp. 683–692. doi.org/10.1016/j.jinf.2022.09.016.

Lund, A.J. et al. (2021) 'Exposure, hazard, and vulnerability all contribute to Schistosoma haematobium re-infection in northern Senegal', PLOS Neglected Tropical Diseases, 15(10), p. e0009806. doi:10.1371/journal.pntd.0009806.

Luo, D. et al. (1995) 'Socio-economic status and micro-environmental factors in relation to the risk of Japanese encephalitis: a case-control study', The Southeast Asian Journal of Tropical Medicine and Public Health, 26(2), pp. 276–279.

Luo, L.J. (2010) 'Breeding for water-saving and drought-resistance rice (WDR) in China', Journal of Experimental Botany, 61(13), pp. 3509–3517. doi:10.1093/jxb/erq185.

M. Khormi, H. and Kumar, L. (2014) 'Climate change and the potential global distribution of Aedes aegypti: spatial modelling using geographical information system and CLIMEX', Geospatial Health, 8, pp. 405–415.

MacDonald, A.J. and Mordecai, E.A. (2019) 'Amazon deforestation drives malaria transmission, and malaria burden reduces forest clearing', Proceedings of the National Academy of Sciences, 116(44), pp. 22212–22218. doi:10.1073/pnas.1905315116.

Mackenzie, J.S., Gubler, D.J. and Petersen, L.R. (2004) 'Emerging flaviviruses: the spread and resurgence of Japanese encephalitis, West Nile and dengue viruses.', Nature medicine, 10(12 Suppl), pp. S98–S109. doi:10.1038/nm1144.

Maeki, T. et al. (2019) 'Analysis of cross-reactivity between flaviviruses with sera of patients with Japanese encephalitis showed the importance of neutralization tests for the diagnosis of Japanese encephalitis', Journal of Infection and Chemotherapy: Official Journal of the Japan Society of Chemotherapy, 25(10), pp. 786–790. doi:10.1016/j.jiac.2019.04.003.

Mahanta, R., Sarma, D. and Choudhury, A. (2013) 'Heavy rainfall occurrences in northeast India', International Journal of Climatology, 33(6), pp. 1456–1469. doi:10.1002/joc.3526.

Malakar, M. and Choudhury, M. (2014) 'Positivity rate of Japanese encephalitis in the Goalpara district of Assam, India', International Journal of Pharmaceutical Science and Health Care, 2(4). Available at: https://rspublication.com/ijphc/2014/april14/19.pdf.

Malecela, M.N. (2019) 'Reflections on the decade of the neglected tropical diseases', International Health, 11(5), pp. 338–340. doi:10.1093/inthealth/ihz048.

Manlove, K.R. et al. (2016) '"One Health" or Three? Publication Silos Among the One Health Disciplines', PLOS Biology, 14(4), p. e1002448. doi.org/10.1371/journal.pbio.1002448.

Mandal, S., Sarkar, R. and Sinha, S. (2011) 'Mathematical models of malaria - A review', Malaria Journal, 10(1), p. 202. doi:10.1186/1475-2875-10-202.

Mariappan, T. et al. (2014) 'Entomological investigations into an epidemic of Japanese encephalitis (JE) in northern districts of West Bengal, India (2011-2012)', The Indian Journal of Medical Research, 139(5), pp. 754–761.

Marin-Ferrer, M., Vernaccini, L. and Poljansek, K. (2017) Index for Risk Management INFORM Concept and Methodology Report. EUR 28655 EN. doi:10.2760/094023 (Accessed: 23 February 2023).

Marotzke, J., Semmann, D. and Milinski, M. (2020) 'The economic interaction between climate change mitigation, climate migration and poverty', Nature Climate Change, 10(6), pp. 518–525. doi.org/10.1038/s41558-020-0783-3.

Marshall, E.C. and Spiegelhalter, D.J. (2003) 'Approximate cross-validatory predictive checks in disease mapping models', Statistics in Medicine, 22(10), pp. 1649–1660. doi:10.1002/sim.1403.

Masuoka, P. et al. (2010) 'Modeling the distribution of Culex tritaeniorhynchus to predict Japanese encephalitis distribution in the Republic of Korea', Geospatial Health, pp. 45–57. doi:10.4081/gh.2010.186.

Matsuzaki, S. (1990) 'Population dynamics of Culex tritaeniorhynchus in relation to the epidemics of Japanese encephalitis in Kochi Prefecture, Japan.', Japanese Journal of Sanitary Zoology, 41(3), pp. 247–255.

McElreath, R. (2020a) '7.1 The problem with parameters', in Statistical Rethinking: A Bayesian Course with Examples in R and STAN. Second. Chapman and Hall/CRC, p. 195. Available at: https://www.routledge.com/Statistical-Rethinking-A-Bayesian-Course-with-

Examples-in-R-and-
STAN/McElreath/p/book/9780367139919?utm_source=crcpress.com&utm_medium=referral.

McElreath, R. (2020b) '7.4 Predicting predictive accuracy', in Statistical Rethinking: A
Bayesian Course with Examples in R and STAN. Second. Boca Raton, Florida: CRC Press,
pp. 217–225.

McElreath, R. (2020c) Statistical Rethinking: A Bayesian Course with Examples in R and
STAN. Second. Boca Raton, Florida: CRC Press. Available at:
https://www.routledge.com/Statistical-Rethinking-A-Bayesian-Course-with-Examples-in-R-
and-
STAN/McElreath/p/book/9780367139919?utm_source=crcpress.com&utm_medium=referral
(Accessed: 16 June 2020).

McGough, S.F. et al. (2021) 'A dynamic, ensemble learning approach to forecast dengue
fever epidemic years in Brazil using weather and population susceptibility cycles', Journal of
The Royal Society Interface, 18(179), p. 20201006. doi:10.1098/rsif.2020.1006.

McNaughton, H., Singh, A. and Khan, S.A. (2018) 'An outbreak of Japanese encephalitis in a
non-endemic region of north-east India', The Journal of the Royal College of Physicians of
Edinburgh, 48(1), pp. 25–29. doi:10.4997/JRCPE.2018.105.

McPherson, M. et al. (2017) 'Expansion of the Lyme Disease Vector Ixodes Scapularis in
Canada Inferred from CMIP5 Climate Projections', Environmental Health Perspectives,
125(5), p. 057008. doi.org/10.1289/EHP57.

Medhi, M. et al. (2017) 'Incidence of Japanese Encephalitis amongst acute encephalitis
syndrome cases in upper Assam districts from 2012 to 2014: A report from a tertiary care
hospital', The Indian Journal of Medical Research, 146(2), pp. 267–271.
doi:10.4103/ijmr.IJMR_1303_15.

Messina, J.P. et al. (2015) 'The many projected futures of dengue', Nature Reviews
Microbiology, 13(4), pp. 230–239. doi:10.1038/nrmicro3430.

Messina, J.P. et al. (2019) 'The current and future global distribution and population at risk of
dengue', Nature Microbiology, 4(9), pp. 1508–1515. doi:10.1038/s41564-019-0476-8.

Metelka, J., Robertson, C. and Stephen, C. (2015) 'Japanese Encephalitis: Estimating
Future Trends in Asia', AIMS public health, 2(4), pp. 601–615.
doi:10.3934/publichealth.2015.4.601.

Millennium Ecosystem Assessment (2005) Ecosystems and Human Well-being: Synthesis. Washington, D.C.: World Resources Institute. doi:10.1196/annals.1439.003.

Miller, R.H. et al. (2012) 'Ecological niche modeling to estimate the distribution of Japanese encephalitis virus in Asia', PLoS Neglected Tropical Diseases, 6(6). doi:10.1371/journal.pntd.0001678.

Ministry of Health & Family Welfare, Government of India (2020) Weekly Outbreaks, Integrated Disease Surveillance Programme. Available at: https://www.idsp.nic.in/index4.php?lang=1&level=0&linkid=406&lid=3689 (Accessed: 8 April 2020).

Misra, B.R. and Gore, M. (2015) 'Malathion Resistance Status and Mutations in Acetylcholinesterase Gene (Ace) in Japanese Encephalitis and Filariasis Vectors from Endemic Area in India', Journal of Medical Entomology, 52(3), pp. 442–446. doi:10.1093/jme/tjv015.

Misra, U.K. and Kalita, J. (2010) 'Overview: Japanese encephalitis', Progress in Neurobiology, 91(2), pp. 108–120. doi:10.1016/j.pneurobio.2010.01.008.

MOEF (2019) Implementation of India's National Biodiversity Action Plan An Overview 2019. New Delhi, Delhi: Ministry of Environment, Forest and Climate Change, Government of India. Available at: https://www.cbd.int/doc/world/in/in-nbsap-other-en.pdf (Accessed: 18 December 2019).

Monaghan, Andrew J. et al. (2018) 'The potential impacts of 21st century climatic and population changes on human exposure to the virus vector mosquito Aedes aegypti', Climatic Change, 146(3), pp. 487–500. doi:10.1007/s10584-016-1679-0.

Monroe, A. et al. (2020) 'Methods and indicators for measuring patterns of human exposure to malaria vectors', Malaria Journal, 19(1), p. 207. doi:10.1186/s12936-020-03271-z.

Moo-Llanes, D. et al. (2013) 'Current and Future Niche of North and Central American Sand Flies (Diptera: Psychodidae) in Climate Change Scenarios', PLOS Neglected Tropical Diseases, 7(9), p. e2421. doi.org/10.1371/journal.pntd.0002421.

Moore, S.M. (2021) 'The current burden of Japanese encephalitis and the estimated impacts of vaccination: Combining estimates of the spatial distribution and transmission intensity of a zoonotic pathogen', PLOS Neglected Tropical Diseases, 15(10), p. e0009385. doi:10.1371/journal.pntd.0009385.

Moore, S.M., Borer, E.T. and Hosseini, P.R. (2010) 'Predators indirectly control vector-borne disease: linking predator-prey and host-pathogen models', Journal of The Royal Society Interface, 7(42), pp. 161–176. doi:10.1098/rsif.2009.0131.

Mordecai, E.A., Cohen, J.M., Evans, M. V, et al. (2017) 'Detecting the impact of temperature on transmission of Zika, dengue, and chikungunya using mechanistic models', PLOS Neglected Tropical Diseases, 11(4), p. e0005568.

Mordecai, E.A. et al. (2019) 'Thermal biology of mosquito-borne disease', Ecology Letters, 22(10), pp. 1690–1708. doi:10.1111/ele.13335.

Mordecai, E.A. et al. (2020) 'Climate change could shift disease burden from malaria to arboviruses in Africa', The Lancet. Planetary Health, 4(9), pp. e416–e423. doi:10.1016/S2542-5196(20)30178-9.

Morens, D.M. and Fauci, A.S. (2012) 'Emerging Infectious Diseases in 2012: 20 Years after the Institute of Medicine Report', mBio, 3(6). doi:10.1128/mBio.00494-12.

Morin, C.W., Comrie, A.C. and Ernst, K. (2013) 'Climate and Dengue Transmission: Evidence and Implications', Environmental Health Perspectives, 121(11–12), pp. 1264–1272. doi:10.1289/ehp.1306556.

Morita, K., Nabeshima, T. and Buerano, C.C. (2015) 'Japanese encephalitis Aetiological', Revue scientifique et technique (International Office of Epizootics), 34(2), pp. 441–452.

Mtema, Z. et al. (2016) 'Mobile Phones as Surveillance Tools: Implementing and Evaluating a Large-Scale Intersectoral Surveillance System for Rabies in Tanzania', PLOS Medicine, 13(4), p. e1002002. doi:10.1371/journal.pmed.1002002.

Mukhtar, M. et al. (2003) 'Role of wastewater irrigation in mosquito breeding in south Punjab, Pakistan', Southeast Asian Journal of Tropical Medicine and Public Health, 34(1), pp. 72–80.

Mukundarajan, H. et al. (2017) 'Using mobile phones as acoustic sensors for high-throughput mosquito surveillance', eLife, 6, p. e27854. doi:10.7554/eLife.27854.

Mulligan, K. et al. (2015) 'Is dengue a disease of poverty? A systematic review', Pathogens and Global Health, 109(1), pp. 10–18. doi:10.1179/2047773214Y.0000000168.

Muniaraj, M. and Rajamannar, V. (2019) 'Impact of SA 14-14-2 vaccination on the occurrence of Japanese encephalitis in India', Human Vaccines & Immunotherapeutics, 15(4), pp. 834–840. doi:10.1080/21645515.2018.1564435.

Murakami, D., Yoshida, T. and Yamagata, Y. (2021) 'Gridded GDP Projections Compatible With the Five SSPs (Shared Socioeconomic Pathways)', Frontiers in Built Environment, 7. Available at: https://www.frontiersin.org/article/10.3389/fbuil.2021.760306 (Accessed: 28 March 2022).

Murdock, C.C. et al. (2012) 'Complex effects of temperature on mosquito immune function', Proceedings of the Royal Society B: Biological Sciences, 279(1741), pp. 3357–3366. doi:10.1098/rspb.2012.0638.

Murdock, C.C. et al. (2017) 'Fine-scale variation in microclimate across an urban landscape shapes variation in mosquito population dynamics and the potential of Aedes albopictus to transmit arboviral disease', PLOS Neglected Tropical Diseases, 11(5), p. e0005640.

Murdock, C.C., Sternberg, E.D. and Thomas, M.B. (2016) 'Malaria transmission potential could be reduced with current and future climate change', Scientific Reports, 6, p. 27771.

Murhekar, M.V. et al. (2017) 'Coverage & missed opportunity for Japanese encephalitis vaccine, Gorakhpur division, Uttar Pradesh, India, 2015: Implications for Japanese encephalitis control', Indian Journal of Medical Research, 145(1), p. 63. doi:10.4103/ijmr.IJMR_712_16.

Murty, U.S., Rao, M.S. and Arunachalam, N. (2010) 'The effects of climatic factors on the distribution and abundance of Japanese encephalitis vectors in Kurnool district of Andhra Pradesh, India', Journal of Vector Borne Diseases, (47), pp. 26–32.

Mweya, C.N. et al. (2016) 'Climate Change Influences Potential Distribution of Infected Aedes aegypti Co-Occurrence with Dengue Epidemics Risk Areas in Tanzania', PLOS ONE, 11(9), pp. 1–13. doi:10.1371/journal.pone.0162649.

Mweya, C.N., Mboera, L.E.G. and Kimera, S.I. (2017) 'Climate Influence on Emerging Risk Areas for Rift Valley Fever Epidemics in Tanzania', The American Journal of Tropical Medicine and Hygiene, 97(1), pp. 109–114.

National Academies of Sciences, Engineering and Medicine (2016) Global Health Impacts of Vector-Borne Diseases: Workshop Summary. Edited by A. Mack. Washington, DC: The National Academies Press. doi:10.17226/21792.

Nealon, J. et al. (2019) 'Serological Evidence of Japanese Encephalitis Virus Circulation in Asian Children From Dengue-Endemic Countries', The Journal of Infectious Diseases, 219(3), pp. 375–381. doi.org/10.1093/infdis/jiy513.

Neupane, N., Goldbloom-Helzner, A. and Arab, A. (2021) 'Spatio-temporal modeling for confirmed cases of lyme disease in Virginia', Ticks and Tick-borne Diseases, 12(6), p. 101822. doi.org/10.1016/j.ttbdis.2021.101822.

Newbold, T. et al. (2015) 'Global effects of land use on local terrestrial biodiversity.', Nature, 520(7545), pp. 45–50. doi:10.1038/nature14324.

Newbold, T. (2018) 'Future effects of climate and land-use change on terrestrial vertebrate community diversity under different scenarios', Proceedings of the Royal Society of London B: Biological Sciences, 285(1881).

Ngonghala, C.N. et al. (2014) 'Poverty, Disease, and the Ecology of Complex Systems', PLoS Biology, 12(4), pp. 1–9. doi.org/10.1371/journal.pbio.1001827.

Ngonghala, C.N. et al. (2017) 'General ecological models for human subsistence, health and poverty', Nature Ecology and Evolution, 1(8), pp. 1153–1159. doi:10.1038/s41559-017-0221-8.

Niaz, S. and Reisen, W.K. (1981) 'Culex tritaeniorhnchus Giles: some effects of temperature and photoperiod on larval development and selected adult attributes', Japanese Journal of Medical Hygiene, 9(1), pp. 37–47.

Nunes, M.R.T. et al. (2014) 'Air Travel Is Associated with Intracontinental Spread of Dengue Virus Serotypes 1-3 in Brazil', PLoS Neglected Tropical Diseases, 8(4). doi:10.1371/journal.pntd.0002769.

Ochieng, A.O. et al. (2016) 'Ecological niche modelling of Rift Valley fever virus vectors in Baringo, Kenya.', Infection Ecology & Epidemiology, 6, p. 32322. doi:10.3402/iee.v6.32322.

Ogden, N.H. et al. (2014a) 'Estimated Effects of Projected Climate Change on the Basic Reproductive Number of the Lyme Disease Vector Ixodes scapularis', Environmental Health Perspectives, 122(6), pp. 631–638. doi.org/10.1289/ehp.1307799.

Ogden, N.H. et al. (2014b) 'Recent and projected future climatic suitability of North America for the Asian tiger mosquito Aedes albopictus', Parasites & Vectors. London. doi:10.1186/s13071-014-0532-4.

Ohba, S.Y., Matsuo, T. and Takagi, M. (2013) 'Mosquitoes and other aquatic insects in fallow field biotopes and rice paddy fields', Medical and Veterinary Entomology, 27(1), pp. 96–103. doi:10.1111/j.1365-2915.2012.01045.x.

Ohm, J.R. et al. (2018) 'Rethinking the extrinsic incubation period of malaria parasites', Parasites and Vectors, 11(1), pp. 1–9. doi:10.1186/s13071-018-2761-4.

Oladosu, Y. et al. (2019) 'Drought Resistance in Rice from Conventional to Molecular Breeding: A Review', International Journal of Molecular Sciences, 20(14), p. 3519. doi:10.3390/ijms20143519.

One Health Commission (2021) 'What is One Health?', One Health Commission. Available at: https://www.onehealthcommission.org/en/why_one_health/what_is_one_health/ (Accessed: 14 March 2022).

O'Neill, B.C. et al. (2016) 'The Scenario Model Intercomparison Project (ScenarioMIP) for CMIP6', Geoscientific Model Development, 9(9), pp. 3461–3482. doi:10.5194/gmd-9-3461-2016.

Onojeghuo, A.O. et al. (2018) 'Rice crop phenology mapping at high spatial and temporal resolution using downscaled MODIS time-series', GIScience & Remote Sensing, 55(5), pp. 659–677. doi:10.1080/15481603.2018.1423725.

Ostfeld, R.S. and Keesing, F. (2000) 'Biodiversity and Disease Risk: the Case of Lyme Disease', Conservation Biology, 14(3), pp. 722–728. doi:10.1046/j.1523-1739.2000.99014.x.

Oviedo-Pastrana, M. et al. (2017) 'Epidemic outbreak of Chikungunya in two neighboring towns in the Colombian Caribbean: a survival analysis', Archives of Public Health, 75(1), p. 1. doi:10.1186/s13690-016-0169-1.

Paaijmans, K.P. et al. (2010) 'Influence of climate on malaria transmission depends on daily temperature variation', Proceedings of the National Academy of Sciences of the United States of America, 107(34), pp. 15135–15139. doi:10.1073/pnas.1006422107.

Paaijmans, K.P. et al. (2012) 'Warmer temperatures reduce the vectorial capacity of malaria mosquitoes', Biology Letters, 8(3), pp. 465–468. doi:10.1098/rsbl.2011.1075.

Paaijmans, K.P. et al. (2013) 'Temperature variation makes ectotherms more sensitive to climate change', Global Change Biology, 19(8), pp. 2373–2380. doi:10.1111/gcb.12240.

Paaijmans, K.P. et al. (2014) 'Downscaling reveals diverse effects of anthropogenic climate warming on the potential for local environments to support malaria transmission', Climatic Change, 125(3), pp. 479–488. doi:10.1007/s10584-014-1172-6.

Pagel, J. et al. (2014) 'Quantifying range-wide variation in population trends from local abundance surveys and widespread opportunistic occurrence records', Methods in Ecology and Evolution, 5(8), pp. 751–760. doi:10.1111/2041-210X.12221.

Paixão, E.S., Teixeira, M.G. and Rodrigues, L.C. (2017) 'Zika, chikungunya and dengue: the causes and threats of new and re-emerging arboviral diseases', BMJ Global Health, 2(4), p. e000530. doi:10.1136/bmjgh-2017-000530.

Palmer, J.R.B. et al. (2017) 'Citizen science provides a reliable and scalable tool to track disease-carrying mosquitoes', Nature Communications, 8(1), p. 916. doi:10.1038/s41467-017-00914-9.

Pandit, P.S. et al. (2018) 'Predicting wildlife reservoirs and global vulnerability to zoonotic Flaviviruses', Nature Communications, 9(1), p. 5425. doi:10.1038/s41467-018-07896-2.

Paramasivan, R., Dhananjeyan, K.J. and Pandian, R.S. (2013) 'A preliminary report on DNA barcoding and phylogenetic relationships of certain public health important mosquito species recorded in rural areas of south India', Journal of Vector Borne Diseases, 50(2), pp. 144–146.

Parham, P.E. et al. (2015) 'Climate, environmental and socio-economic change: weighing up the balance in vector-borne disease transmission', Philosophical Transactions of the Royal Society B: Biological Sciences, 370(1665), p. 20130551. doi:10.1098/rstb.2013.0551.

Parida, M. et al. (2006) 'Japanese encephalitis Outbreak, India, 2005', Emerging Infectious Diseases, 12(9), pp. 1427–1430. doi.org/10.3201/eid1209.060200.

Pataki, B.A. et al. (2021) 'Deep learning identification for citizen science surveillance of tiger mosquitoes', Scientific Reports, 11(1), p. 4718. doi:10.1038/s41598-021-83657-4.

Patz, J.A. et al. (2000) 'Effects of environmental change on emerging parasitic diseases', International Journal for Parasitology, 30(12–13), pp. 1395–1405. doi:10.1016/S0020-7519(00)00141-7.

Patz, J.A. et al. (2004) 'Unhealthy landscapes: Policy recommendations on land use change and infectious disease emergence', Environmental Health Perspectives, 112(10), pp. 1092–1098. doi:10.1289/ehp.6877.

Paul, R.C. et al. (2011) 'A novel low-cost approach to estimate the incidence of Japanese encephalitis in the catchment area of three hospitals in Bangladesh', American Journal of Tropical Medicine and Hygiene, 85(2), pp. 379–385. doi:10.4269/ajtmh.2011.10-0706.

Paul, R.E.L. et al. (2016) 'Environmental factors influencing tick densities over seven years in a French suburban forest', Parasites & Vectors, 9(1), p. 309. doi.org/10.1186/s13071-016-1591-5.

Paz, S. (2015) 'Climate change impacts on West Nile virus transmission in a global context', Philosophical Transactions of the Royal Society B: Biological Sciences, 370(1665), pp. 20130561–20130561. doi:10.1098/rstb.2013.0561.

Pearce, J.C. et al. (2018) 'Japanese encephalitis: the vectors, ecology and potential for expansion', Journal of Travel Medicine, 25(suppl_1), pp. S16–S26. doi:10.1093/jtm/tay009.

Pech-May, A. et al. (2016) 'Population genetics and ecological niche of invasive Aedes albopictus in Mexico', Acta Tropica, 157, pp. 30–41. doi:https://doi.org/10.1016/j.actatropica.2016.01.021.

Peralbo-Moreno, A. et al. (2022) 'Environmental factors driving fine-scale ixodid tick abundance patterns', Science of The Total Environment, 853, p. 158633. doi.org/10.1016/j.scitotenv.2022.158633.

Peterson, A.T. (2008) 'Biogeography of diseases: A framework for analysis', Naturwissenschaften, 95(6), pp. 483–491. doi:10.1007/s00114-008-0352-5.

Peterson, A.T. (2014) Mapping Disease Transmission Risk: Enriching Models Using Biogeography and Ecology. JHU Press.

Petrić, M. et al. (2017) 'Modelling the regional impact of climate change on the suitability of the establishment of the Asian tiger mosquito (Aedes albopictus) in Serbia', Climatic Change, 142(3), pp. 361–374. doi:10.1007/s10584-017-1946-8.

Pettit, L.I. (1990) 'The Conditional Predictive Ordinate for the Normal Distribution', Journal of the Royal Statistical Society. Series B (Methodological), 52(1), pp. 175–184.

Phillips, S., Anderson, R. and Schapire, R. (2006) 'Maximum entropy modeling of species geographic distributions', Ecological Modelling, 190, pp. 231–259. doi:10.1016/j.ecolmodel.2005.03.026.

Phillips, S.J. et al. (2009) 'Sample selection bias and presence-only distribution models: implications for background and pseudo-absence data', Ecological Applications, 19(1), pp. 181–197. doi:10.1890/07-2153.1.

Phukan, A.C., Borah, P.K. and Mahanta, J. (2004) 'Japanese encephalitis in Assam, northeast India', The Southeast Asian Journal of Tropical Medicine and Public Health, 35(3), pp. 618–622.

Pley, C. et al. (2021) 'Digital and technological innovation in vector-borne disease surveillance to predict, detect, and control climate-driven outbreaks', The Lancet Planetary Health, 5(10), pp. e739–e745. doi:10.1016/S2542-5196(21)00141-8.

Plowright, R.K. et al. (2008) 'Causal inference in disease ecology: investigating ecological drivers of disease emergence', Frontiers in Ecology and the Environment, 6(8), pp. 420–429. doi:10.1890/070086.

Plowright, R.K. et al. (2017) 'Pathways to zoonotic spillover', Nature Reviews Microbiology, 15(8), pp. 502–510. doi:10.1038/nrmicro.2017.45.

Plowright, R.K. et al. (2021) 'Land use-induced spillover: a call to action to safeguard environmental, animal, and human health', The Lancet Planetary Health, 0(0). doi:10.1016/S2542-5196(21)00031-0.

Pongsiri, M.J. et al. (2017) 'The need for a systems approach to planetary health', The Lancet Planetary Health, 1(7), pp. e257–e259. doi:10.1016/S2542-5196(17)30116-X.

Popp, A. et al. (2017) 'Land-use futures in the shared socio-economic pathways', Global Environmental Change, 42, pp. 331–345. doi:10.1016/j.gloenvcha.2016.10.002.

Potula, R., Badrinath, S. and Srinivasan, S. (2003) 'Japanese Encephalitis in and around Pondicherry, South India: a Clinical Appraisal and Prognostic Indicators for the Outcome', Journal of Tropical Pediatrics, 49(1), pp. 48–53. doi.org/10.1093/tropej/49.1.48.

Proestos, Y. et al. (2015) 'Present and future projections of habitat suitability of the Asian tiger mosquito, a vector of viral pathogens, from global climate simulation', Philosophical

Transactions of the Royal Society B: Biological Sciences, 370(1665), pp. 20130554–20130554. doi:10.1098/rstb.2013.0554.

Prokop, P. (2020) 'Remote sensing of severely degraded land: Detection of long-term land-use changes using high-resolution satellite images on the Meghalaya Plateau, northeast India', Remote Sensing Applications: Society and Environment, 20, p. 100432. doi:10.1016/j.rsase.2020.100432.

Purse, B.V. et al. (2017) 'How will climate change pathways and mitigation options alter incidence of vector-borne diseases? A framework for leishmaniasis in South and Meso-America', PLOS ONE, 12(10), p. e0183583. doi.org/10.1371/journal.pone.0183583.

Purse, B.V. et al. (2020) 'Predicting disease risk areas through co-production of spatial models: The example of Kyasanur Forest Disease in India's forest landscapes', PLOS Neglected Tropical Diseases, 14(4), p. e0008179. doi.org/10.1371/journal.pntd.0008179.

Qi, Q. et al. (2012) 'The effects of urbanization on global Plasmodium vivax malaria transmission', Malaria Journal, 11(1), p. 403. doi:10.1186/1475-2875-11-403.

Quan, T.M. et al. (2020) 'Estimates of the global burden of Japanese encephalitis and the impact of vaccination from 2000-2015', eLife. Edited by E. Franco, 9, p. e51027. doi:10.7554/eLife.51027.

R Core Team (2020) R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. Available at: https://www.R-project.org/.

Rahman, A.P. (2016) 'Climate change linked to surge in Japanese encephalitis in North East India', The Third Pole, 12 October. Available at: https://www.thethirdpole.net/en/climate/climate-change-linked-to-surge-in-japanese-encephalitis-in-north-east-india/ (Accessed: 23 March 2022).

Rajagopalan, P.K. and Panicker, K.N. (1978) 'A note on the 1976 epidemic of Japanese encephalitis in Burdwan district, West Bengal', The Indian Journal of Medical Research, 68, p. 3938.

Rajavel, A.R. and Natarajan, R. (2008) 'Mosquitoes of the mangrove forests of India: part 7–an overview.', Journal of the American Mosquito Control Association, 24(4), pp. 478–488. doi:10.2987/08-5762.1.

Rajavel, A.R., Natarajan, R. and Vaidyanathan, K. (2005a) 'Mosquitoes of the mangrove forests of India: Part 1--Bhitarkanika, Orissa', Journal of the American Mosquito Control Association, 21(2), pp. 131–135. doi:10.2987/8756-971X(2005)21[131:MOTMFO]2.0.CO;2.

Rajavel, A.R., Natarajan, R. and Vaidyanathan, K. (2005b) 'Mosquitoes of the mangrove forests of India: Part 2--Sundarbans, West Bengal', Journal of the American Mosquito Control Association, 21(2), pp. 136–138. doi:10.2987/8756-971X(2005)21[136:MOTMFO]2.0.CO;2.

Rajavel, A.R., Natarajan, R. and Vaidyanathan, K. (2006a) 'Mosquitoes of the mangrove forests of India: Part 4--Coringa, Andhra Pradesh', Journal of the American Mosquito Control Association, 22(4), pp. 579–581. doi:10.2987/8756-971X(2006)22[579:MOTMFO]2.0.CO;2.

Rajavel, A.R., Natarajan, R. and Vaidyanathan, K. (2006b) 'Mosquitoes of the mangrove forests of India: Part 6--Kundapur, Karnataka and Kannur, Kerala', Journal of the American Mosquito Control Association, 22(4), pp. 582–585. doi:10.2987/8756-971X(2006)22[582:MOTMFO]2.0.CO;2.

Rajendran, R. et al. (2003) 'Longitudinal studies in South Indian villages on Japanese encephalitis virus infection in mosquitoes and seroconversion in goats.', Tropical medicine & international health : TM & IH, 8(2), pp. 174–81.

Rajeevan, M. et al. (2012) 'Northeast monsoon over India: variability and prediction', Meteorological Applications, 19(2), pp. 226–236. doi.org/10.1002/met.1322.

Raju, H.K. et al. (2016) 'A Preliminary Study to Forecast Japanese Encephalitis Vector Abundance in Paddy Growing Area, with the Aid of Radar Satellite Images', Vector-Borne and Zoonotic Diseases, 16(2), pp. 117–123. doi:10.1089/vbz.2014.1757.

Raju, H.K. et al. (2018) 'Validating the Association of Japanese Encephalitis Vector Abundance with Paddy Growth, Using MODIS Data', Vector-Borne and Zoonotic Diseases, 18(10), pp. 560–562. doi:10.1089/vbz.2017.2250.

Ramasamy, R. and Surendran, S.N. (2012) 'Global Climate Change and Its Potential Impact on Disease Transmission by Salinity-Tolerant Mosquito Vectors in Coastal Zones', Frontiers in Physiology, 3, p. 198. doi:10.3389/fphys.2012.00198.

Ramesh, D. et al. (2015) 'Seasonal abundance & role of predominant Japanese encephalitis vectors Culex tritaeniorhynchus & Cx. gelidus Theobald in Cuddalore district, Tamil Nadu',

The Indian Journal of Medical Research, 142(Suppl 1), pp. S23–S29. doi:10.4103/0971-5916.176607.

Ramli, N.S. et al. (2022) 'Seroepidemiological Studies on Japanese Encephalitis: A Systematic Review', Oman Medical Journal, 37(2), p. e366. doi.org/10.5001/omj.2021.86.

Randolph, S.E. and Dobson, A.D.M. (2012) 'Pangloss revisited: a critique of the dilution effect and the biodiversity-buffers-disease paradigm', Parasitology, 139(07), pp. 847–863. doi:10.1017/S0031182012000200.

Rathnayake, C., Joshi, S. and Cerratto-Pargman, T. (2020) 'Mapping the current landscape of citizen-driven environmental monitoring: a systematic literature review', Sustainability: Science, Practice and Policy, 16(1), pp. 326–334. doi:10.1080/15487733.2020.1829845.

Rattanavong, S. et al. (2020) 'Spatial epidemiology of Japanese encephalitis virus and other infections of the central nervous system infections in Lao PDR (2003–2011): A retrospective analysis', PLOS Neglected Tropical Diseases, 14(5), p. e0008333. doi:10.1371/journal.pntd.0008333.

Ravindranath, N.H. et al. (2011) 'Climate change vulnerability profiles for North East India', Current Science, 101(3), pp. 384–394.

Redding, D.W. et al. (2016) 'Environmental-mechanistic modelling of the impact of global change on human zoonotic disease emergence: a case study of Lassa fever', Methods in Ecology and Evolution, 7(6), pp. 646–655. doi:10.1111/2041-210X.12549.

Redding, D.W., Lucas, T.C.D., Blackburn, T.M. and Jones, Kate E (2017a) 'Evaluating Bayesian spatial methods for modelling species distributions with clumped and restricted occurrence data', PLoS ONE, 12(11), pp. 1–13. doi:10.1371/journal.pone.0187602.

Redding, D.W., Tiedt, Sonia, Iacono, G.L., Bett, Bernard and Jones, K.E. (2017b) 'Spatial, seasonal and climatic predictive models of Rift Valley fever disease across Africa', Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 372(1725). doi:10.1098/rstb.2016.0165.

Redding, D.W. et al. (2019) 'Impacts of environmental and socio-economic factors on emergence and epidemic potential of Ebola in Africa', Nature Communications, 10, p. 4531. doi:10.1038/s41467-019-12499-6.

Reis, R.B. et al. (2008) 'Impact of environment and social gradient on Leptospira infection in urban slums', PLoS neglected tropical diseases, 2(4), p. e228. doi:10.1371/journal.pntd.0000228.

Reisen, W., Aslamkhan, M. and Basia, R. (1976) 'The effects of climatic patterns and agricultural practices on the population dynamics of Culex tritaeniorhynchus in Asia', Southeast Asian J Trop Med Public Health, 7(61–71).

Reisen, W.K., Fang, Y. and Martinez, V.M. (2006) 'Effects of Temperature on the Transmission of West Nile Virus by Culex tarsalis (Diptera: Culicidae)', J. Med. Entomol, 43(2), pp. 309–317. doi:10.1603/0022-2585(2006)043[0309:EOTOTT]2.0.CO;2.

Reiter, P. (2001) 'Climate Change and Mosquito-Borne Disease', Environmental Health Perspectives, 109, pp. 141–161.

Reiter, P. et al. (2003) 'Texas Lifestyle Limits Transmission of Dengue Virus', Emerging Infectious Diseases, 9(1), pp. 86–89. doi:10.3201/eid0901.020220.

Riahi, K. et al. (2017) 'The Shared Socioeconomic Pathways and their energy, land use, and greenhouse gas emissions implications: An overview', Global Environmental Change, 42, pp. 153–168. doi:10.1016/j.gloenvcha.2016.05.009.

Ribeiro, R. et al. (2019) 'Using imperfect data in predictive mapping of vectors: a regional example of Ixodes ricinus distribution', Parasites & Vectors, 12(1), p. 536. doi.org/10.1186/s13071-019-3784-1.

Richards, E.E. et al. (2010) 'The relationship between mosquito abundance and rice field density in the Republic of Korea', International Journal of Health Geographics, 9(1), p. 32. doi:10.1186/1476-072X-9-32.

Richardson, A.J., Taylor, I.R. and Growns, J.E. (2001) 'The Foraging Ecology of Egrets in Rice Fields in Southern New South Wales, Australia', Waterbirds: The International Journal of Waterbird Biology, 24(2), pp. 255–264. doi:10.2307/1522039.

Rinaldo, D. et al. (2021) 'The economic impact of schistosomiasis', Infectious Diseases of Poverty, 10(1), p. 134. doi.org/10.1186/s40249-021-00919-z.

Roberts, D.R. et al. (2017) 'Cross-validation strategies for data with temporal, spatial, hierarchical, or phylogenetic structure', Ecography, 40(8), pp. 913–929. doi:10.1111/ecog.02881.

Robertson, C. et al. (2013) 'Comparative Spatial Dynamics of Japanese Encephalitis and Acute Encephalitis Syndrome in Nepal', PLOS ONE, 8(7), p. e66168. doi:10.1371/journal.pone.0066168.

Roche, B. et al. (2013) 'The impact of community organization on vector-borne pathogens.', The American naturalist, 181(1), pp. 1–11. doi:10.1086/668591.

Rocklöv, J. and Dubrow, R. (2020) 'Climate change: an enduring challenge for vector-borne disease prevention and control', Nature Immunology, 21(5), pp. 479–483. doi:10.1038/s41590-020-0648-y.

Rohat, G. et al. (2020) 'Intersecting vulnerabilities: climatic and demographic contributions to future population exposure to Aedes-borne viruses in the United States', Environmental Research Letters, 15(8), p. 084046. doi.org/10.1088/1748-9326/ab9141.

Roiz, D. et al. (2014) 'Climatic effects on mosquito abundance in Mediterranean wetlands', Parasites & Vectors, 7(1), p. 333. doi:10.1186/1756-3305-7-333.

Romanelli, C. et al. (2015) Connecting global priorities: biodiversity and human health: a state of knowledge review. World Health Organization and Secretariat of the Convention on Biological Diversity, p. 344. doi.org/10.13140/RG.2.1.3679.6565

Roy, A. et al. (2015) 'Food Security in North-East Region of India — A State-wise Analysis', in Agricultural Economics Research Review. Analysis, Agricultural Economics Research Association (India).

RStudio Team (2020) RStudio: Integrated Development Environment for R. Boston, MA: RStudio, PBC. Available at: http://www.rstudio.com/.

Rue, H., Martino, S. and Chopin, N. (2009) 'Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations', Journal of the Royal Statistical Society: Series B (Statistical Methodology), 71(2), pp. 319–392. doi:10.1111/j.1467-9868.2008.00700.x.

Rueda Páramo, M.E., López Lastra, C.C. and García, J.J. (2015) 'Persistence and pathogenicity of a native isolate of Leptolegnia chapmanii against Aedes aegypti larvae in different anthropic environments', Biocontrol Science and Technology, 25(2), pp. 238–243. doi:10.1080/09583157.2014.967177.

Rund, S.S.C. et al. (2019) 'Rescuing troves of hidden ecological data to tackle emerging mosquito-borne diseases', Journal of the American Mosquito Control Association, 35(1), pp. 75–83. doi:10.2987/18-6781.1.

Russell, R.C. et al. (2009) 'Dengue and climate change in Australia: predictions for the future should incorporate knowledge from the past', Medical Journal of Australia, 190(5).

Russell, M.C. et al. (2022) 'Both consumptive and non-consumptive effects of predators impact mosquito populations and have implications for disease transmission', eLife. Edited by S.E. Cobey, C. Rutz, and A. Meadows, 11, p. e71503. doi:10.7554/eLife.71503.

Ryan, S.J. et al. (2015) 'Mapping Physiological Suitability Limits for Malaria in Africa Under Climate Change', 15(12), pp. 718–725. doi:10.1089/vbz.2015.1822.

Ryan, S.J., Carlson, Colin J., et al. (2019) 'Global expansion and redistribution of Aedes-borne virus transmission risk with climate change', PLOS Neglected Tropical Diseases, 13(3), p. e0007213. doi:10.1371/journal.pntd.0007213.

Sabesan, S., Raju Konuganti, H.K. and Perumal, V. (2008) 'Spatial Delimitation, Forecasting and Control of Japanese Encephalitis: India - A Case Study', The Open Parasitology Journal, 2(1), pp. 59–63. doi:10.2174/1874421400802010059.

Sachs, J. and Malaney, P. (2002) 'The economic and social burden of malaria', Nature, 415, p. 680.

SAGE Working Group on Japanese encephalitis vaccines (2014) Background Paper on Japanese Encephalitis Vacccines. SAGE Working Group on Japanese encephalitis vaccines. Available at: https://www.who.int/immunization/sage/meetings/2014/october/1_JE_Vaccine_Background_Paper.pdf (Accessed: 29 January 2021).

Saikia, A. (2017) Japanese encephalitis continues to kill in Assam despite immunisation against the virus, Scroll.in. Available at: https://scroll.in/pulse/845647/japanese-encephalitis%EF%BF%BEcontinues-to-kill-in-assam-despite-immunisation%EF%BF%BEagainst-the-virus (Accessed: 8 January 2023).

Sakamoto, R. et al. (2019) 'Flourishing Japanese Encephalitis, Associated with Global Warming and Urbanisation in Asia, Demands Widespread Integrated Vaccination Programmes', Annals of Global Health, 85(1), p. 111. doi.org/10.5334/aogh.2580.

Saker, L. et al. (2004) Globalization and infectious diseases: a review of the linkages. Geneva, Sw.

Salahi-Moghaddam, A. et al. (2017) 'Spatial changes in the distribution of malaria vectors during the past 5 decades in Iran', Acta Tropica, 166, pp. 45–53. doi:https://doi.org/10.1016/j.actatropica.2016.11.001.

Samaranayake, N., Limaye, S. and Wuthnow, J. (2016) Water Resource Competition in the Brahmaputra River Basin: China, India and Bangladesh. Arlington, VA: CNA Analysis and Solutions. Available at: https://www.cna.org/cna_files/pdf/cna-brahmaputra-study-2016.pdf (Accessed: 21 February 2022).

Samuel, P.P. et al. (2010) 'Temporal Variation in the Susceptibility of Culex tritaeniorhynchus (Diptera: Culicidae) to Japanese Encephalitis Virus in an Endemic Area of Tamil Nadu, South India', Vector-Borne and Zoonotic Diseases, 10(10), pp. 1003–1008. doi:10.1089/vbz.2009.0072.

Samuel, P.P. et al. (2016) 'Japanese Encephalitis vector abundance and infection frequency in Cuddalore District, Tamil Nadu, India: a five-year longitudinal study', Journal of Entomological and Acarological Research, 48(3), pp. 366–371. doi:10.4081/jear.2016.5630.

Samy, A.M. et al. (2016) 'Climate Change Influences on the Global Potential Distribution of the Mosquito Culex quinquefasciatus, Vector of West Nile Virus and Lymphatic Filariasis', Plos One, 11(10), p. e0163863. doi:10.1371/journal.pone.0163863.

Samy, A.M. et al. (2018) 'Mapping the potential distributions of etiological agent, vectors, and reservoirs of Japanese Encephalitis in Asia and Australia', Acta Tropica, 188, pp. 108–117. doi:10.1016/j.actatropica.2018.08.014.

Sarkar, A. et al. (2012) 'Influence of socio-economic status and environmental factors on serologically diagnosed Japanese encephalitis cases in the state of West Bengal, India during 2005-2010', Health, 4(1), pp. 6–12. doi:10.4236/health.2012.41002.

Sarkar, A. et al. (2013) 'Envelope protein gene based molecular characterization of Japanese encephalitis virus clinical isolates from West Bengal, India: a comparative approach with respect to SA14-14-2 live attenuated vaccine strain', BMC infectious diseases, 13, p. 368. doi:10.1186/1471-2334-13-368.

Sarma, N. et al. (2019) 'The Economic Burden of Malaria: Revisiting the Evidence', The American Journal of Tropical Medicine and Hygiene, 101(6), pp. 1405–1415. doi:10.4269/ajtmh.19-0386.

Scherer, W.F. et al. (1959) 'Ecologic Studies of Japanese Encephalitis Virus in Japan VI. Swine Infection', The American Society of Tropical Medicine and Hygiene, 8, pp. 698–706.

Scherer, W.F. and Buescher, E.L. (1959) 'Ecologic studies of Japanese encephalitis virus in Japan. I. Introduction', American Journal of Tropical Medicine and Hygiene, 8.

Scherer, W.F., Buescher, E.L. and McClure, H.E. (1959) 'Ecologic Studies of Japanese Encephalitis Virus in Japan V. Avian Factors', The American Society of Tropical Medicine and Hygiene, 8, pp. 689–697.

Schuh, A.J. et al. (2013) 'Phylogeography of Japanese Encephalitis Virus: Genotype Is Associated with Climate', PLoS Neglected Tropical Diseases, 7(8), p. e2411. doi.org/10.1371/journal.pntd.0002411.

Schuh, A.J. et al. (2014) 'Dynamics of the Emergence and Establishment of a Newly Dominant Genotype of Japanese Encephalitis Virus throughout Asia', Journal of Virology, 88(8), pp. 4522–4532. doi:10.1128/JVI.02686-13.

Seidahmed, O.M.E. et al. (2018) 'Patterns of Urban Housing Shape Dengue Distribution in Singapore at Neighborhood and Country Scales', GeoHealth, 2(1), pp. 54–67. doi:10.1002/2017GH000080.

Semenza, J.C. et al. (2016) 'Climate change projections of West Nile virus infections in Europe: implications for blood safety practices', Environmental Health. London. doi:10.1186/s12940-016-0105-4.

Service, M.W. (1991) 'Agricultural development and arthropod-borne diseases: a review.', Revista de Saude Publica, 25(3), pp. 165–178. doi:10.1590/S0034-89101991000300002.

Shah, H.A. et al. (2019) 'Agricultural land-uses consistently exacerbate infectious disease risks in Southeast Asia', Nature Communications, 10(1), p. 4299. doi:10.1038/s41467-019-12333-z.

Sharma, R. et al. (2012) 'Media scanning and verification system as a supplemental tool to disease outbreak detection & reporting at National Centre for Disease Control, Delhi', The Journal of Communicable Diseases, 44(1), pp. 9–14.

Shukla, R., Chakraborty, A. and Joshi, P.K. (2017) 'Vulnerability of agro-ecological zones in India under the earth system climate model scenarios', Mitigation and Adaptation Strategies for Global Change; Dordrecht, 22(3), pp. 399–425. doi.org.libproxy.ucl.ac.uk/10.1007/s11027-015-9677-5.

Simpson, D.P. et al. (2017) 'Penalising model component complexity: A principled, practical approach to constructing priors', Statistical Science, 32(1), pp. 1–28.

Singer, M. and Bulled, N. (2013) 'Interlocked infections: the health burdens of syndemics of neglected tropical diseases', Annals of Anthropological Practice, 36, pp. 328–345.

Singh, A. et al. (2015) 'A Japanese Encephalitis Vaccine From India Induces Durable and Cross-protective Immunity Against Temporally and Spatially Wide-ranging Global Field Strains', The Journal of Infectious Diseases, 212(5), pp. 715–725. doi.org/10.1093/infdis/jiv023.

Singh, B. et al. (2021) 'Growing Rice with Less Water: Improving Productivity by Decreasing Water Demand', in Ali, J. and Wani, S.H. (eds) Rice Improvement: Physiological, Molecular Breeding and Genetic Perspectives. Cham: Springer International Publishing, pp. 147–170. doi:10.1007/978-3-030-66530-2_5.

Singh, H., Singh, N. and Mall, R.K. (2020) 'Japanese Encephalitis and Associated Environmental Risk Factors in Eastern Uttar Pradesh: A time series analysis from 2001 to 2016', Acta Tropica, 212, p. 105701. doi:10.1016/j.actatropica.2020.105701.

Singh, L.S. et al. (2019) 'A descriptive study on prevalence pattern of Japanese encephalitis in State of Manipur', Indian Journal of Medical Microbiology, 37(2), pp. 235–240. doi:10.4103/ijmm.IJMM_18_180.

Singh, R.K. et al. (2020) 'Hydrodynamic modeling for identifying flood vulnerability zones in lower Damodar river of eastern India', Ain Shams Engineering Journal, 11(4), pp. 1035–1046. doi:10.1016/j.asej.2020.01.011.

Singha, M. et al. (2019) 'High resolution paddy rice maps in cloud-prone Bangladesh and Northeast India using Sentinel-1 data', Scientific Data, 6(1), p. 26. doi:10.1038/s41597-019-0036-3.

Sinka, M.E. et al. (2021) 'HumBug – An Acoustic Mosquito Monitoring Tool for use on budget smartphones', Methods in Ecology and Evolution, 12(10), pp. 1848–1859. doi:10.1111/2041-210X.13663.

Siraj, A. et al. (2014) 'Altitudinal changes in malaria incidence in highlands of Ethiopia and Colombia', Science, 343(March), pp. 1154–1158. doi:10.1126/science.1244325.

Slatculescu, A.M. et al. (2020) 'Species distribution models for the eastern blacklegged tick, Ixodes scapularis, and the Lyme disease pathogen, Borrelia burgdorferi, in Ontario, Canada', PLOS ONE, 15(9), p. e0238126. doi.org/10.1371/journal.pone.0238126.

Smith, D.L., Dushoff, J. and McKenzie, F.E. (2004) 'The Risk of a Mosquito-Borne Infection in a Heterogeneous Environment', PLoS Biology. Edited by Andy P. Dobson, 2(11), p. e368. doi:10.1371/journal.pbio.0020368.

Smith, G.C. et al. (2008) 'What is the future of wildlife rabies control in Europe?', Developments in Biologicals, 131, pp. 283–289.

Smith, K.F. et al. (2014) 'Global rise in human infectious disease outbreaks', Journal of The Royal Society Interface, 11(101), p. 20140950. doi:10.1098/rsif.2014.0950.

SoIB (2020a) State of India's Birds factsheet: Black-crowned Night Heron Nycticorax nycticorax, State of India's Birds. Available at: https://www.stateofindiasbirds.in/species/bcnher/ (Accessed: 4 March 2022).

SoIB (2020b) State of India's Birds factsheet: Cattle Egret Bubulcus ibis, State of India's Birds. Available at: https://www.stateofindiasbirds.in/species/categr/ (Accessed: 4 March 2022).

SoIB (2020c) State of India's Birds factsheet: Indian Pond Heron Ardeola grayii, State of India's Birds. Available at: https://www.stateofindiasbirds.in/species/inpher1/ (Accessed: 4 March 2022).

SoIB (2020d) State of India's Birds factsheet: Intermediate Egret Ardea intermedia, State of India's Birds. Available at: https://www.stateofindiasbirds.in/species/integr/ (Accessed: 4 March 2022).

SoIB (2020e) State of India's Birds factsheet: Little Egret Egretta garzetta, State of India's Birds. Available at: https://www.stateofindiasbirds.in/species/litegr/ (Accessed: 4 March 2022).

Sokolow, S.H. et al. (2015) 'Reduced transmission of human schistosomiasis after restoration of a native river prawn that preys on the snail intermediate host', Proceedings of the National Academy of Sciences, 112(31), pp. 9650–9655. doi:10.1073/pnas.1502651112.

Sokolow, S.H. et al. (2017) 'Nearly 400 million people are at higher risk of schistosomiasis because dams block the migration of snail-eating river prawns', Philosophical Transactions of the Royal Society B: Biological Sciences, 372(1722). doi:10.1098/rstb.2016.0127.

Sokolow, S.H. et al. (2022) 'Ecological and socioeconomic factors associated with the human burden of environmentally mediated pathogens: a global analysis', The Lancet Planetary Health, 6(11), pp. e870–e879. doi.org/10.1016/S2542-5196(22)00248-0.

Solomon, T. et al. (2000) 'Japanese encephalitis', Journal of Neurosurgery and Psychiatry, 68, pp. 405–415.

Solomon, T. and Vaughn, D.W. (2002) 'Pathogenesis and clinical features of Japanese encephalitis and West Nile virus infections', Current Topics in Microbiology and Immunology, 267, pp. 171–194. doi.org/10.1007/978-3-642-59403-8_9.

Solomon, T. (2006) 'Control of Japanese encephalitis-within our grasp?', New England Journal of Medicine, 355. doi:10.1056/NEJMp058263.

Song, X.-P. et al. (2018) 'Global land change from 1982 to 2016', Nature [Preprint]. doi:10.1038/s41586-018-0411-9.

Soti, V. et al. (2012) 'Combining hydrology and mosquito population models to identify the drivers of Rift Valley fever emergence in semi-arid regions of West Africa', PLoS Negl Trop Dis, 6(8), p. e1795. doi:10.1371/journal.pntd.0001795.

Sousa, L.B. et al. (2022) 'Methodological Diversity in Citizen Science Mosquito Surveillance: A Scoping Review', Citizen Science: Theory and Practice, 7(1), p. 8. doi:10.5334/cstp.469.

Srivastava, V.K., Singh, A. and Thapar, B.R. (2008) 'Field evaluation of malathion fogging against Japanese encephalitis vector, Culex tritaeniorhynchus', Journal of Vector Borne Diseases, 45(3), pp. 249–250.

Stamatis, D.H. (2014) Introduction to Risk and Failures: Tools and Methodologies. CRC Press. doi:10.1201/b16855.

Stanaway, J.D. et al. (2016) 'The global burden of dengue: an analysis from the Global Burden of Disease Study 2013', The Lancet Infectious Diseases, 16(6), pp. 712–723. doi:10.1016/S1473-3099(16)00026-8.

Steffen, W. et al. (2011) 'The anthropocene: Conceptual and historical perspectives', Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences, 369(1938), pp. 842–867. doi:10.1098/rsta.2010.0327.

Steffen, W. et al. (2015) 'Planetary boundaries: guiding human development on a changing planet.', Science (New York, N.Y.), 347(6223), p. 1259855. doi:10.1126/science.1259855.

Stewart Ibarra, A.M. et al. (2013) 'Dengue Vector Dynamics (Aedes aegypti) Influenced by Climate and Social Factors in Ecuador: Implications for Targeted Control', PLOS ONE, 8(11), p. e78263.

Stoddard, S.T. et al. (2009) 'The Role of Human Movement in the Transmission of Vector-Borne Pathogens', PLOS Neglected Tropical Diseases, 3(7), p. e481. doi.org/10.1371/journal.pntd.0000481.

Stratton, L. et al. (2008) 'The persistent problem of malaria: Addressing the fundamental causes of a global killer', Social Science and Medicine, 67(5), pp. 854–862. doi:10.1016/j.socscimed.2008.05.013.

Sudjaritruk, T. et al. (2022) 'Seroepidemiological study of Japanese encephalitis virus in Chiang Mai: Immunity and susceptibility 28 years after introduction of a vaccination programme', PLOS Neglected Tropical Diseases, 16(8), p. e0010674. doi.org/10.1371/journal.pntd.0010674.

Sunwoo, J.-S. et al. (2016) 'Reemergence of Japanese Encephalitis in South Korea, 2010-2015', Emerging Infectious Diseases, 22(10), pp. 1841–1843. doi.org/10.3201/eid2210.160288.

Suryanarayana Murty, U. et al. (2002) 'Seasonal prevalence of Culex vishnui subgroup, the major vectors of Japanese encephalitis virus in an endemic district of Andhra Pradesh, India.', Journal of the American Mosquito Control Association, 18(4), pp. 290–3.

Suryanarayana Murty, U., Srinivasa Rao, M. and Arunachalam, N. (2010) 'The effects of climatic factors on the distribution and abundance of Japanese encephalitis vectors in Kurnool district of Andhra Pradesh, India', Journal of Vector Borne Diseases, (47), pp. 26–32.

Sutherst, R.W. (2004) 'Global Change and Human Vulnerability to Vector-Borne Diseases Global Change and Human Vulnerability to Vector-Borne Diseases', Clinical Microbiology Reviews, 17(1), pp. 136–173. doi:10.1128/CMR.17.1.136.

Swei, A. et al. (2020) 'Patterns, Drivers, and Challenges of Vector-Borne Disease Emergence', Vector Borne and Zoonotic Diseases, 20(3), pp. 159–170. doi:10.1089/vbz.2018.2432.

Tabachnick, W.J. (2010) 'Challenges in predicting climate and environmental effects on vector-borne disease episystems in a changing world', The Journal of Experimental Biology, 213(6), pp. 946–954. doi:10.1242/jeb.037564.

Tandale, B.V. et al. (2018) 'Effectiveness of Japanese encephalitis SA 14-14-2 live attenuated vaccine among Indian children: Retrospective 1:4 matched case-control study', Journal of Infection and Public Health, 11(5), pp. 713–719. doi.org/10.1016/j.jiph.2018.04.011.

Tatem, A.J. et al. (2013) 'Urbanization and the global malaria recession', Malaria Journal, 12, p. 133.

Tennant, W.S.D. et al. (2021) 'Modelling the persistence and control of Rift Valley fever virus in a spatially heterogeneous landscape', Nature Communications, 12(1), p. 5593. doi:10.1038/s41467-021-25833-8.

The National Center for Atmospheric Research (2020) The climate data guide: Palmer drought severity index (PDSI). Available at: https://climatedataguide.ucar.edu/climate-data/palmer-drought-severity-index-pdsi (Accessed: 18 January 2022).

The World Bank (2016) The United Nations Population Divisions World Urbanization Prospects: Urban population (% of total). Available at: https://data.worldbank.org/indicator/SP.URB.TOTL.IN.ZS?view=chart (Accessed: 31 August 2017).

Thenmozhi, V. et al. (2013) 'Japanese encephalitis virus isolation from mosquitoes during an outbreak in 2011 in Alappuzha district, Kerala', Journal of Vector Borne Diseases, 50(3), pp. 229–231.

Thomas, S.M. et al. (2014) 'Implementing cargo movement into climate based risk assessment of vector-borne diseases', International Journal of Environmental Research and Public Health, 11(3), pp. 3360–3374. doi:10.3390/ijerph110303360.

Thumbi, S.M. et al. (2019) 'Mobile phone-based surveillance for animal disease in rural communities: implications for detection of zoonoses spillover', Philosophical Transactions of

the Royal Society B: Biological Sciences, 374(1782), p. 20190020. doi:10.1098/rstb.2019.0020.

Tian, H.Y. et al. (2015) 'How environmental conditions impact mosquito ecology and Japanese encephalitis: An eco-epidemiological approach', Environment International, 79, pp. 17–24. doi:10.1016/j.envint.2015.03.002.

Tjaden, N.B. et al. (2013) 'Extrinsic Incubation Period of Dengue: Knowledge, Backlog, and Applications of Temperature Dependence', PLOS Neglected Tropical Diseases, 7(6), p. e2207.

Tjaden, N.B. et al. (2017) 'Modelling the effects of global climate change on Chikungunya transmission in the 21st century', Scientific Reports, 7(1), p. 3813. doi:10.1038/s41598-017-03566-3.

Tjaden, N.B. et al. (2018) 'Mosquito-Borne Diseases: Advances in Modelling Climate-Change Impacts', Trends in Parasitology, 34(3), pp. 227–245. doi:10.1016/j.pt.2017.11.006.

Tricco, A.C. et al. (2015) 'A scoping review of rapid review methods', BMC Medicine, 13(1), p. 224. doi.org/10.1186/s12916-015-0465-6.

Trienekens, S.C.M. et al. (2022) 'Variation in water contact behaviour and risk of Schistosoma mansoni (re)infection among Ugandan school-aged children in an area with persistent high endemicity', Parasites & Vectors, 15(1), p. 15. doi.org/10.1186/s13071-021-05121-6.

Tolle, M.A. (2009) 'Mosquito-borne Diseases', Current Problems in Pediatric and Adolescent Health Care, 39(4), pp. 97–140. doi:10.1016/j.cppeds.2009.01.001.

Tompkins, A.M. and Caporaso, L. (2016) 'Assessment of malaria transmission changes in Africa, due to the climate impact of land use change using Coupled Model Intercomparison Project Phase 5 earth system models', Geospatial Health, 11(1 Suppl), p. 380. doi:10.4081/gh.2016.380.

Tompkins, A.M. and Ermert, V. (2013) 'A regional-scale, high resolution dynamical malaria model that accounts for population density, climate and surface hydrology', Malaria Journal, 12(1), p. 65. doi:10.1186/1475-2875-12-65.

Trájer, A. et al. (2014) 'Seasonality and geographical occurrence of West Nile fever and distribution of Asian tiger mosquito', Idojaras, 118(1), pp. 19–40.

Trawinski, P.R. and Mackay, D.S. (2010) 'Identification of Environmental Covariates of West Nile Virus Vector Mosquito Population Abundance', Vector-Borne and Zoonotic Diseases, 10(5), pp. 515–526. doi:10.1089/vbz.2008.0063.

Tu, T. et al. (2021) 'Association between meteorological factors and the prevalence dynamics of Japanese encephalitis', PLOS ONE, 16(3), p. e0247980. doi:10.1371/journal.pone.0247980.

Turtle, L. and Solomon, T. (2018) 'Japanese encephalitis — the prospects for new treatments', Nature Reviews Neurology, 14(5), pp. 298–313. doi:10.1038/nrneurol.2018.30.

Tyagi, B. et al. (2016) 'Determination of critical density and vectorial capacity for Culex tritaeniorhynchus Giles, 1901 (Diptera: Culicidae), the primary vector for Japanese encephalitis in southern India', International Journal of Mosquito Research, 3(2), pp. 39–46.

UN Global Pulse (2012) Big Data for Development: Opportunities and Challenges. Available at: https://www.unglobalpulse.org/wp-content/uploads/2012/05/BigDataforDevelopment-UNGlobalPulseMay2012.pdf (Accessed: 9 March 2022).

UNDP and OPHI (2021) Global Multidimensional Poverty Index 2021 – Unmasking disparities by ethnicity, caste and gender. United Nations Development Programme and Oxford Poverty and Human Development Initiative. Available at: https://ophi.org.uk/wp-content/uploads/UNDP_OPHI_GMPI_2021_Report_Unmasking.pdf.

UNECE (2021) Water-food-energy-ecosystem nexus, UNECE. Available at: https://unece.org/environment-policy/water/areas-work-convention/water-food-energy-ecosystem-nexus (Accessed: 7 March 2022).

United Nations, Department of Economic and Social Affairs, P.D. (2014) World Urbanization Prospects: The 2014 Revision, Highlights (ST/ESA/SER.A/352). New York.

Urfi, A.J. (2011) 'Climate change and its impacts on Indian birds: monsoon phenology and monitoring heronry birds', Current Science, 101(9), pp. 1140–1142.

Utzinger, J. and Tanner, M. (2013) 'Socioeconomic development to fight malaria, and beyond', The Lancet, 382(9896), pp. 920–922. doi:10.1016/S0140-6736(13)61211-8.

Valavi, R. et al. (2019) 'blockCV: An r package for generating spatially or environmentally separated folds for k-fold cross-validation of species distribution models', Methods in Ecology and Evolution, 10(2), pp. 225–232. doi:10.1111/2041-210X.13107.

Valdez, L D et al. (2017) 'Effects of rainfall on Culex mosquito population dynamics', Journal of Theoretical Biology, 421, pp. 28–38. doi:https://doi.org/10.1016/j.jtbi.2017.03.024.

Vannice, K.S. et al. (2021) 'The future of Japanese encephalitis vaccination: expert recommendations for achieving and maintaining optimal JE control', npj Vaccines, 6(1), pp. 1–9. doi:10.1038/s41541-021-00338-z.

Vanwambeke, S.O. and Schimit, P.H.T. (2021) 'Tick bite risk resulting from spatially heterogeneous hazard, exposure and coping capacity', Ecological Complexity, 48, p. 100967. doi.org/10.1016/j.ecocom.2021.100967.

Vasconcelos, D. et al. (2019) 'LOCOMOBIS: a low-cost acoustic-based sensing system to monitor and classify mosquitoes', in 2019 16th IEEE Annual Consumer Communications Networking Conference (CCNC). 2019 16th IEEE Annual Consumer Communications Networking Conference (CCNC), pp. 1–6. doi:10.1109/CCNC.2019.8651767.

Vasconcelos, P.F.C. et al. (2001) 'Inadequate management of natural ecosystem in the Brazilian Amazon region results in the emergence and reemergence of arboviruses', Cadernos de Saúde Pública, 17(suppl), pp. S155–S164. doi:10.1590/S0102-311X2001000700025.

Vashishtha, V.M. and Ramachandran, V. (2015) 'Vaccination Policy for Japanese Encephalitis in India: Tread with Caution!', INDIAN PEDIATRICS, 52, p. 3.

Vaughn, D.W. and Hoke, C.H. (1992) 'The Epidemiology of Japanese Encephalitis: Prospects for Prevention', Epidemiologic Reviews, 14(1), pp. 197–221. doi:10.1093/oxfordjournals.epirev.a036087.

Verhoef, F.A., Venter, G.J. and Weldon, C.W. (2014) 'Thermal limits of two biting midges, Culicoides imicola Kieffer and C. bolitinos Meiswinkel (Diptera: Ceratopogonidae)', Parasites & Vectors, 7, p. 384. doi.org/10.1186/1756-3305-7-384.

Vittor, A.Y. et al. (2009) 'Linking Deforestation to Malaria in the Amazon: Characterization of the Breeding Habitat of the Principal Malaria Vector, Anopheles darlingi', The American journal of tropical medicine and hygiene, 81(1), pp. 5–12.

van Vuuren, D.P. et al. (2011) 'The representative concentration pathways: an overview', Climatic Change, 109(1), p. 5. doi:10.1007/s10584-011-0148-z.

Vythilingam, I. et al. (1997) 'Abundance, parity, and Japanese encephalitis virus infection of mosquitoes (Diptera:Culicidae) in Sepang District, Malaysia.', Journal of medical entomology, 34(3), pp. 257–262.

Wada, Y. et al. (1975) 'Ecology of Japanese encephalitis virus in Japan. II. The population of vector mosquitoes and the epidemic of Japanese encephalitis', Tropical Medicine, 17(3), pp. 111–127.

Walker, P.G.T. et al. (2020) 'The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries', Science, 369(6502), pp. 413–422. doi:10.1126/science.abc0035.

Walsh, A.S. et al. (2008) 'Predicting seasonal abundance of mosquitoes based on off-season meteorological conditions', Environmental and Ecological Statistics, 15(3), pp. 279–291. doi:10.1007/s10651-007-0056-6.

Walsh, M.G. et al. (2021) 'High risk landscapes of Japanese encephalitis virus outbreaks in India converge on wetlands, rainfed agriculture, wild Ardeidae, and domestic pigs'. medRxiv, p. 2021.09.07.21263238. doi:10.1101/2021.09.07.21263238.

Wang, L. et al. (2014) 'The role of environmental factors in the spatial distribution of Japanese encephalitis in mainland China', Environment International, 73, pp. 1–9. doi:10.1016/j.envint.2014.07.004.

Wangchuk, S. et al. (2020) 'Japanese Encephalitis Virus as Cause of Acute Encephalitis, Bhutan', Emerging Infectious Diseases, 26(9). doi:10.3201/eid2609.200620.

Warren, R. et al. (2018) 'The projected effect on insects, vertebrates, and plants of limiting global warming to 1.5°C rather than 2°C', Science, 360(6390), pp. 791–795. doi:10.1126/science.aar3646.

Washburne, A.D. et al. (2019) 'Percolation models of pathogen spillover', Philosophical Transactions of the Royal Society B: Biological Sciences, 374(1782), p. 20180331. doi:10.1098/rstb.2018.0331.

Watts, N. et al. (2017) 'The Lancet Countdown on health and climate change: From 25 years of inaction to a global transformation for public health', The Lancet, 6736(17). doi:10.1016/S0140-6736(17)32464-9.

Watts, N. et al. (2021) 'The 2020 report of The Lancet Countdown on health and climate change: responding to converging crises', The Lancet, 397(10269), pp. 129–170. doi:10.1016/S0140-6736(20)32290-X.

Waugh, C., Lam, S.S. and Sonne, C. (2020) 'One Health or Planetary Health for pandemic prevention?', The Lancet, 396(10266), p. 1882. doi:10.1016/S0140-6736(20)32387-4.

Weaver, S.C. (2013) 'Urbanization and geographic expansion of zoonotic arboviral diseases: Mechanisms and potential strategies for prevention', Trends in Microbiology, 21(8), pp. 360–363. doi:10.1016/j.tim.2013.03.003.

Weaver, S.C. and Reisen, W.K. (2010) 'Present and future arboviral threats', Antiviral Research, 85(2), pp. 328–345. doi:10.1016/j.antiviral.2009.10.008.

Wesolowski, A. et al. (2015) 'Impact of human mobility on the emergence of dengue epidemics in Pakistan', PNAS, 112(38), pp. 11887–11892. doi:10.1073/pnas.1504964112.

Westbrook, C.J. et al. (2010) 'Larval environmental temperature and the susceptibility of Aedes albopictus Skuse (Diptera: Culicidae) to Chikungunya virus.', Vector borne and zoonotic diseases, 10(3), pp. 241–247. doi:10.1089/vbz.2009.0035.

White, S.M. et al. (2017) 'Mechanistic model for predicting the seasonal abundance of Culicoides biting midges and the impacts of insecticide control', Parasites & Vectors, 10(1), p. 162. doi:10.1186/s13071-017-2097-5.

Whitmee, S. et al. (2015) 'Safeguarding human health in the Anthropocene epoch: Report of the Rockefeller Foundation-Lancet Commission on planetary health', The Lancet, 386(10007), pp. 1973–2028. doi:10.1016/S0140-6736(15)60901-1.

WHO (2010) 'First WHO report on neglected tropical diseases: working to overcome the global impact of neglected tropical diseases', World Health Organization, pp. 1–184. doi:10.1177/1757913912449575.

WHO (2011) mHealth: new horizons for health through mobile technologies. Geneva, Switzerland: World Health Organization. Available at: https://www.who.int/goe/publications/goe_mhealth_web.pdf.

WHO (2012) 'Global Strategy for Dengue Prevention and Control 2012–2020', World Health Organiszation, p. 43. doi:/entity/denguecontrol/9789241504034/en/index.html.

WHO (2014) A global brief on vector-borne diseases. Geneva, Sw.

WHO (2015a) Japanese encephalitis. Available at:
http://www.who.int/mediacentre/factsheets/fs386/en/ (Accessed: 4 September 2017).

WHO (2015b) 'Japanese Encephalitis Vaccines: WHO position paper', Weekly
Epidemiological Record, 90, pp. 69–87.

WHO (2017) Global vector control response 2017–2030. License: CC BY-NC-SA 3.0 IGO.
Geneva: World Health Organization. Available at:
https://apps.who.int/iris/bitstream/handle/10665/259205/9789241512978-
eng.pdf;jsessionid=5E3751A18758EB696D0C57C7DA7F7093?sequence=1.

WHO (2020a) Ending the neglect to attain the Sustainable Development Goals: a road map
for neglected tropical diseases 2021–2030. Licence: CC BY-NC-SA 3.0 IGO. Geneva,
Switzerland: World Health Organization. Available at:
https://apps.who.int/iris/handle/10665/346561.

WHO (2020b) Global Health Expenditure Database. Available at:
https://apps.who.int/nha/database/country_profile/Index/en (Accessed: 10 February 2022).

WHO (2021) World malaria report 2021. Licence: CC BY-NC-SA 3.0 IGO. Geneva,
Switzerland: World Health Organization. Available at: https://www.who.int/publications-detail-
redirect/9789240040496 (Accessed: 30 December 2021).

WHO, FAO and OIE (2019) Taking a Multisectoral, One Health Approach: A Tripartite Guide
to Addressing Zoonotic Diseases in Countries. Geneva, Switzerland: World Health
Organization (WHO), Food and Agriculture Organization of the United Nations (FAO) and
World Organisation for Animal Health (OIE),. Available at:
https://www.oie.int/app/uploads/2021/03/en-tripartitezoonosesguide-webversion.pdf.

WHO in collaboration with FAO, UNEP, and U. (1996) 'Agricultural Development and
Vector-borne Diseases Training and Information Materials on Vector Biology and Control'.

Wilcox, B. a and Gubler, D.J. (2005) 'Disease ecology and the global emergence of zoonotic
pathogens.', Environmental health and preventive medicine, 10(5), pp. 263–272.
doi:10.1007/BF02897701.

Williams, C.R. et al. (2014) 'Bionomic response of Aedes aegypti to two future climate change scenarios in far north Queensland, Australia: implications for dengue outbreaks', Parasites & Vectors, 7(1), p. 447. doi:10.1186/1756-3305-7-447.

Williams, C.R. et al. (2016) 'Projections of increased and decreased dengue incidence under climate change', Epidemiology and Infection, 144(14), pp. 3091–3100. doi:10.1017/S095026881600162X.

Williams, H.W. et al. (2015) 'Climate suitability for European ticks: assessing species distribution models against null models and projection under AR5 climate', Parasites & Vectors, 8(1), p. 440. doi.org/10.1186/s13071-015-1046-4.

Willmott, C. and Matsuura, K. (2005) 'Advantages of the mean absolute error (MAE) over the root mean square error (RMSE) in assessing average model performance', Climate Research, 30, pp. 79–82. doi:10.3354/cr030079.

Wong, M.C. et al. (2020) 'The potential impact of vulnerability and coping capacity on the pandemic control of COVID-19', Journal of Infection, 81(5), pp. 816–846. doi.org/10.1016/j.jinf.2020.05.060.

Wood, C.L. et al. (2017) 'Human infectious disease burdens decrease with urbanization but not with biodiversity', Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 372, p. 20160122. doi:10.1016/S0140-6736(12)61689-4.

World Health Organization, Convention on Biological Diversity, and United Nations Environment Programme (2015) Connecting global priorities: biodiversity and human health: a state of knowledge review. Available at: http://apps.who.int/iris/bitstream/10665/174012/1/9789241508537_eng.pdf?ua=1 (Accessed: 28 March 2020).

World Health Organization and Department of Control of Neglected Tropical Diseases (2017) Integrating neglected tropical diseases into global health and development: fourth WHO report on neglected tropical diseases. Available at: http://www.who.int/neglected_diseases/resources/9789241565448/en/.

Xu, C. et al. (2022) 'A Bibliometric Analysis of Global Research on Japanese Encephalitis From 1934 to 2020', Frontiers in Cellular and Infection Microbiology, 12, p. 833701. doi:10.3389/fcimb.2022.833701.

Yadav, R., Sharma, V. and Chand, S. (1997) 'Mosquito breeding and resting in treeholes in a forest ecosystem in Orissa.', Indian Journal of Malariology [Preprint].

Ye, X. et al. (2023) 'Associations of socioeconomic status with infectious diseases mediated by lifestyle, environmental pollution and chronic comorbidities: a comprehensive evaluation based on UK Biobank', Infectious Diseases of Poverty, 12(1), p. 5. doi.org/10.1186/s40249-023-01056-5.

Yee, D.A., Ezeakacha, N.F. and Abbott, K.C. (2017) 'The interactive effects of photoperiod and future climate change may have negative consequences for a wide-spread invasive insect', Oikos, 126(1), pp. 40–51. doi:10.1111/oik.03635.

Yen, N.T. et al. (2010) 'Surveillance for Japanese Encephalitis in Vietnam, 1998–2007', The American Journal of Tropical Medicine and Hygiene, 83(4), pp. 816–819. doi.org/10.4269/ajtmh.2010.10-0262.

Zabel, F. et al. (2019) 'Global impacts of future cropland expansion and intensification on agricultural markets and biodiversity', Nature Communications, 10(1), p. 2844. doi:10.1038/s41467-019-10775-z.

Zhang, G. et al. (2017) 'Spatiotemporal patterns of paddy rice croplands in China and India from 2000 to 2015', Science of The Total Environment, 579, pp. 82–92. doi:10.1016/j.scitotenv.2016.10.223.

Appendices

Appendix 1: Supplementary figures and data for Chapter 2

This appendix provides supplementary figures, tables and information on data sources for the analyses conducted in Chapter 2, 'The impact of global change on mosquito-borne disease'. The items contained in this appendix are:

Text S2.1. Search strategy and selection criteria.

Text S2.2. Glossary.

Table S2.1. Results of rapid review of modelling studies published from 2014- March 2018, that investigated the impact of climate change on mosquito-borne disease.

Text S2.1: Search strategy and selection criteria

I searched PubMed and Web of Science, for all papers from 1st January 2014 to 28th March 2018 inclusive to reflect the field since the publication of the WHO published 'A global brief on vector-borne diseases' in 2014 which called for further research (WHO 2014). Search terms were related to models of human mosquito-borne diseases and climate change: ("mosquito*" or "mosquito-borne disease*" or "mosquito borne disease*") AND ("climate chang*" or "climat* change*" or "climat* warm*" or "chang* climat*") AND ("model*" or "modelling"). I excluded treatment papers, reviews, case studies and surveillance reports and focused on modelling studies that evaluated the effect of climate change on mosquito borne diseases and their vectors. Climate change was defined as an alteration (either observed or projected) to climatic parameters and studies were included in the analysis if they considered the effects of climate change over several decades rather than within-decade timescales.

Text S2.2: Glossary

Mosquito-borne disease risk: the probability that the simultaneous presence of an infected host and competent vector may impact a susceptible population (Bergquist, Stensgaard and Rinaldi, 2018).

Correlative models of MBD: use statistical approaches to identify correlative associations of disease risk to a suite of explanatory variables such as environmental or socioeconomic conditions.

Mechanistic models of MBD: make explicit assumptions about the biological or environmental processes that drive disease risk.

Table S2.1. Results of rapid review of modelling studies published from 2014- March 2018, that investigated the impact of climate change on mosquito-borne disease.

The table shows the spatial scale of the study, the disease and mosquito vectors, the type of model and projection and, the climatic parameters analysed. The table illustrates the direction of the relationship between the climatic parameters and the change in distribution of disease transmission risk. Details are provided regrading whether mosquito biological thresholds and other global change drivers were considered within the study.

SPATIAL SCALE and AUTHORS	DISEASE	MOSQUITO VECTORS	MODEL TYPE	STUDY PROJECTION	CLIMATE PARAMETERS INCLUDED	DIRECTION OF RELATIONSHIP (+ or -)	CONSIDERED CRITICAL CLIMATE THRESHOLDS*	CONSIDERED OTHER GLOBAL CHANGE DRIVERS
Zonal								
Australia								
(Williams *et al.*, 2014)	Dengue	*Aedes aegypti*	Mechanistic	Prospective	T, P, H	+/-	Y	N
(Ho, Speldewinde and Cook, 2016)	MVEV	*Culex annulirostris*	Mechanistic	Prospective	T, P, H	-	Y	Y#

China								
(Jia *et al.*, 2017)	*(NA)*	*Aedes albopictus*	Mechanistic	Retrospective	T	+/-	Y	N
Kenya								
(Paaijmans *et al.*, 2014)	Malaria	*(NA)*	Mechanistic	Prospective	T	+/-	Y	N
(Ochieng *et al.*, 2016)	RVF	*Culex quinquefasciatus, Culex univitattus, Mansonia africana, Mansonia uniformis*	Correlative	Prospective	T, P	+/-	N	Y δ
Spain								
(Roiz *et al.*, 2014)	*(NA)*	*Anopheles atroparvus, Culex pipiens,*	Correlative	Prospective	T, P, H, W, S, E, Ph	+/-	N	N

		Culex theileri, Culex modestus, *Culex perexiguus, Ochlerotatus caspius, Ochlerotatus detritus*						
National								
Australia								
(Hill, Axford and Hoffmann, 2014)	*(NA)*	*Ae. albopictus*	Hybrid correlative	Prospective	T, P, S, Sm	+	Y	N
(Williams *et al.*, 2016)	Dengue	*(NA)*	Mechanistic	Prospective	T, P, H	-	Y	N
Brazil								

(Cardoso-Leite *et al.*, 2014)	Dengue	*Ae. aegypti*	Correlative	Prospective	T, P	-	N	N
Germany								
(Koch *et al.*, 2016)	*(NA)*	*Ae. albopictus*	Correlative	Prospective	T, P	+	N	N
Iran								
(Salahi-Moghaddam *et al.*, 2017)	Malaria	*Anopheles* spp.	Correlative	Retrospective	T, P, H	+/-	N	N
Mexico								
(Pech-May *et al.*, 2016)	*(NA)*	*Ae. albopictus*	Correlative	Prospective	T, P	+	N	N
(Equihua *et al.*, 2017)	Dengue	*Ae. aegypti*	Correlative	Prospective	T, P	+	N	N

Republic of Korea								
(Linthicum et al., 2014)	Malaria	*(NA)*	Mechanistic	Retrospective	T	+	N	N
Serbia								
(Petrić et al., 2017)	*(NA)*	*Ae. albopictus*	Mechanistic	Prospective	T, P, Ph	+/-	Y	N
Taiwan								
(Lin et al., 2017)	JEV	*(NA)*	Correlative	Retrospective	T, P, H, Ph	+	N	N
Tanzania								
(Mweya et al., 2016)	Dengue	*Ae. aegypti*	Correlative	Prospective	T, P	+	N	N

(Mweya, Mboera and Kimera, 2017)	RVF	*Cx. pipiens* complex	Correlative	Prospective	T, P	+/-	N	N
United Kingdom								
(Ewing *et al.*, 2016)	(*NA*)	*Cx. pipiens*	Mechanistic	Prospective	T	+	Y	N
USA								
(Brown *et al.*, 2015)	WNV	*Cx. pipiens, Culex tarsalis*	Mechanistic	Prospective	T, p	+	Y	N
(Butterworth, Morin and Comrie, 2017)	Dengue	*Ae. aegypti*	Mechanistic	Prospective	T, P	+	Y	N

(Yee, Ezeakacha and Abbott, 2017)	(NA)	Ae. albopictus	Mechanistic	Prospective	T, Ph	-	Y	N
Regional								
Africa								
(Drake and Beier, 2014)	Malaria	Anopheles arabiensis	Correlative	Prospective	T, P	-	N	N
(Ryan et al., 2015)	Malaria	An. gambiae	Mechanistic	Prospective	T	+	Y	Y¥
Europe								
(Thomas et al., 2014)	(NA)	Ae. albopictus	Correlative	Prospective	T, P	+	N	Y€
(Bouzid et al., 2014)	Dengue	(NA)	Correlative	Prospective	T, P, H	+	N	Yβ

(Trájer *et al.*, 2014)	WNV	*Ae. Albopictus*	Correlative	Prospective	T, P	+	N	N
(Proestos *et al.*, 2015)	*(NA)*	*Ae. Albopictus*	Mechanistic	Prospective	T, P, H	+	Y	N
(Cunze, Koch, *et al.*, 2016)	*(NA)*	*Aedes albopictus, Aedes japonicus*	Correlative	Prospective	T, P	+/-	N	N
(Cunze, Kochmann, *et al.*, 2016)	*(NA)*	*Ae. Albopictus*	Correlative	Prospective	T, P, Ph	+	Y	N
(Liu-Helmersson *et al.*, 2016)	Dengue	*Ae. Aegypti, Ae. Albopictus*	Mechanistic	Retrospective and prospective	T	+	Y	N
(Semenza *et al.*, 2016)	WNV	*(NA)*	Correlative	Prospective	T	+	N	Yγ
North America								

249

(Ogden et al., 2014b)	*(NA)*	*Ae. albopictus*	Mechanistic	Prospective	T, P	+	Y	N
South America								
(Laporta et al., 2015)	Malaria	*Anopheles* spp.	Correlative	Prospective	T, P	+/-	N	Y[δ]
South and Southeast Asia								
(Khormi and Kumar, 2016)	Malaria	*Anopheles* spp.	Hybrid correlative	Prospective	T, P, H	+/-	Y	N
Global								
(Liu-Helmersson et al., 2014)	*(NA)*	*Ae. aegypti*	Mechanistic	Prospective	T	+/-	Y	N

(M. Khormi and Kumar, 2014)	Dengue	*Ae. aegypti*	Correlative	Prospective	T, p, h	+/-	Y	N
(Capinha, C., Rocha, J. Sousa, 2014)	*(NA)*	*Ae. aegypti*	Correlative	Prospective	T, p	+	N	N
(Campbell *et al.*, 2015)	*(NA)*	*Ae. aegypti, Ae. albopictus*	Correlative	Prospective	T, P	+	N	N
(Carlson, Dougherty and Getz, 2016)	Zika, Dengue	*Ae. aegypti, Aedes africanus, Ae. albopictus*	Correlative	Prospective	T, P	+	N	Y[δ]
(Murdock, Sternberg and Thomas, 2016b)	Malaria	*An. gambiae, Anopheles stephensi*	Correlative	Prospective	T	-	Y	N
(Samy *et al.*, 2016)	WNV, LF, SLEV	*Cx. quinquefasciatus*	Correlative	Prospective	T, P	+/-	N	N

(Caminade et al., 2017)	Zika	*Ae. albopictus*	Mechanistic	Retrospective	T, P, El Nino event	+	Y	N
(Valdez et al., 2017)	(*NA*)	*Cx. quinquefasciatus*	Mechanistic	Theoretical	P	+/-	Y	N
(Tjaden et al., 2017)	Chikungunya	(*NA*)	Correlative	Prospective	T, P	+	N	Y[λ]
(Monaghan et al., 2018)	(*NA*)	*Ae. aegypti*	Correlative	Prospective	T, P	+	Y	Y[β]

Abbreviations: (*NA*), data not available; MVEV, Murray Valley encephalitis virus; RVF, Rift valley fever; JEV, Japanese encephalitis virus; SLEV, St Louis encephalitis virus; LF, lymphatic filariasis; WNV, West Nile virus; T, temperature; P, precipitation; H, humidity; W, wind; S, solar radiation; E, evapotranspiration; Ph, photoperiod; Sm, soil moisture;

*Inclusion of critical climate thresholds that may impact specific vector life history traits (e.g., temperature thresholds for mosquito survival).
[#] Land cover, human population density; animal host migration
[δ] Land cover
[¥] Land cover, human population density
[€] Trade
[β] Human population density, urbanisation, GDP per capita
[ᵞ] Land cover, animal host migration
[λ] Human population density

Appendix 2: Supplementary figures and data for Chapter 3

This appendix provides supplementary figures, tables and information on data sources for the analyses conducted in Chapter 3, 'Joint spatiotemporal modelling reveals seasonally dynamic patterns of Japanese encephalitis vector abundance across India'. The items contained in this appendix are:

Table S3.1. Vector surveillance data used in analyses.

Table S3.2. Data and rationale for covariates included in analyses.

Table S3.3. Impact of additional inferred absence data on selection results for models of increasing complexity.

Table S3.4. Model comparison results for observed JE outbreaks.

Figure S3.1. Maps of covariates used in models.

Figure S3.2. Diagnostic plots for joint likelihood models; scatterplot of predicted versus observed vector abundance (logscale) data.

Figure S3.3. Histograms of CPO and PIT values for joint likelihood models.

Figure S3.4. Random spatiotemporal cross-validation of the final model.

Figure S3.5. Association between one-month lagged vector abundance and predicted JE outbreak probability.

Table S3.1. Vector surveillance data used in analyses.

The table includes the study from which the data were extracted, the state or union territory in India in which the survey was conducted, the year of the survey, the type of data collected, the survey method, the total number of months that were surveyed, the number of sampling sites per study and the total number of datapoints (occurrence and abundance) generated from the study.

Study reference	Surveyed state/ union territory	Date range	Type of vector surveillance data*	Survey method for adult mosquitos	Total number of months surveyed	Number of sampling sites	Number of occurrence datapoints	Number of abundance datapoints	Total number of datapoints
(Rajavel, Natarajan and Vaidyanathan, 2006a)	Andhra Pradesh	2003-2004	OC	Aspirator	1	2	3	-	3
(Bhattacharyya *et al.*, **1994)**	Assam	1993	OC	Aspirator	1	1	1	-	1
(Dhiman *et al.*, **2013)**	Assam	2011	OC	Indoor light trap, aspirator	1	3	3	-	3

(Kumari *et al.*, 2013)	Delhi	2011	OC, AB	Aspirator, net sweeping	1	2	2	2	4
(Korgaonkar *et al.*, 2012)	Goa	2006	OC, AB	Human landing catch	1	1	1	1	2
(Rajavel and Natarajan, 2008)	Gujarat	2003	OC, AB	Aspirator	1	1	1	1	2
(Srivastava, Singh and Thapar, 2008)	Gujarat, Uttar Pradesh	2005	OC, AB	Aspirator	1	2	2	2	4
(Rajavel, Natarajan and Vaidyanathan, 2006b, p. 6)	Karnataka, Kerala	2003	OC	Aspirator	1	2	2	-	2
(Kanojia *et al.*, 2010)	Karnataka, Maharashtra, Tamil Nadu	2007	OC	Aspirator	1	3	3	-	3

(Thenmozhi *et al.*, 2013)	Kerala	2011	OC, AB	Aspirator	1	1	1	1	2
(Yadav, Sharma and Chand, 1997)	Odisha	1990-1991	OC, AB	Aspirator	24	1	24	18	42
(Dash *et al.*, 2001)	Odisha	1993	OC, AB	Aspirator	1	1	1	1	2
(Rajavel, Natarajan and Vaidyanathan, 2005a)	Odisha	2000	OC, AB	Light trap, aspirator	1	2	2	1	3
(Rajendran *et al.*, 2003)	Tamil Nadu	1998-2000	OC, AB	Aspirator	23	2	46	23	69
(Samuel *et al.*, 2010)	Tamil Nadu	2003-2006	OC, AB	Hand catch	4	9	20	4	24

(Samuel *et al.*, 2016)	Tamil Nadu	2006-2011	OC, AB	Aspirator	60	3	180	180	360
(Paramasivan, Dhananjeyan and Pandian, 2013)	Tamil Nadu	2007-2008	OC	Not described	1	1	2	-	2
(Tyagi *et al.*, 2016)	Tamil Nadu	2011-2012	OC, AB	Aspirator	21	1	21	21	42
(Das, Lal and Saxena, 2004)	Telangana	2003	OC, AB	Aspirator	1	6	6	6	12
(Kanojia, Shetty and Geevarghese, 2003)	Uttar Pradesh	1991	OC	Aspirator	1	4	4	-	4
(Kanojia and Geevarghese, 2005)	Uttar Pradesh	1991-2000	OC	Aspirator	1	1	3	-	3

(Misra and Gore, 2015)	Uttar Pradesh	2011	OC, AB	Aspirator	1	2	2	2	4
(Rajavel, Natarajan and Vaidyanathan, 2005b, p. 2)	West Bengal	2000	OC	Light trap, aspirator	1	2	2	-	2
(Mariappan *et al.*, 2014)	West Bengal	2011-2012	OC, AB	Aspirator	2	4	8	4	12
Totals						57	340	267	607

*OC = occurrence data; AB = abundance data

Table S3.2. Data and rationale for covariates included in analyses.

The table includes the sources and rationale (hypothesises) for inclusion of covariates in spatiotemporal models of vector abundance.

Covariate	Dataset	Description	Spatial resolution	Temporal resolution	Data classification	Source	Rationale
Mean, min and max air temperature	TerraClimate	High-spatial resolution data WorldClim is combined with coarser spatial resolution, but time-varying data from CRU Ts4.0 and JRA55.	1/24°, ~4 km; Global.	Monthly: 1958–2019.	Maximum temperature, minimum temperature, and derived mean temperature (°C).	http://www.climatologylab.org/terraclimate.html	Temperature affects important vector life history traits such as development rate and survival (Mordecai *et al.*, 2019).
Mean precipitation	TerraClimate	High-spatial resolution data WorldClim is combined with coarser spatial resolution, but time-varying data from CRU Ts4.0 and JRA55.	1/24°, ~4 km; Global.	Monthly: 1958–2019.	Precipitation (mm).	http://www.climatologylab.org/terraclimate.html	Rainfall has been shown to influence vector populations due to the creation of standing water for vector breeding (Reisen, Aslamkhan and Basia, 1976; Vythilingam *et al.*, 1997; Suryanarayana Murty, Srinivasa Rao and Arunachalam, 2010).

Land cover	European Space Agency Climate Change Initiative (CCI) Land Cover; version 3.14.	Land cover time series produced with the reprocessing and the interpretation of five different satellite missions providing daily observation of the Earth.	300m, Global.	Annual: 1992 - 2015.	37 UN Land Cover Classes, derived into six broad groups: agricultural, mixed agricultural, forest, mixed vegetation, urban and water.	http://maps.elie.ucl.ac.be/CCI/viewer/index.php	Irrigated agricultural practices provide suitable habitat for vector development and *C. tritaeniorhynchus* is reported to preferentially breed in rice paddy fields (Keiser et al., 2005; Sabesan, Raju Konuganti and Perumal, 2008a).
Land-use intensity metrics for rice crop cultivation	RiceAtlas; version 2.	Database of rice planting and harvesting dates by growing season and estimates of monthly production for all rice-producing countries.	Second level subdivisions (i.e., district-level for India), Global.	2010–2012 average.	Location information – geographic scale / crop calendar -planting, harvesting, growing / production / area.	(Laborte *et al.*, 2017)	Vector abundance is positively associated with rice field density (Richards *et al.*, 2010), rice crop growth stage (Raju *et al.*, 2016, 2018) and standing water availability (Rajagopalan and Panicker, 1978; Keiser et al., 2005).

Table S3.3. Impact of additional inferred absence data on selection results for models of increasing complexity.

The table details the structure of the joint-likelihood models and the difference between their corresponding within-sample predictive accuracy assessed on Watanabe-Akaike Information Criterion (WAIC) values when additional absence data is excluded. The differences (Δ) in WAIC between the other models and the best fitting environmental model are still equivalently large when compared to the ΔWAIC values when the additional absence data is included.

	Model	Fixed effects	Random intercepts	WAIC	ΔWAIC	ΔWAIC for model with additional absence data
1	Baseline model	-	ST, S	721.60	72.94	77.53
2	Seasonal model	-	ST, S, M	652.62	3.96	6.52
3	Environmental model	Precipitation, Agri. land proportion, Annual rice crops, Annual rice area, Annual rice production, Nonlinear temp. function	ST, S, M	648.66	0.00	0.00

Table S3.4. Model comparison results for observed JE outbreaks.

AIC, odds ratio and 95% confidence intervals reported from logistic regression of JE outbreak probability as a function of model predicted vector abundance. Vector abundance predictions were generated from the final model with and without a one-month lag. A null model (i.e., intercept only) was developed to assess the ability of vector abundance predictions in estimating JE outbreaks when compared to predictions expected at random.

Model	AIC	ΔAIC	Akaike weight	Odds ratio	95% Confidence interval
Null (intercept-only)	168.02	23.85	0	-	-
No lag (JE outbreak probability as a function of predicted vector abundance in the same month)	147.66	3.49	0	2.25	1.35 - 3.74
One month lag (JE outbreak probability as a function of predicted vector abundance in the previous month)	144.17	0.00	1	2.45	1.52 - 4.08

Figure S3.1. Maps of covariates used in models.

(A) average mean temperature per month (ºC) (example given for the year 2005);
(B) average precipitation per month (mm) (example given for the year 2005); (C)
number of rice crop rotations per year (average for period 2010-12); (D) total annual
rice area cultivated per year in hectares (average for period 2010-12); (E) total rice
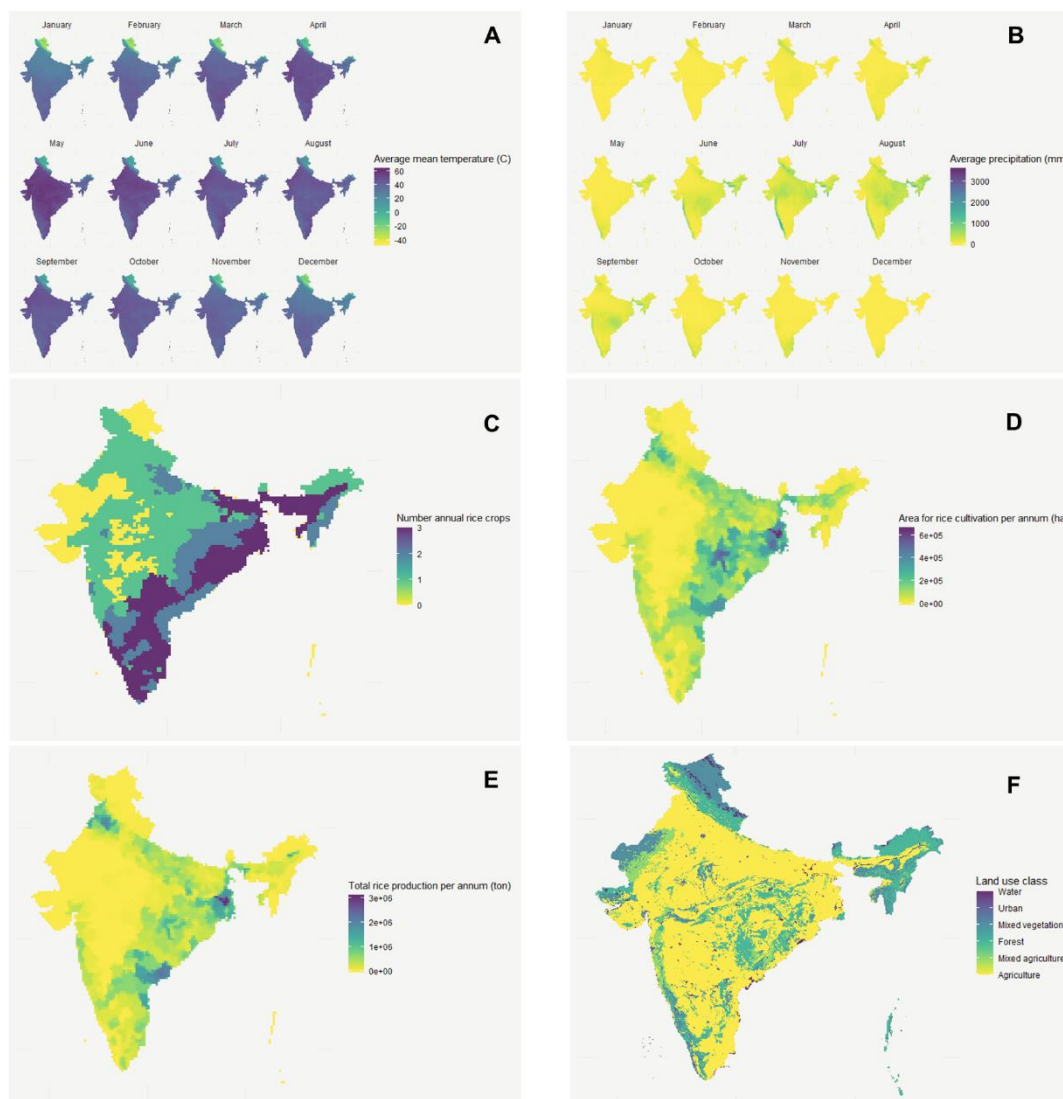produced per year in tonnes (average for period 2010-12); (F) land-use classes
(example given for the year 2005).

Figure S3.2. Diagnostic plots for joint likelihood models; scatterplot of predicted versus observed vector abundance (logscale) data.

Plots show observed data against model predicted values, and the red line shows the expectation if observed equals predicted for each model: (A) baseline (spatial effects and study- level random effects), (B) seasonal (spatial, seasonal, and random effects), (C) environmental (spatial, seasonal, and random effects and environmental covariates).
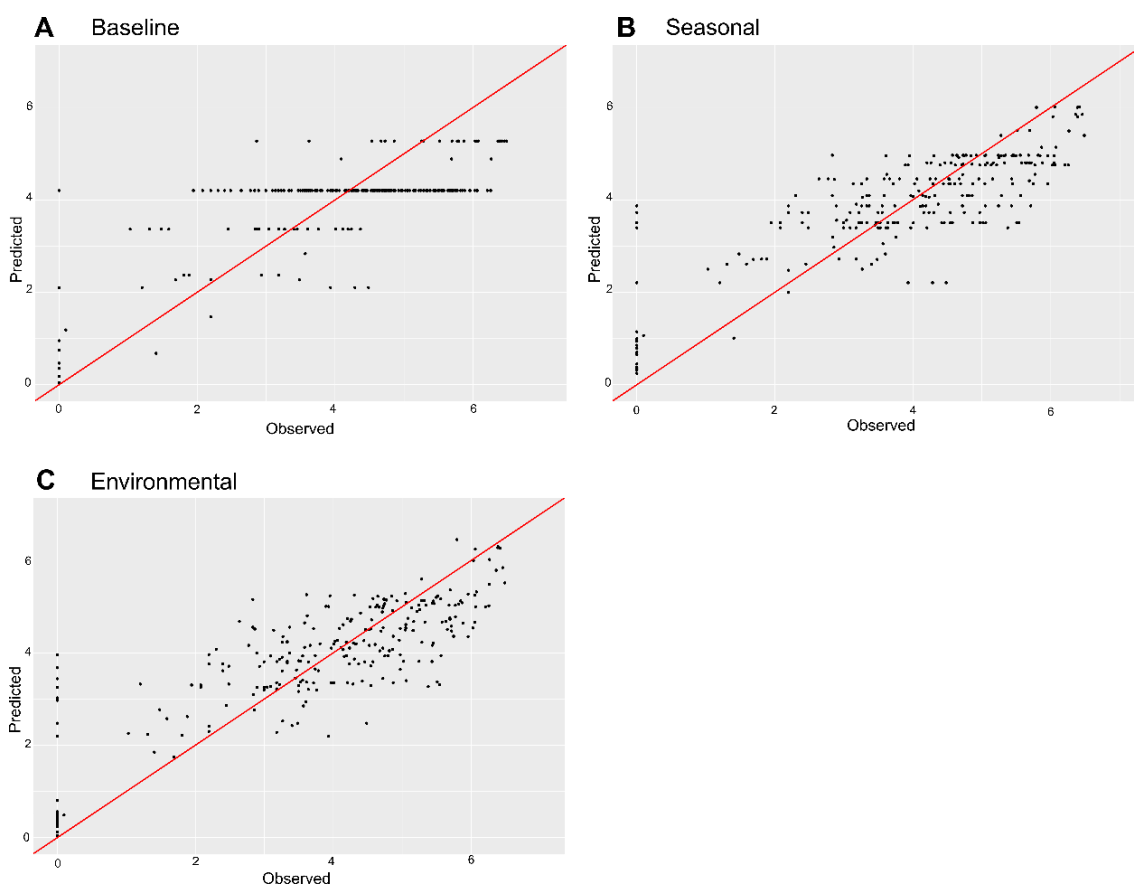
Figure S3.3. Histograms of CPO and PIT values for joint likelihood models.

Plots show CPO and PIT histograms, with the red line indicating the level of the of the different values if their distribution was uniform: (A) baseline (spatial effects and study- level random effects), (B) seasonal (spatial, seasonal and random effects), (C) environmental (spatial, seasonal and random effects and environmental covariates).
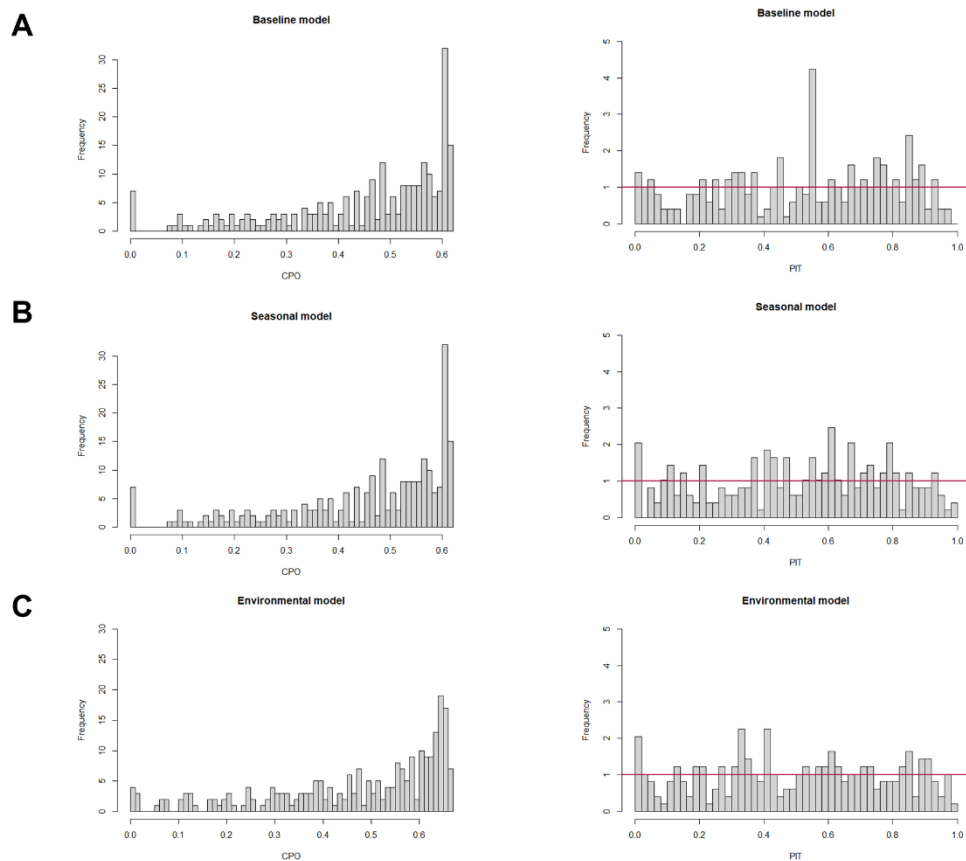
Figure S3.4. Random spatiotemporal cross-validation of the final model.

I tested the sensitivity of fixed effects estimates to random (10-fold) subsampling. Points and error bars show posterior marginal parameter distributions for each hold-out model (median and 95% quantile range), with colour denoting hold-out group. Directionality and magnitude of fixed-effects estimates are robust to all tests.
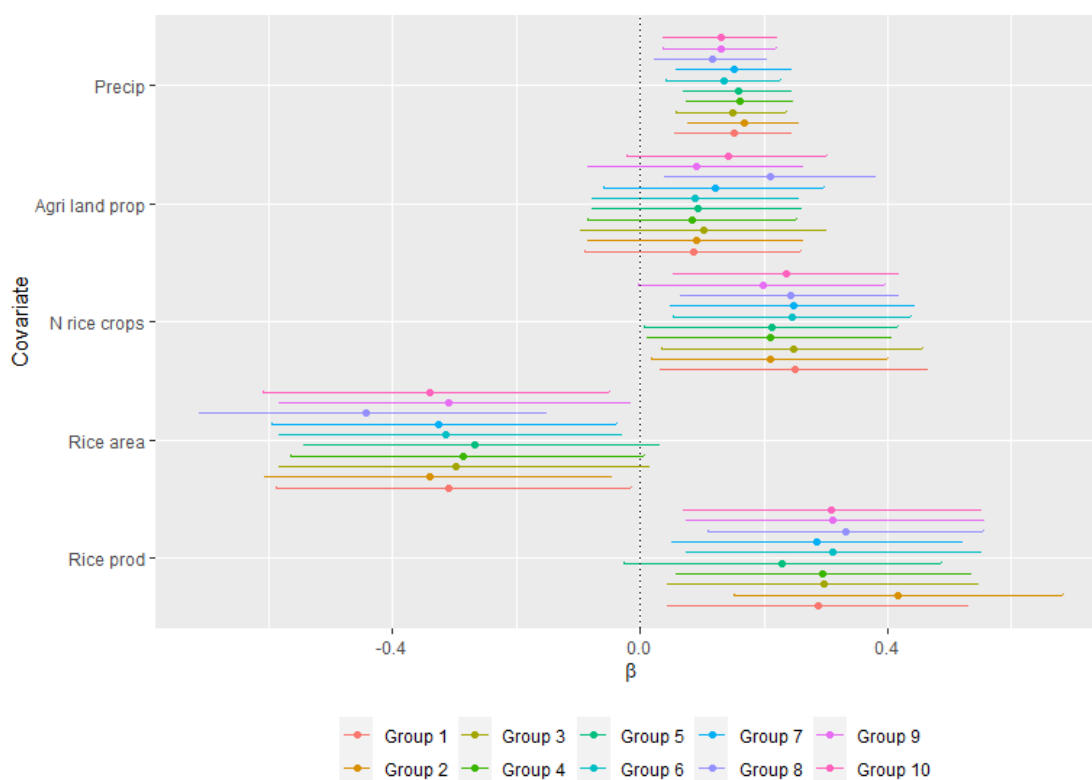
Figure S3.5. Association between one-month lagged vector abundance and predicted JE outbreak probability.

Vertical axis displays model predicted JE outbreak probability, and vertical axis gives predicted vector abundance on the log scale. Smooth line highlights the non-linear relationship of JE outbreak probability to predicted vector abundance with a one-month lag.
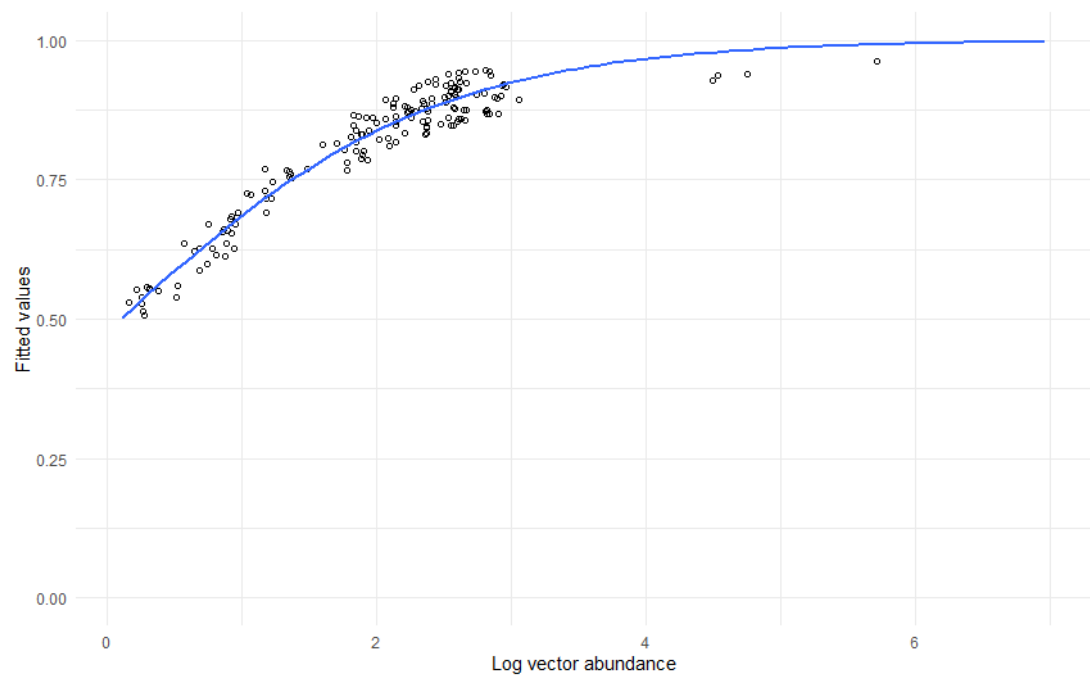
Appendix 3: Supplementary figures and data for Chapter 4

This appendix provides supplementary figures, tables and information on data sources for the analyses conducted in Chapter 4, 'Climate, land-use and socioeconomic factors predict spatiotemporal dynamics of Japanese encephalitis risk'. The items contained in this appendix are:

Text S4.1: Mapping the spatial distribution of Ardeid bird reservoir host occurrence.

Table S4.1. Japanese surveillance data collected for northeast India from 2009-2019 (115 districts).

Table S4.2. Data sources for all covariates included in analyses.

Table S4.3. Results of univariate analysis for spatial model covariates.

Table S4.4. Results of multivariate analysis for spatial model covariates.

Table S4.5. Model adequacy results for predictive spatial models of increasing complexity.

Table S4.6. Model predictive accuracy results for temporal models of increasing complexity.

Table S4.7. Parameter values from the evaluative spatial model of JE outbreak occurrence.

Table S4.8. Model selection results for models predicting spatial JE outbreak occurrence in northeast India for outbreak threshold of 3 confirmed cases.

Figure S4.1. Indian climatic regions and biomes.

Figure S4.2. The spatiotemporal pattern in Japanese encephalitis cases across India, 2009 - 2019.

Figure S4.3. A map of cattle egret (*B. ibis)* occurrence in northeast India.

Figure S4.4. A map of intermediate egret (*A. intermedia)* occurrence in northeast India.

Figure S4.5. A map of little egret (*E. garzetta)* occurrence in northeast India.

Figure S4.6. A map of Indian pond heron (*A. grayii)* occurrence in northeast India.

Figure S4.7. A map of black-crowned night heron (*N. nycticorax)* occurrence in northeast India.

Figure S4.8. The spatial pattern of JE outbreaks between 2009 and 2019 in northeast India.

Figure S4.9. Time series of monthly confirmed JE cases per district in the state of Assam*, 2009–2019.

Figure S4.10. Correlates of annual JE occurrence in northeast India 2009–2019 for different JE outbreak occurrence thresholds.

Figure S4.11. Random 5-fold cross-validation for the spatial model of JE occurrence.

Figure S4.12. The difference in Brier score between the baseline (random effects only) and socio-ecological model per district.

Figure S4.13. Comparative effect of the inclusion of vaccination data at different lags on the predictive accuracy of the temporal model of JE incidence in endemic districts of Assam.

Text S4.1: Mapping the spatial distribution of Ardeid bird reservoir host occurrence

Methods

To estimate the geographical distribution of sylvatic JE reservoir host species (van den Hurk, Ritchie and Mackenzie, 2009; Pearce *et al.*, 2018b), I fitted species distribution models (SDMs) with Bayesian additive regression trees (BART) (Carlson, 2020) to Intermediate egret (*Ardea intermedia*), Little egret (*Egretta garzetta*), Cattle egret (*Bubulcus ibis*), Indian pond heron (*Ardeola grayii*), and Black-crowned night heron (*Nycticorax nycticorax*) occurrence data, using the *embarcadero* package in R (Carlson, 2021). The BART approach was chosen since it adds a Bayesian component to classification tree methods that handles model uncertainty (i.e., builds a posterior distribution) and is comparable to the Bayesian approach I have taken in this Chapter.

To account for uneven sampling effort across the geographical range, I generated the same number of random background (pseudo-absence) points as presence points for each host species (Phillips *et al.*, 2009).

Data

Occurrence data for the five species recorded from January 2009 to December 2019 was obtained from ebird (eBird, 2021) and Global Biodiversity Information Facility (GBIF) (GBIF, 2021f, 2021d, 2021b, 2021i, 2021e, 2021g, 2021h, 2021a, 2021c). I retrieved data on the presence and absence of the reservoir hosts for the Indian states in the northeast region, Bangladesh and Bhutan to achieve a more accurate projection of potential species distributions that are unlikely to reflect country borders.

I obtained yearly precipitation, and minimum and maximum temperature from the Terraclimate dataset (Abatzoglou *et al.*, 2018) and averaged over 2009-2019. I extracted percentage land cover data from the ESA Climate Change

Initiative Land Cover dataset for the year 2014 (i.e., the middle of the study period). I extracted data for land cover classes that are reported to be preferrable host habitat (i.e., irrigated cropland, rainfed cropland, flood vegetation water bodies and grassland cover) as predictors in the models (see Appendix 3 Table S4.2 for details of the data used in the SDMs).

Results

The SDMs performed well with high area under the ROC curve (AUC) values for each of the species (i.e., *B. ibis* AUC = 0.83, *A. intermedia* AUC = 0.79, *E. garzetta* AUC = 0.81, *N. nycticorax* AUC = 0.76, *A. grayii* AUC = 0.81). The models reported low uncertainty (i.e., posterior width) in general with highest uncertainty reported in central regions of the study area.

All JE hosts had similar distributions and response curves to covariates. Overall, the probability of occurrence for each species; increases with increasing minimum temperature until peak at 22ºC, increases at lower rainfall values, and decreases with cropland land cover. Only the intermediate and little egret are strongly influenced by water bodies (positive effect). Despite irrigated cropland being described as an important habitat for these hosts (Czech and Parsons, 2002; Elphick *et al.*, 2010), all SDMs apart from for *B.ibis* did not reflect this. However, this may be an artefactual problem due to less observations by ebird reporters in anthropogenic-dominated habitats such as agricultural cropland.

Partial dependence plots showing the marginal response of each JE host to all covariates and the corresponding predicted distribution of each JE host in northeast India is shown in Appendix 3 Figure S4.X.

Table S4.1. Japanese surveillance data collected for northeast India from 2009-2019 (115 districts).

The table includes the source from which the data were extracted, and information of the spatial and temporal scales of the data, and the total number of data points for each source (suspected, confirmed positive and confirmed negative cases).

Source	N	Years	Months	States	Districts	Reference
Indian government's Integrated Disease Surveillance Programme (IDSP)	138	2009–19	1-10	7	48	(Government of India, 2021b)
Indian government's Health Management Information System (HMIS)	255	2017-18	1-12	7	35	(Government of India, 2021a)
National Centre for Disease Control's (NCDC) Media scanning and verification system	16	2016-19	5-7	5	12	(Sharma *et al.*, 2012)
ProMed	99	2010-19	5-9	5	39	(International Society for Infectious Diseases, 2021)
Published literature	122	2016–17	1-12	1	9	(Singh *et al.*, 2019)
Published literature	24	2015-16	1-12	1	2	(Baruah *et al.*, 2018)
Published literature	24	2009–10	1-12	1	1	(Borah *et al.*, 2013)
Published literature	278	2011-12	1-12	1	18	(Bandyopadhyay *et al.*, 2013)
Published literature	7	2011-12	8-10	1	6	(Sarkar *et al.*, 2013)

Table S4.2. Data sources for all covariates included in analyses.

The table includes the sources and rationale (hypothesis) for inclusion of covariates in spatial and temporal models of Japanese encephalitis risk incidence across northeast India. Modelling is described in full in Methods.

Covariate	Dataset	Description	Spatial resolution	Temporal resolution	Units	Source	Rationale
District ID	India census 2011.	640 districts that were present in 2011.	District	2011	N/A	(Government of India, 2011)	Proxy for public access with links to state-level surveillance infrastructure.
Mean, min and max air temperature	TerraClimate.	High-spatial resolution data WorldClim is combined with coarser spatial resolution, but time-varying data from CRU Ts4.0 and JRA55.	1/24°, ~4 km; Global.	Monthly: 1958–2019.	degrees C	(Abatzoglou *et al.*, 2018)	Temperature affects important vector life history traits such as development rate and survival (Mordecai *et al.*, 2019) and the environmental niche of avian species (Hafner, 1997; Barnagaud *et al.*, 2012).
Mean precipitation	TerraClimate.	High-spatial resolution data WorldClim is combined with coarser spatial resolution, but time-varying data from CRU Ts4.0 and JRA55.	1/24°, ~4 km; Global.	Monthly: 1958–2019.	mm	(Abatzoglou *et al.*, 2018)	Rainfall has been shown to influence vector populations due to the creation of standing water for vector breeding (Reisen, Aslamkhan and Basia, 1976; Vythilingam *et al.*, 1997; Murty, Rao and Arunachalam, 2010) and suitable ardeid bird

								feeding habitat (Hafner, 1997).
Mean Palmer Drought Index (PDSI)	TerraClimate.	High-spatial resolution data WorldClim is combined with coarser spatial resolution, but time-varying data from CRU Ts4.0 and JRA55.	1/24°, ~4 km; Global.	Monthly: 1958–2019.	Palmer Drought Index	(Abatzoglou *et al.*, 2018)	Extremely wet conditions can provide increased vector breeding (Ramesh *et al.*, 2015) and host feeding habitats (Urfi, 2011), but can also destroy vector habiatats (Chen *et al.*, 2012). Droughts can reduce aquatic habitat of some mosquito species (Chareonviriyaphap *et al.*, 2003).
Rainfed agricultural land cover	European Space Agency Climate Change Initiative (CCI) Land Cover; (version 3.14).	Land cover time series produced with the reprocessing and the interpretation of five different satellite missions providing daily observation of the Earth.	300m, Global.	Annual: 1992 - 2020.	Proportion district area	https://www.esa-landcover-cci.org/	Agricultural land provides suitable habitat for vector development (Keiser et al., 2005; Sabesan, Raju Konuganti and Perumal, 2008a) and reservoir host feeding (Richardson, Taylor and Growns, 2001).

Irrigated agricultural land cover	European Space Agency Climate Change Initiative (CCI) Land Cover; (version 3.14).	Land cover time series produced with the reprocessing and the interpretation of five different satellite missions providing daily observation of the Earth.	300m, Global.	Annual: 1992 - 2020.	Proportion district area	https://www.esa-landcover-cci.org/	Agricultural land provides suitable habitat for vector development (Keiser *et al.*, 2005b; Sabesan, Raju Konuganti and Perumal, 2008) and reservoir host feeding (Richardson, Taylor and Growns, 2001).
Water bodies land cover	European Space Agency Climate Change Initiative (CCI) Land Cover; (version 3.14).	Land cover time series produced with the reprocessing and the interpretation of five different satellite missions providing daily observation of the Earth.	300m, Global.	Annual: 1992 - 2020.	Proportion district area	https://www.esa-landcover-cci.org/	River and freshwater marshlands are associtaed with JEV wildlife host presence (Walsh *et al.*, 2021).
Mosaic vegetation land cover	European Space Agency Climate Change Initiative (CCI) Land Cover; (version 3.14).	Land cover time series produced with the reprocessing and the interpretation of five different satellite missions providing daily	300m, Global.	Annual: 1992 - 2020.	Proportion district area	https://www.esa-landcover-cci.org/	Agricultural land provides suitable habitat for vector development (Keiser *et al.*, 2005b; Sabesan, Raju Konuganti and Perumal, 2008) and reservoir host feeding (Richardson, Taylor and Growns, 2001). Fragmented agriculural land is associtaed with JEV

		observation of the Earth.					wildlife host presence (Walsh *et al.*, 2021).
Mean Normalized Difference Vegetation Index (NDVI)	MOD13C2 MODIS/Terra Vegetation Indices (version 006).	This product is generated from the MODIS/006/MOD09GA surface reflectance composites.	0.05°, ~5.6km; Global.	Monthly: 2000-Present.	NDVI	(Didan, 2015)	A positive relationship has been reported between NDVI and JE vector population density in India (Raju *et al.*, 2018).
Mean probability of presence for sylvatic reservoir hosts (individual species and combined)	Species distribution models (see Appendix 3 Text S4.1).	Intermediate egret (*Ardea intermedia*), Little egret (*Egretta garzetta*), Cattle egret (*Bubulcus ibis*), Indian pond heron (*Ardeola grayii*) , and Black-crowned night heron (*Nycticorax nycticorax*) occurrence probability.	1/24°, ~4 km; Northeast India.	Static (study period 2009-2019)	Logistic probability per district	(see Appendix 3 Text S4.1)	Japanese encephalitis virus is maintained in an enzootic transmission cycle with vertebrate reservoir hosts including ardeid wading birds (Buescher et al., 1959; van den Hurk, Ritchie and Mackenzie, 2009; Le Flohic *et al.*, 2013).

Mean pig population density	Gridded Livestock of the World (version 3).	Global population densities of pigs retrieved from census data.	0.083333 °, ~10 km; Global.	2010	Density per district area	(Gilbert *et al.*, 2018)	Japanese encephalitis virus is maintained in an enzootic transmission cycle with vertebrate reservoir hosts including domestic pigs (van den Hurk, Ritchie and Mackenzie, 2009; Le Flohic *et al.*, 2013).
Proportion of the population living in rural areas	India census 2011.	The most current Indian Census of the population provides population enumeration data.	District	2011	Proportion district area	(Government of India, 2011)	Rural populations have potentially higher exposure to JE due to the presenece of vectors in ahgricultiral land (Keiser et al., 2005; Sabesan, Raju Konuganti and Perumal, 2008a).
Proportion of population working in agriculture,	India census 2011	The most current Indian Census of the population provides population enumeration data.	District	2011	Proportion district area	(Government of India, 2011)	Agricultural workers have potentially higher exposure to JE due to the presenece of vectors in ahgricultiral land (Keiser et al., 2005; Sabesan, Raju Konuganti and Perumal, 2008a).
Proportion of the population under 6 years old	India census 2011	The most current Indian Census of the population provides population enumeration data.	District	2011	Proportion district area	(Government of India, 2011)	Most JE cases occur in children (Pearce *et al.*, 2018b).

Proportion of population practicing major religions (i.e., Hindus, Muslims, Sikh, Buddhists, Jain, Christians)	India census 2011	The most current Indian Census of the population provides population enumeration data.	District	2011	Proportion district area	(Government of India, 2011)	Pig farming is associated with religion (Lord, Gurley and Pulliam, 2015).
Healthcare access	India Health Management Information System (HMIS) data	Indian government portal to monitor the National Health Mission and other Health programmes.	District	2010-2018	Per capita value for the district	(Government of India, 2021a)	Limited healthcare access results in underreporting of cases (WHO, 2020b).
Proportion of the population living in poverty	Multidimensional Poverty Index (MPI)	The index tracks poverty across several indicators of health, education and living standards.	District	2016	Proportion district area	(Alkire, Oldiges and Kanagaratnam, 2018)	JE risk in increase in poverty settings (Badari, 1985; Luo et al., 1995; Sarkar et al., 2012).
Proportion of the population vaccinated	India HMIS data	Indian government portal to monitor the National Health Mission and other Health programmes.	District	2010-2018	Proportion district area	(Government of India, 2021a)	Vaccination reduces JE cases (Quan et al., 2020).

Table S4.3. Results of univariate analysis for evaluative spatial model covariates.

The change in widely-applicable information criterion (WAIC) and the cross-validated (CV) mean logarithmic score from the baseline model (grey cells) when each covariate is fitted in turn. Lower scores indicate a better fitting model when compared to the baseline.

Model	Δ WAIC	Δ CV mean log score
Baseline	0	0
Baseline + proportion of rainfed and irrigated cropland	-4.022	-0.022
Baseline + mean annual Tmax nonlinear effect	-3.392	-0.019
Baseline + healthcare access per capita	-2.459	-0.014
Baseline + mean annual Tmin	-2.446	-0.013
Baseline + mean annual Tmax	-2.406	-0.013
Baseline + mean annual precipitation	-2.170	-0.012
Baseline + proportion of rainfed cropland	-2.002	-0.011
Baseline + mean annual precipitation nonlinear effect	-1.137	-0.006
Baseline + mean annual Tmin nonlinear effect	-0.918	-0.005
Baseline + pig population density GLW (Gridded Livestock of the World)	-0.830	-0.004
Baseline + proportion of mosaic cropland	-0.696	-0.004
Baseline + proportion of population working in agriculture	-0.590	-0.003
Baseline + proportion of population in poverty	-0.329	-0.002
Baseline + proportion of population under 6	-0.137	-0.001
Baseline + total pigs from Indian census	0.209	0.001
Baseline + presence bird hosts	0.293	0.002
Baseline + healthcare access per rural population	0.512	0.003
Baseline + mean annual PDSI nonlinear effect	0.969	0.006
Baseline + proportion of irrigated cropland	1.061	0.006
Baseline + proportion total population that are children in rural areas	1.322	0.007
Baseline + proportion of population in rural areas	1.664	0.009
Baseline + mean annual PDSI	1.839	0.010

Table S4.4. Results of multivariate analysis for evaluative spatial model covariates.

The widely-applicable information criterion (WAIC) score when each covariate is excluded in turn from the full model (grey cells). If the exclusion of a covariates elevated the WAIC by a threshold of at least five units, they were included in the final model since their addition in the model improved WAIC scores.

Covariate excluded from model	WAIC
Full model (Baseline model + Mean annual Tmax nonlinear effect + Mean annual precipitation + Proportion of rainfed and irrigated cropland + Pig population density GLW + Healthcare access per capita + Proportion of population working in agriculture + Proportion of population in poverty)	201.689
Mean annual Tmax nonlinear effect	218.469
Mean annual precipitation	207.626
Proportion of rainfed and irrigated cropland	210.906
Pig population density GLW (Gridded Livestock of the World)	206.763
Healthcare access per capita	212.061
Proportion of population working in agriculture	185.623
Proportion of population in poverty	208.748

Table S4.5. Model adequacy results for predictive spatial models of increasing complexity.

The out-of-sample predictive ability for a subset of predictive spatial models of increasing complexity determined by the Brier score. Lower scores indicate a model with better predictive ability.

Model	JE outbreak occurrence estimate	Brier score
Baseline	Random effect of year and district-level spatial random effects	0.0653
Tmax	Base model + mean annual Tmax nonlinear effect	0.0641
Precipitation	Base model + mean annual precipitation	0.0651
Cropland	Base model + proportion of rainfed and irrigated cropland	0.0643
Pig population	Base model + pig population density GLW (Gridded Livestock of the World)	0.0671
Healthcare	Base model + healthcare access per capita	0.0668
Poverty	Base model + proportion of population living in poverty	0.0652
Tmax + precipitation	Base model + mean annual Tmax nonlinear effect + mean annual precipitation	0.0644
Tmax + precipitation + cropland	Base model + mean annual Tmax nonlinear effect + mean annual precipitation + agricultural cropland	0.0640
Tmax + precipitation + cropland + healthcare	Base model + mean annual Tmax nonlinear effect + mean annual precipitation + agricultural cropland + healthcare access per capita	0.0637
Tmax + precipitation + cropland + healthcare + poverty	Base model + mean annual Tmax nonlinear effect + mean annual precipitation + agricultural cropland + healthcare access per capita + proportion of population living in poverty	0.0634
Tmax + precipitation + cropland + healthcare + poverty + pig population	Base model + mean annual Tmax nonlinear effect + mean annual precipitation + agricultural cropland + healthcare access per capita + proportion of population living in poverty + pig population density GLW	0.0637

Table S4.6. Model predictive accuracy results for temporal models of increasing complexity.

The out-of-sample predictive ability for a subset of predictive temporal models of increasing complexity (with regards to input covariates and probability distributions) determined by the root mean square error (RMSE). Lower scores indicate a model with better predictive ability.

Model	JE outbreak incidence estimate	RMSE
Baseline	Random effect of data source, year, and month	53.369
Precipitation	Nonlinear precipitation function Nonlinear precipitation 1-month lag function Nonlinear precipitation 2-month lag function Nonlinear precipitation 3-month lag function	102.13 102.13 59.97 101.90
PDSI	Nonlinear PDSI function Nonlinear PDSI 1-month lag function Nonlinear PDSI 2-month lag function Nonlinear PDSI 3-month lag function	50.63 38.53 41.94 101.61
Tmean	Nonlinear Tmean function Nonlinear Tmean 1-month lag function Nonlinear Tmean 2-month lag function Nonlinear Tmean 3-month lag function	56.64 37.92 103.16 58.02
NDVI	Nonlinear NDVI function Nonlinear NDVI 1-month lag function Nonlinear NDVI 2-month lag function Nonlinear NDVI 3-month lag function	61.22 55.33 38.86 103.41
PDSI + Tmean + NDVI	Nonlinear PDSI 1-month lag function + Nonlinear Tmean 1-month lag function + Nonlinear NDVI 2-month lag function	39.82
PDSI + Tmean + Precipitation + Rice area	Nonlinear PDSI 1-month lag function + Nonlinear Tmean 1-month lag function + Nonlinear precipitation 1-month lag function + Rice area under cultivation	33.83
PDSI + Tmean + Precipitation + Rice area + Vaccination	(Nonlinear PDSI 1-month lag function + Nonlinear Tmean 1-month lag function + Nonlinear precipitation 1-month lag function + Rice area under cultivation) + Vaccination + Vaccination 1-month lag + Vaccination 2-month lag + Vaccination 3-month lag + Vaccination 4-month lag + Vaccination 5-month lag + Vaccination 6-month lag	 32.98 36.55 28.80 33.85 52.81 44.63 100.74

Table S4.7. Parameter values from the evaluative spatial model of JE outbreak occurrence.

Posterior means and 95% credible intervals (CI, obtained from the 2.5% and 97.5% quantiles of the marginal posterior distribution) for the model intercept and fixed-effect parameters associated with the explanatory variables.

Parameter	Posterior mean (95% CI)
Intercept	-3.249 (−3.943, -2.645)
Mean annual precipitation	-0.314 (-0.690, 0.024)
Proportion of the population living in poverty	0.344 (0.057, 0.639)
Mean pig population density	0.159 (−0.068, 0.363)
Healthcare access per capita	-0.106 (−0.486, 0.228)
Agricultural land proportion	0.336 (0.152, 0.527)

Table S4.8. Model selection results for models predicting spatial JE outbreak occurrence in northeast India for outbreak threshold of 3 confirmed cases.

The table shows the differences in structure and out-of-sample model fit (Brier score) for the baseline (random effects only) and best-fitting socio-ecological model.

Outbreak threshold	Model	Random effects	Socio-ecological effects	Brier score
3 confirmed cases	Baseline	Year, district-level spatial random effects	-	0.052
	Socio-ecological	Year, district-level spatial random effects	Precipitation Poverty Healthcare access Agricultural land prop. Nonlinear Tmax function	0.050
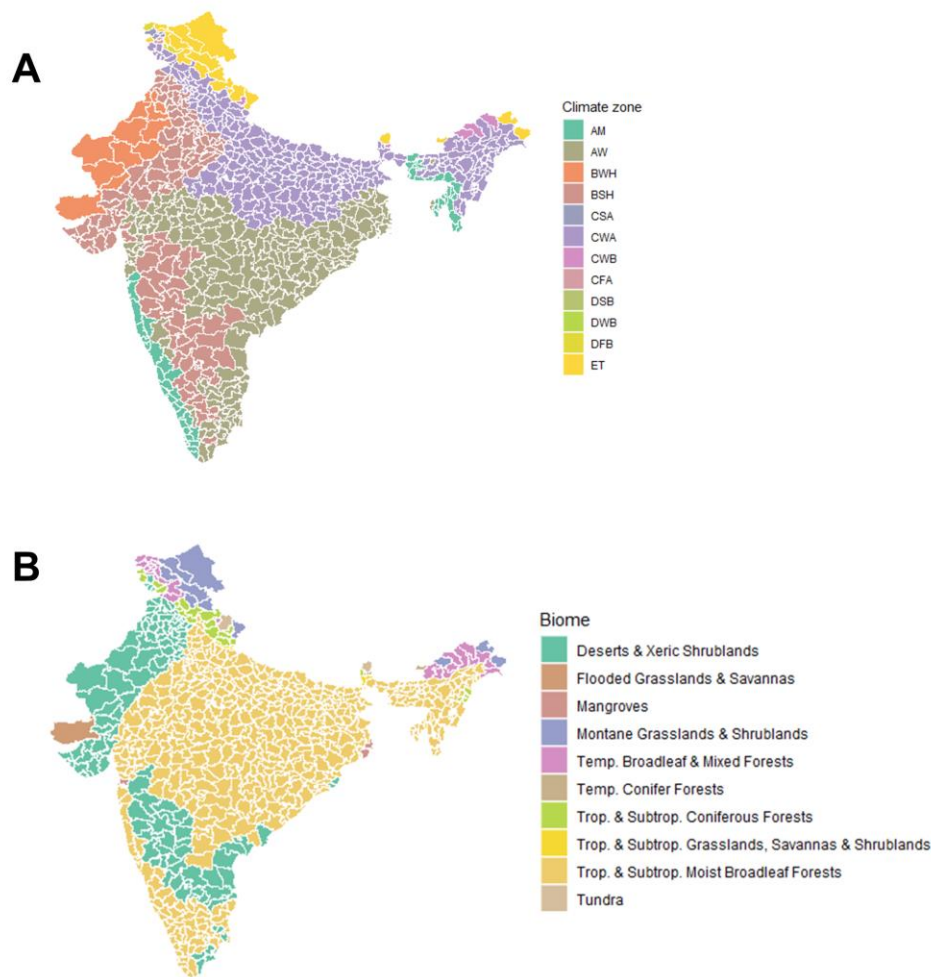
Figure S4.1. Indian climatic regions and biomes.

Location of (A) 12 Köppen climate classification groups (AM: tropical monsoon, AW: tropical savanna, BWH: hot arid, BSH: hot semi-arid, CSA: temperate dry and hot summer, CWA: temperate dry winter and hot summer, CWB: temperate dry winter and warm summer, CFA: temperate no dry season and hot summer, DSB: cold with dry and warm summer, DWB: cold with dry winter and warm summer, DFB: cold with no dry season and warm summer, ET: polar tundra) and (B) ten biomes (desert, savanna, mangrove, montane, temperate broadleaf and conifer forests, tropical broadleaf and coniferous forest, tropical grassland/ savanna and tundra).
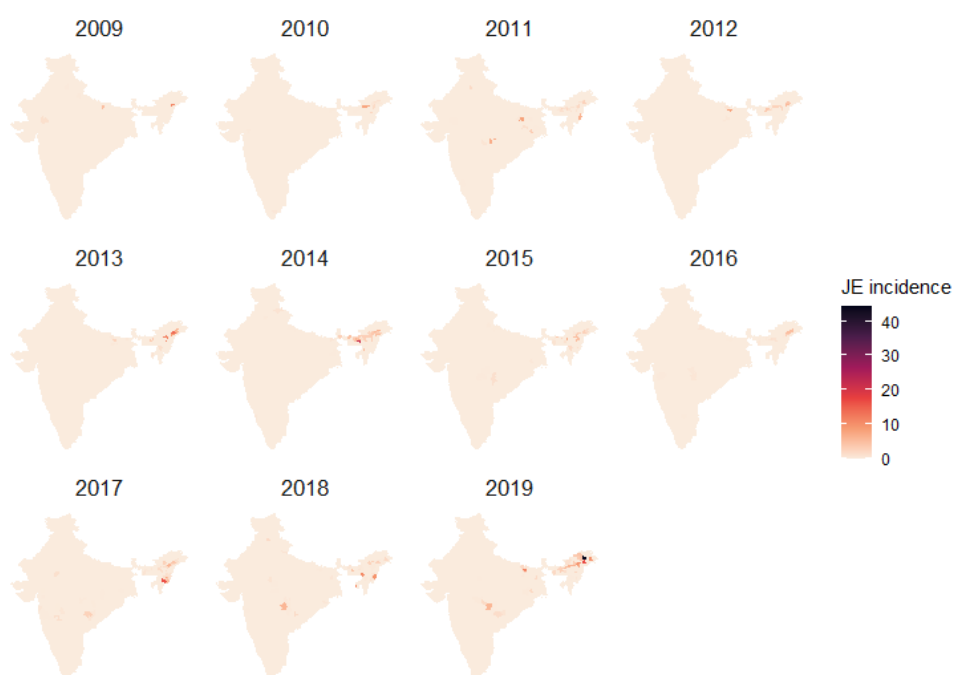
Figure S4.2. The spatiotemporal pattern in Japanese encephalitis cases across India, 2009 - 2019.

Maps show the total reported suspected and confirmed Japanese encephalitis cases in each state and union territory during the specified years.
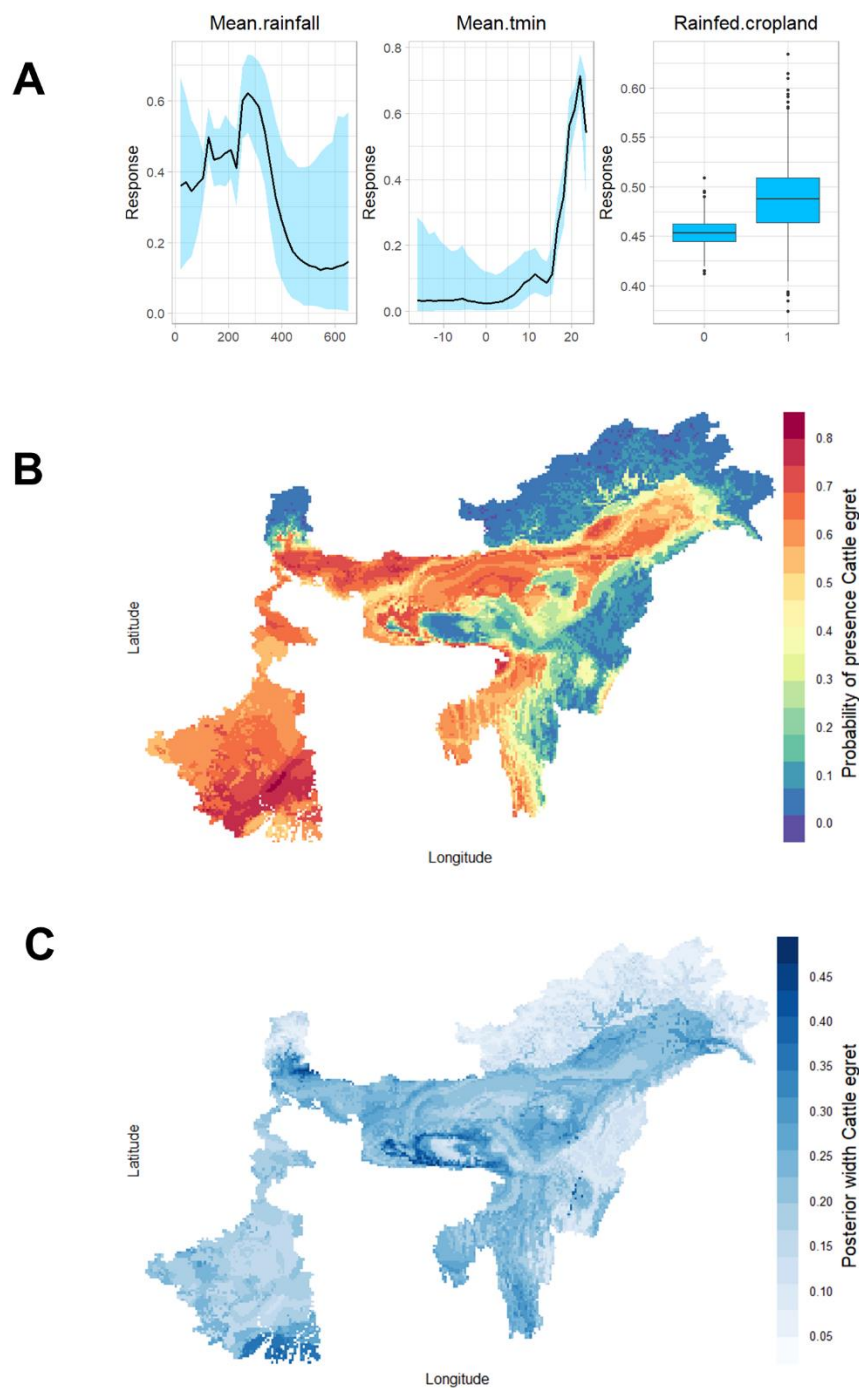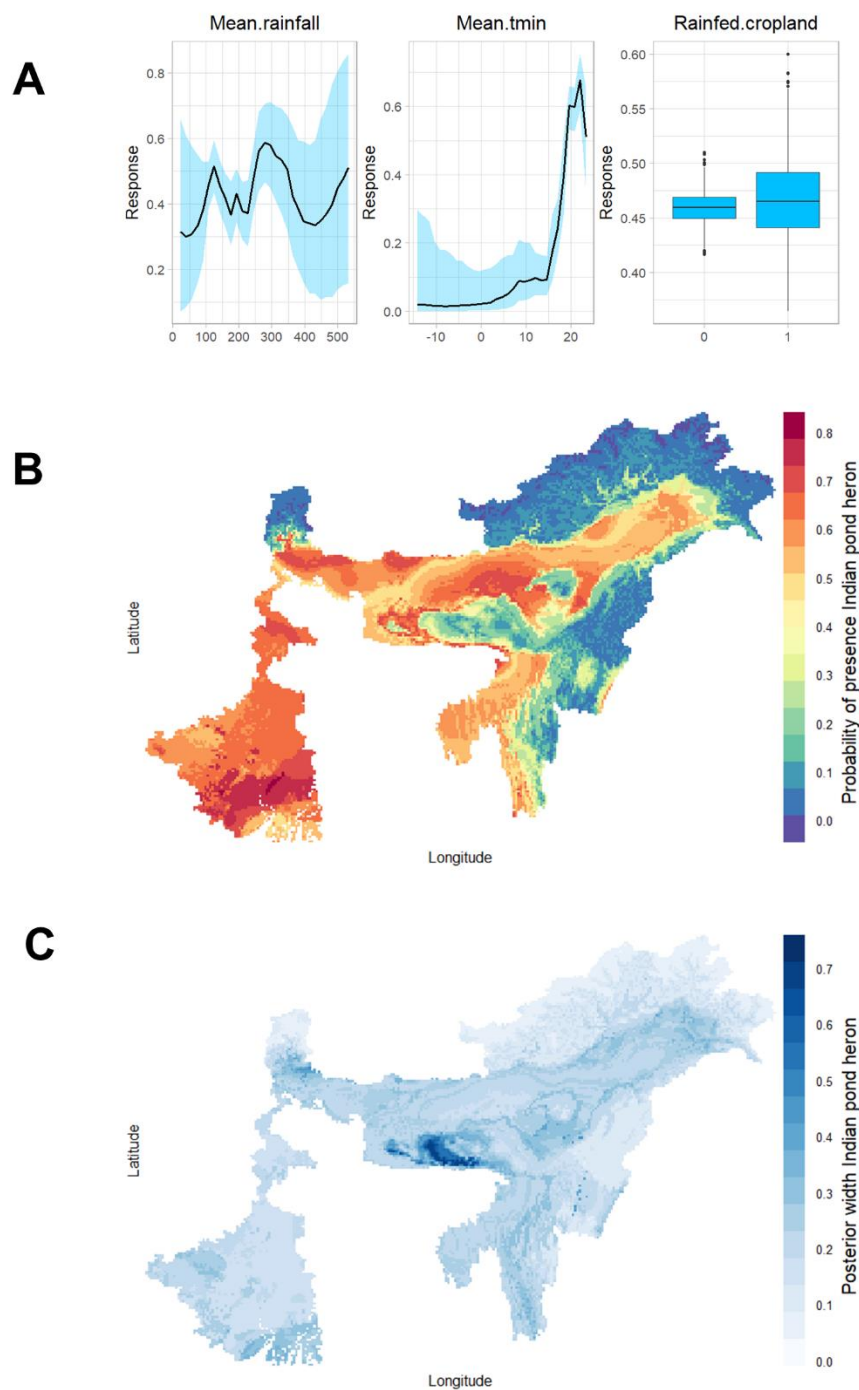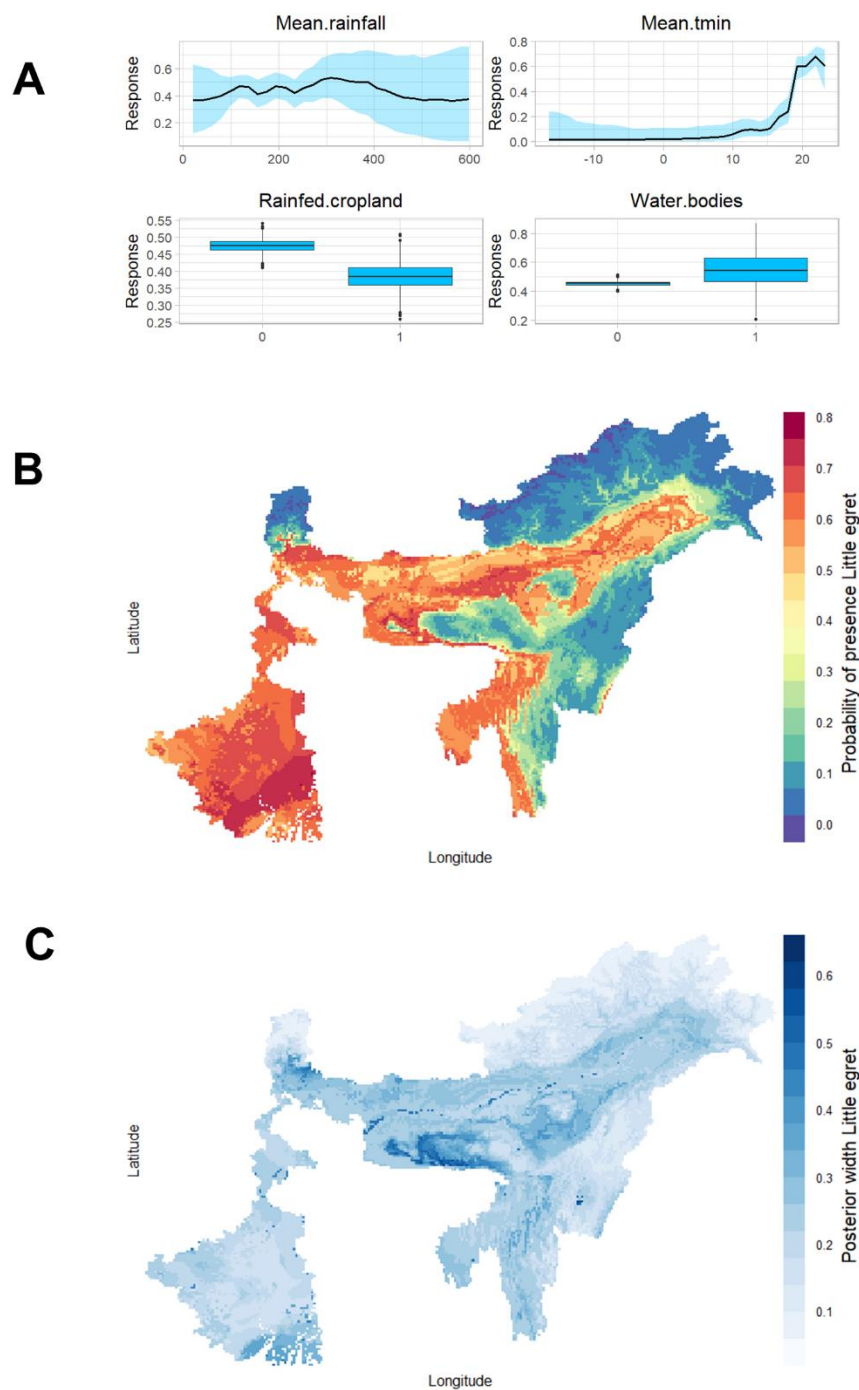
Figure S4.3. A map of cattle egret (*B. ibis)* occurrence in northeast India.

The map is constructed using species distribution modelling with BART (see Appendix 3 Text S4.1), including (A) partial dependence plots, (B) the posterior mean and (C) the posterior width (95% credible interval).
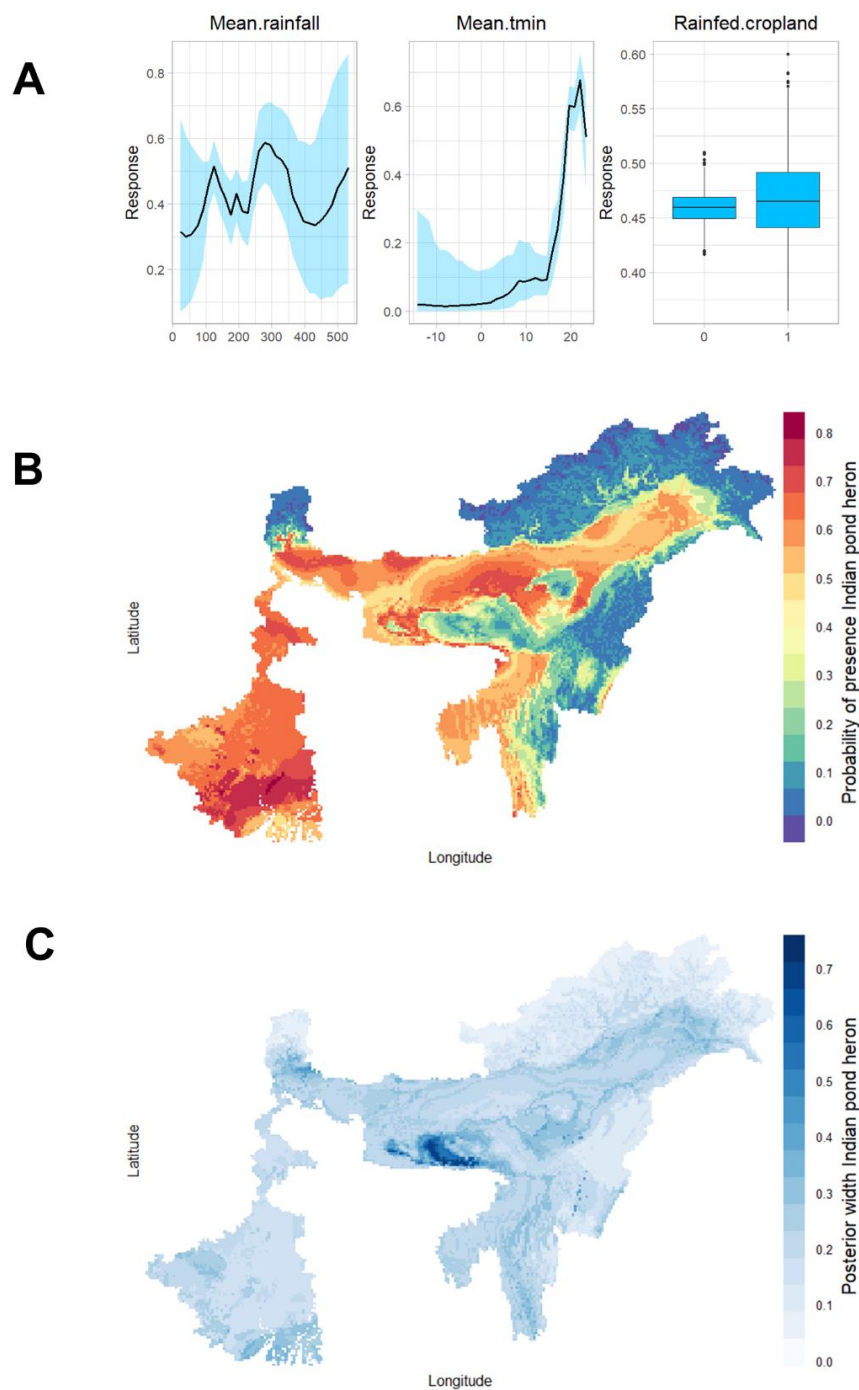
Figure S4.4. A map of intermediate egret (*A. intermedia)* occurrence in northeast India.

The map is constructed using species distribution modelling with BART (see Appendix 3 Text S4.1), including (A) partial dependence plots, (B) the posterior mean and (C) the posterior width (95% credible interval).

Figure S4.5. A map of little egret (*E. garzetta)* occurrence in northeast India.

The map is constructed using species distribution modelling with BART (see Appendix 3 Text S4.1), including (A) partial dependence plots, (B) the posterior mean and (C) the posterior width (95% credible interval).
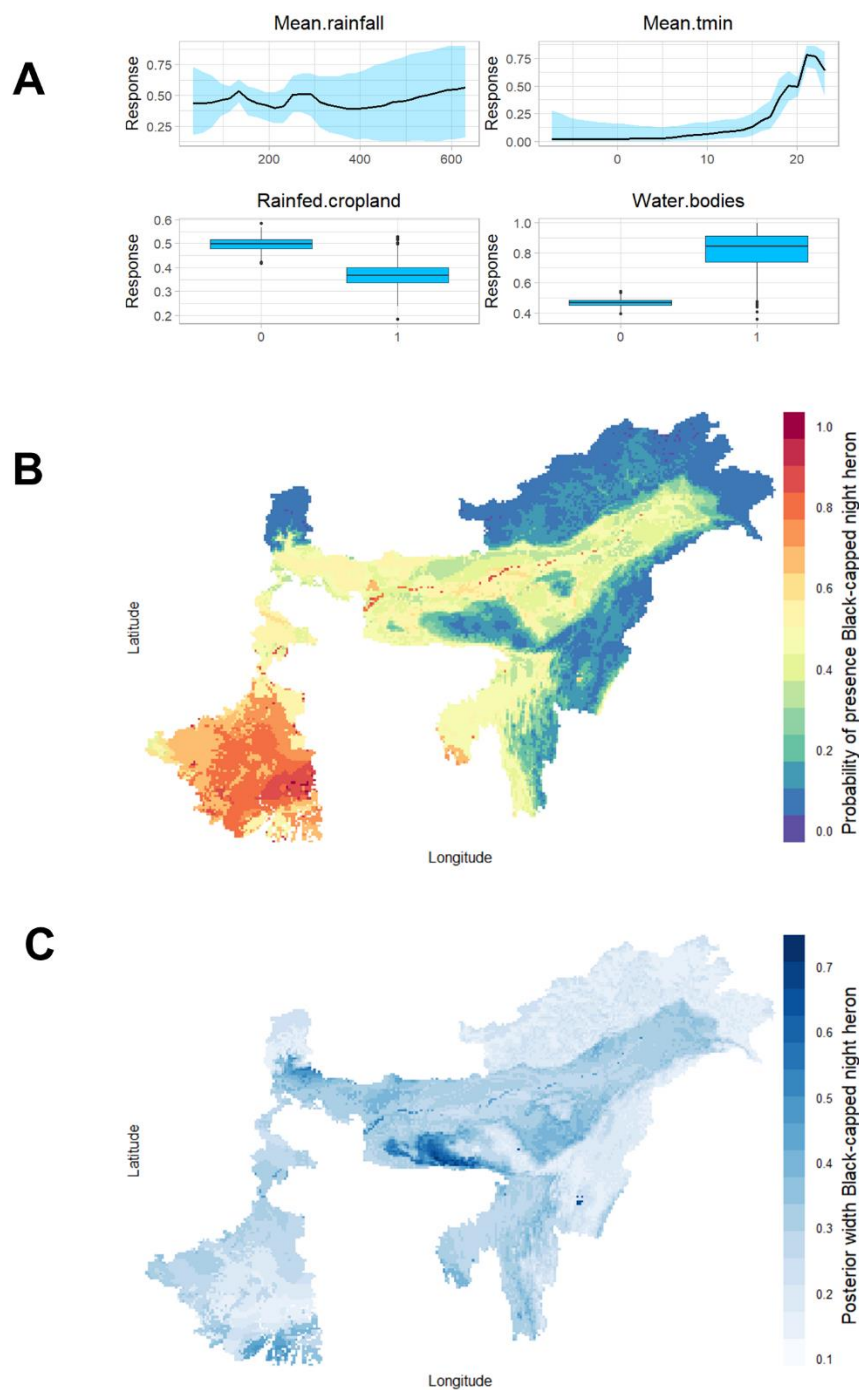
Figure S4.6. A map of Indian pond heron (*A. grayii)* occurrence in northeast India.

The map is constructed using species distribution modelling with BART (see Appendix 3 Text S4.1), including (A) partial dependence plots, (B) the posterior mean and (C) the posterior width (95% credible interval).
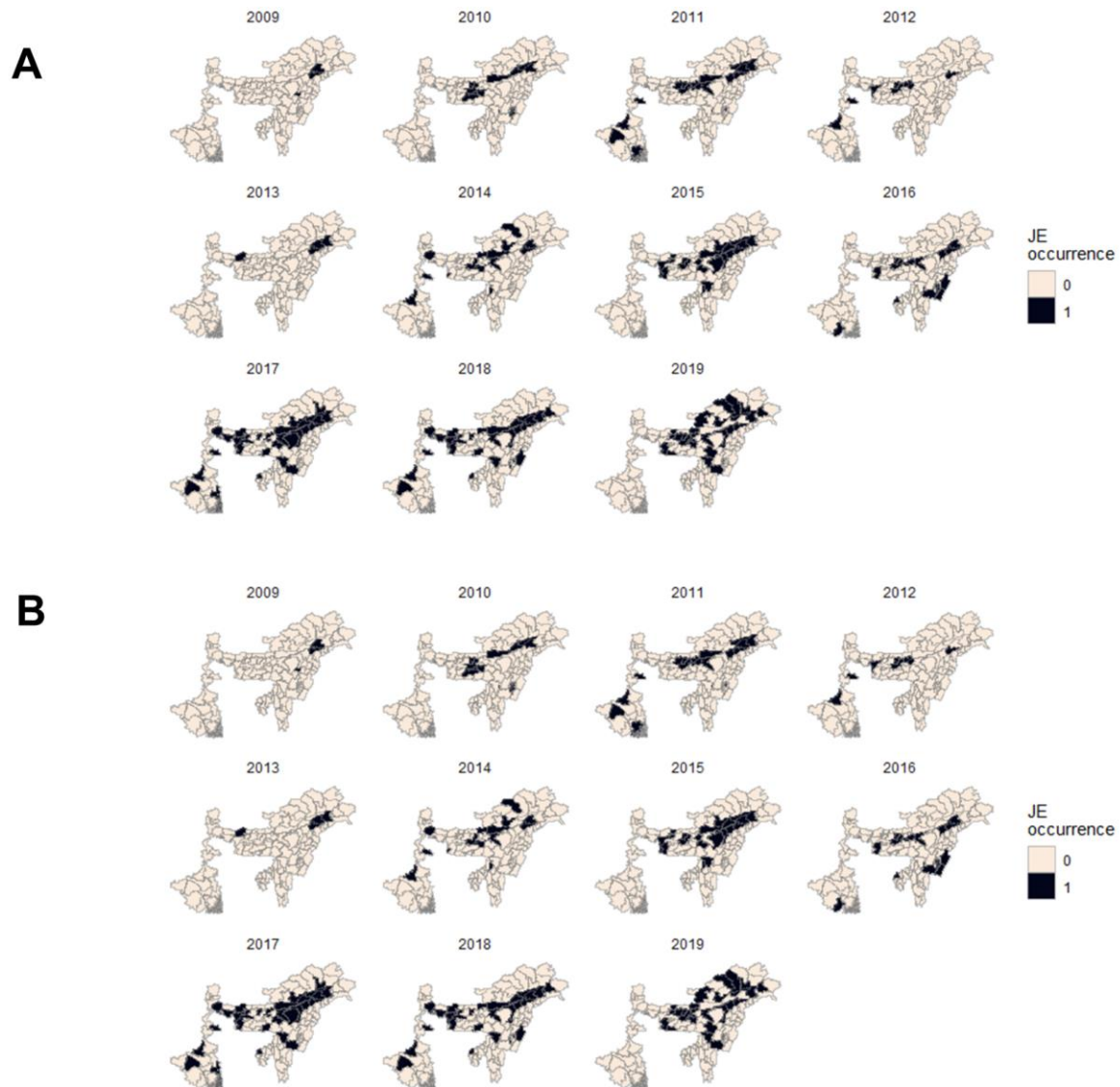
Figure S4.7. A map of black-crowned night heron (*N. nycticorax)* occurrence in northeast India.

The map is constructed using species distribution modelling with BART (see Appendix 3 Text S4.1), including (A) partial dependence plots, (B) the posterior mean and (C) the posterior width (95% credible interval).
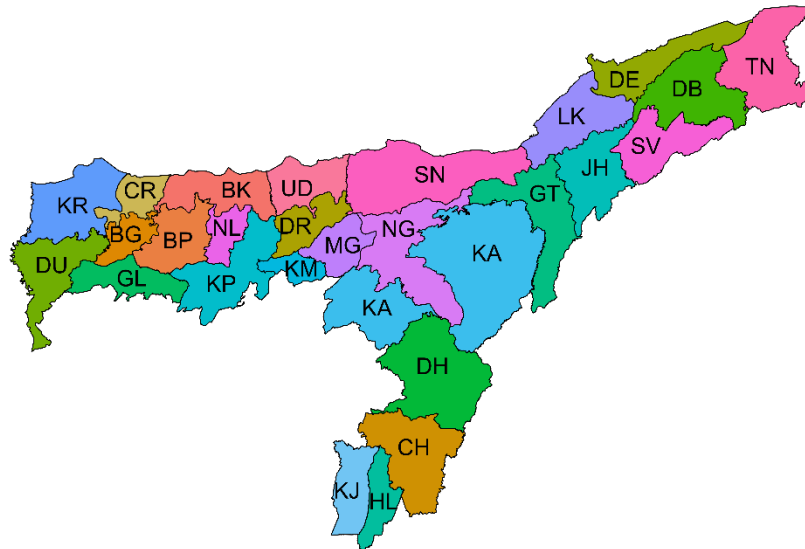
Figure S4.8. The spatial pattern of JE outbreaks between 2009 and 2019 in northeast India.

The presence and absence of JE outbreak occurrence per district per year at a threshold of (A) one confirmed case and (B) three confirmed cases per district, with black donating a confirmed case presence, pale pink denoting absence of reported cases.

Figure S4.9. Time series of monthly confirmed JE cases per district in the state of Assam*, 2009–2019.

(A) The location of districts in Assam and (B) reported confirmed JE cases per district from 2009-2019. *Abbreviations for Assam districts provided for the time series data (B).
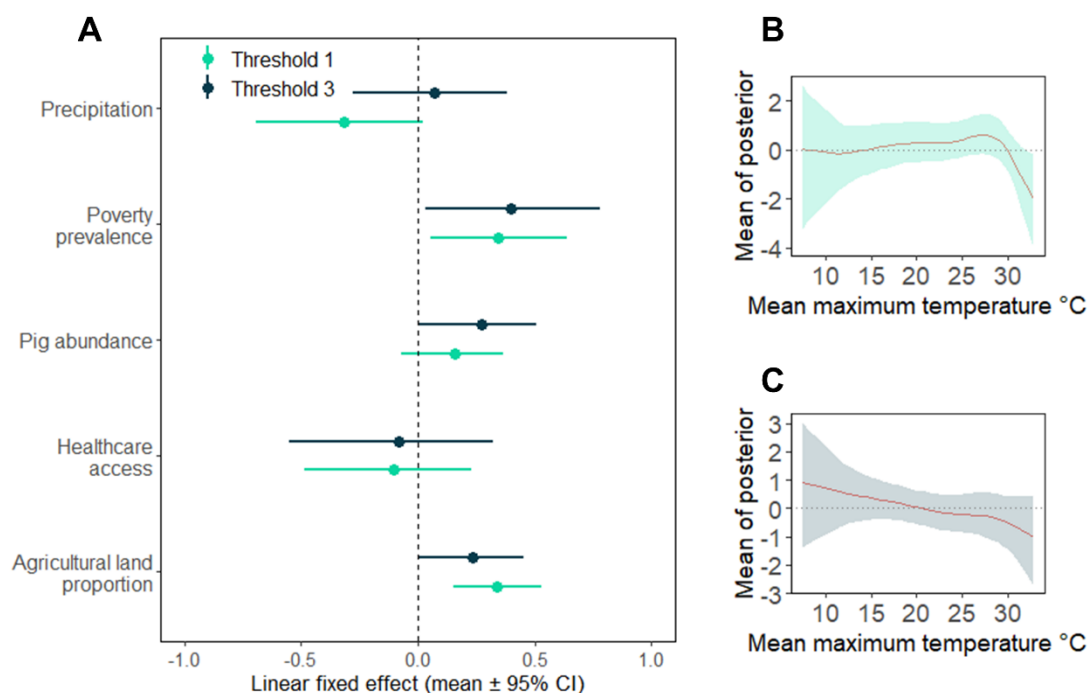
Figure S4.10. Correlates of annual JE occurrence in northeast India 2009–2019 for different JE outbreak occurrence thresholds.

(A) The mean and 95% credible interval of the posterior distribution for each model covariate for the best fitting model with a threshold of one confirmed case and three confirmed cases for comparison. The linear fixed effects are displayed on the standardised z-score scale so parameters measure the effect of 1 scaled unit change in the covariate (1 standard deviation) on the log odds of occurrence. Curves show nonlinear effects of mean annual Tmax on JE outbreak probability for (B) threshold 1 and (C) threshold 3 models.
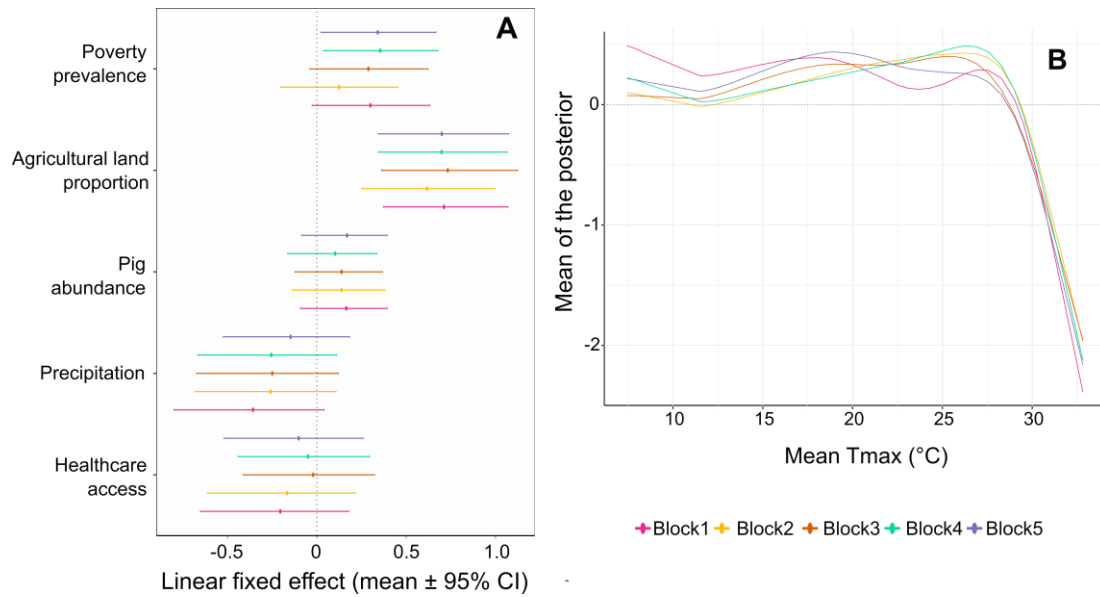
Figure S4.11. Random 5-fold cross-validation for the spatial model of JE occurrence.

The direction and magnitude of linear fixed effects and nonlinear climate effects in the model were robust to 5-fold cross validation. This involved in turn excluding all districts from each of 5 folds, with point or line colour denoting the fold that was excluded in each model iteration. (A) Points and error bars show linear fixed effects (mean and 95% credible interval), (B) lines show fitted nonlinear effects of mean annual Tmax on the probability of JE outbreak occurrence.
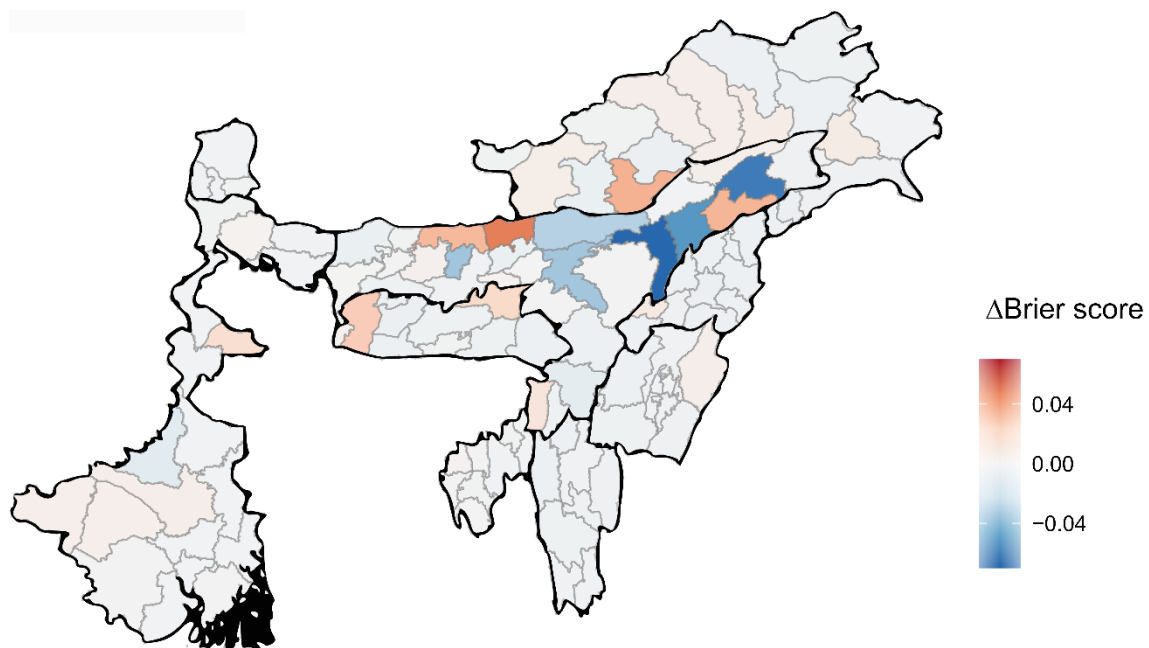
Figure S4.12. The difference in Brier score between the baseline (random effects only) and socio-ecological model per district.

A negative (blue) value indicates that the socio-ecological model performs better on OOS predictive ability for the district when compared to the baseline model, a positive (red) value indicate that the socio-ecological model performs worse than the baseline and, a zero value (white) indicates equivalent performance between models.
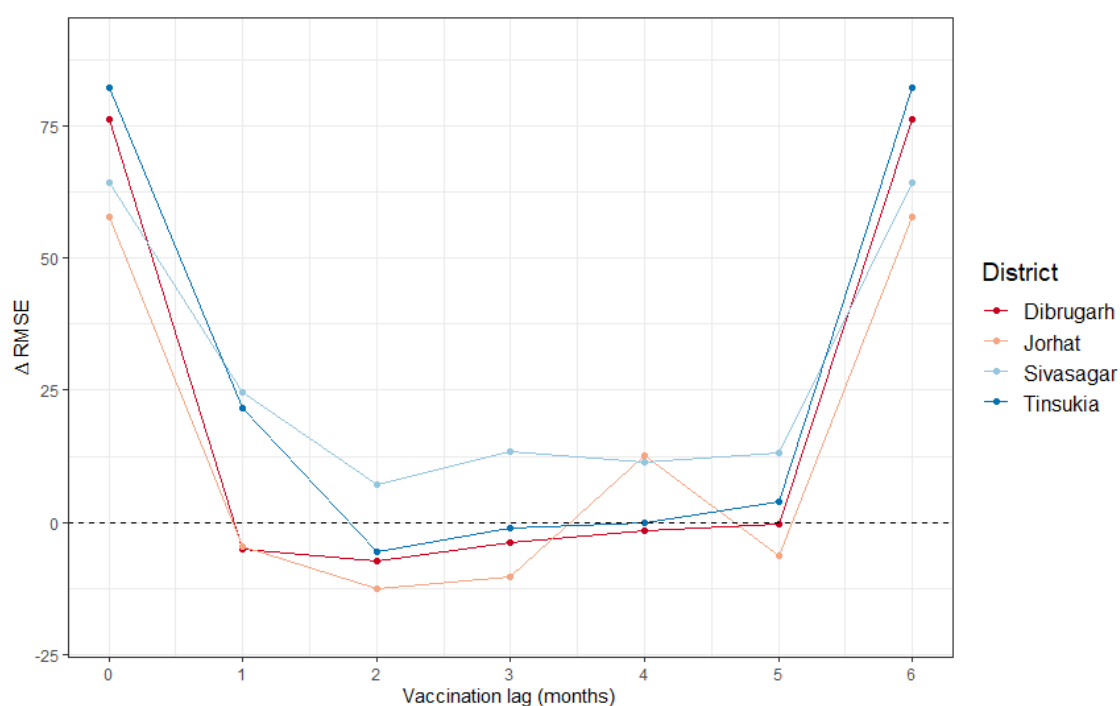
Figure S4.13. Comparative effect of the inclusion of vaccination data at different lags on the predictive accuracy of the temporal model of JE incidence in endemic districts of Assam.

Points show the predictive performance of the environment and vaccine-driven JE incidence model when vaccination data at different lags (months) are included in the model (posterior mean and 95% credible interval). I measured predictive performance as out-of-sample root mean square error (RMSE), calculated for four neighbouring districts in Assam (i.e., Dibrugarh, Jorhat, Sivasagar and Tinsukia) across the entire study period (2009-2019). The model that included vaccination data at a 2-month lag improved out-of-sample RMSE for all districts when compared to the environment-driven model (RMSE value represented by dashed line) and other vaccination lags.

Appendix 4: Supplementary figures and data for Chapter 5

This appendix provides supplementary figures, tables and information on data sources for the analyses conducted in Chapter 5, 'Predicting Japanese encephalitis risk under different scenarios of global change'. The items contained in this appendix are:

Table S5.1. Total human population (in thousands) in per state in northeast India in 2011 (Government of India, 2011) and under different SSP scenarios for 2030, 2050 and 2070 (Jones and O'Neill, 2016).

Table S5.2. Model selection results for models predicting spatial JE outbreak occurrence in northeast India.

Table S5.3. Changing population at risk of JE in northeast India under different SSP-RCP scenarios.

Figure S5.1. Map of India indicating states and union territories.

Table S5.1. Total human population (in thousands) per state in northeast India in 2011 (Government of India, 2011) and under different SSP scenarios for 2030, 2050 and 2070 (Jones and O'Neill, 2016).

State	Total population (in thousands)												
	2011	2030				2050				2070			
		SSP1	SSP2	SSP3	SSP5	SSP1	SSP2	SSP3	SSP5	SSP1	SSP2	SSP3	SSP5
Arunachal Pradesh*	85	92	101	107	93	88	108	127	88	76	105	143	76
Assam	1126	1330	1408	1491	1329	1392	1590	1844	1389	1307	1619	2128	1303
Manipur	314	366	384	399	366	382	429	479	382	362	437	543	361
Meghalaya	332	390	415	441	390	404	466	544	403	375	470	625	373
Mizoram	134	148	160	169	149	145	174	202	145	128	170	228	128
Nagaland	205	227	245	259	227	221	266	308	221	196	260	348	196
Sikkim	128	121	136	140	121	97	133	149	97	71	117	156	71
Tripura	464	549	580	613	547	574	653	755	571	539	663	867	536
West Bengal	4476	5399	5575	5775	5388	5861	6360	7030	5838	5726	6608	8054	5696
Total	**1175**	**1403**	**1462**	**1525**	**1400**	**1499**	**1658**	**1861**	**1494**	**1443**	**1708**	**2134**	**1436**

A part of Arunachal Pradesh is claimed by both India and China

Table S5.2. Model selection results for models predicting spatial JE outbreak occurrence in northeast India.

The table shows the differences in structure and out-of-sample model fit (Brier score) for the baseline (random effects only) and best-fitting environmental model of JE outbreak occurrence.

Outbreak threshold	Model	Random effects	Environmental effects	Brier score
1 confirmed case	Baseline	District-level spatial random effects	-	0.064
	Environmental	District-level spatial random effects	Precipitation Rice cropland proportion Poverty prevalence Nonlinear Tmax function	0.061

Table S5.3. Changing population at risk of JE in northeast India under different SSP-RCP scenarios.
Change in absolute human population at risk in northeast India when compared to present-day, broken down by epoch (2030, 2050, 2070) and SSP-RCP scenarios.

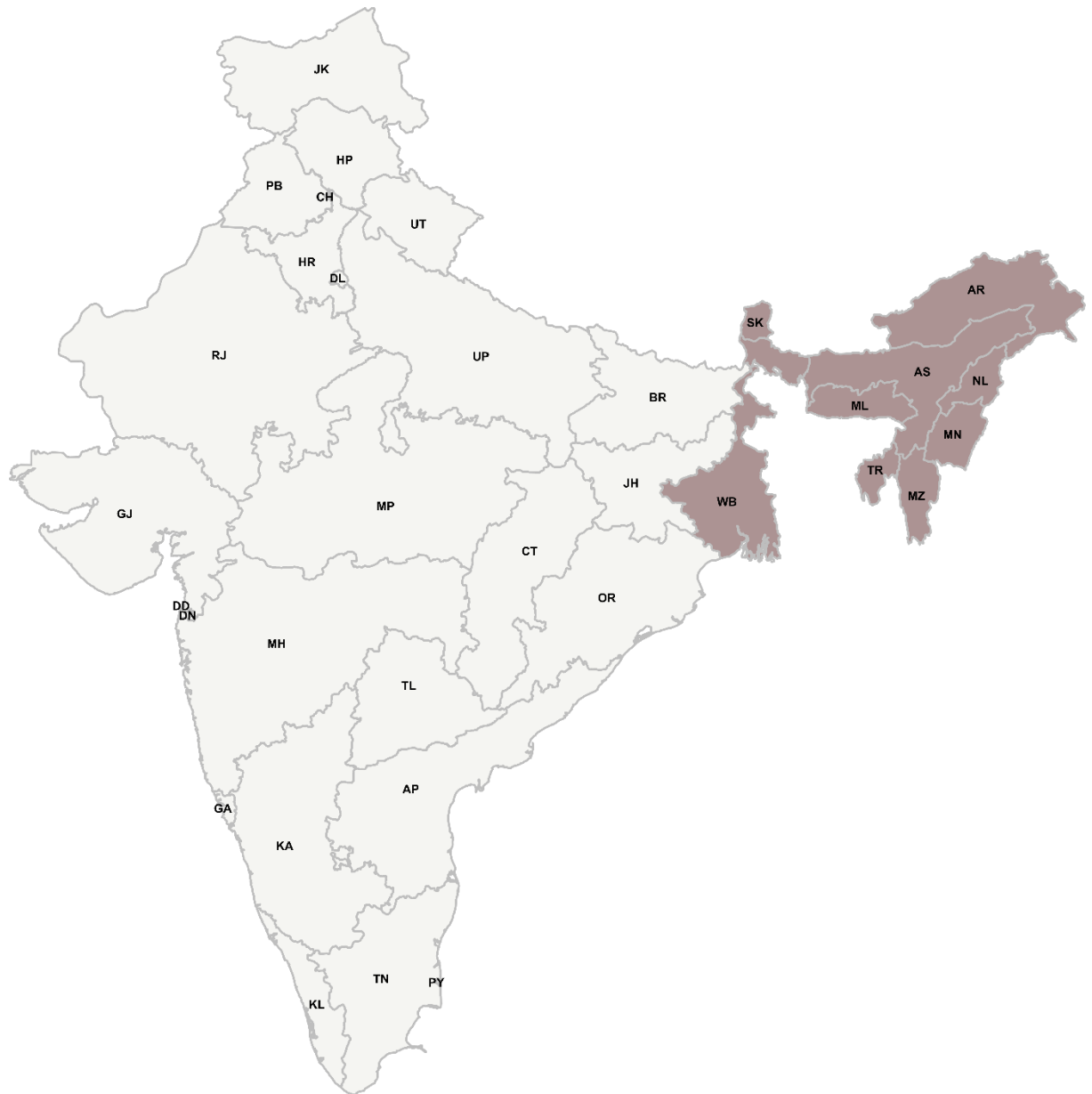| Epoch	SSP-RCP	Change in population at risk from present-day
2030	SSP1-RCP2.6	-9556 (-12475, -6637)
	SSP2-RCP4.5	-2484 (-4074, -894)
	SSP3-RCP6.0	2487 (132, 4843)
	SSP5-RCP8.5	-9442 (-10527, -8357)
2050	SSP1-RCP2.6	-9734 (-13168, -6300)
	SSP2-RCP4.5	4559 (3118, 5999)
	SSP3-RCP6.0	25552 (20460, 30644)
	SSP5-RCP8.5	-13624 (-12476, -14773)
2070	SSP1-RCP2.6	-22338 (-25227, -19450)
	SSP2-RCP4.5	3574 (-906, 8054)
	SSP3-RCP6.0	45739 (38028, 53449)
	SSP5-RCP8.5	-24844 (-25652, -24035)

Figure S5.1. Map of India indicating states and union territories*.

The northeast region described in this study (nine states) is highlight in brown.

*Abbreviations for Indian states and union territories: AP - Andhra Pradesh, AR - Arunachal Pradesh, AS - Assam, BR - Bihar, CH – Chandigarh, CT- Chhattisgarh, DD - Daman and Diu, DL - Delhi, DN - Dadra and Nagar Haveli, GA – Goa, GJ – Gujarat, HP - Himachal Pradesh, HR - Haryana, JH - Jharkhand, JK - Jammu and Kashmir, KA - Karnataka, KL – Kerala, MH - Maharashtra, ML - Meghalaya, MN - Manipur, MP - Madhya Pradesh, MZ - Mizoram, NL - Nagaland, OR - Odisha, PJ - Punjab, PY - Puducherry, RJ - Rajasthan, SK - Sikkim, TL – Telangana, TN – Tamil Nadu, TR - Tripura, UP - Uttar Pradesh, UT - Uttarakhand, WB – West Bengal.

Appendix 5: Typeset publication based on thesis work

Typeset publications based on and informed by thesis work.

Franklinos LHV, Redding DW, Jones KE, Abubakar I (2022) Joint spatiotemporal vector modelling reveals seasonally dynamic hazard patterns of Japanese encephalitis vector abundance across India. PLOS Neglected Tropical Diseases 16 e0010218.https://doi.org/10.1371/journal.pntd.0010218

Hassell JM, Bukachi SA, Muloi DM, Takahashi E, Franklinos LHV (2021) The Natural Environment & Health in Africa. Report commissioned by WWF and Smithsonian Conservation Biology Institute.
https://doi.org/10.5479/10088/111281

Hassell JM, Newbold T, Dobson AP, Linton Y, Franklinos LHV, Zimmerman D, Pagenkopp Lohan KM (2021) Towards an Ecosystem Model of Infectious Disease. Nature Ecology & Evolution 5 907–918.
https://www.nature.com/articles/s41559-021-01454-8

House of Commons Environmental Audit Committee (2021) Growing back better: putting nature and net zero at the heart of the economic recovery, Third Report of Session 2019–21, 17 Feb 2021.
https://committees.parliament.uk/publications/4712/documents/47430/default/

Gibb R, Franklinos LHV, Redding DW, Jones KE (2020) Ecosystem perspectives are needed to manage zoonotic risks in a changing climate. BMJ 371 m3389. https://www.bmj.com/content/371/bmj.m3389.full

Franklinos LHV, Jones KE, Redding DW, Abubakar I (2019) The effect of global change on mosquito-borne disease. Lancet Infectious Diseases 19 e302-e312. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(19)30161-6/abstract