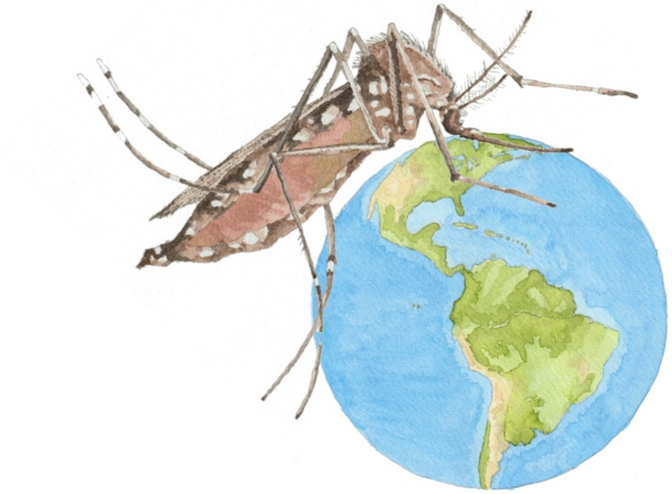
Assessing the impact of global environmental change on mosquito-borne disease: A Planetary Health approach



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Declaration

I, Isabel Fletcher, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Anthropogenic pressures on the Earth's natural systems are mounting, which is having devastating consequences for human health, including an increased threat of mosquito-borne diseases. Climate variation and land-use change influence mosquito-borne disease risk by determining vector occurrence and distribution, in addition to vector-human contact rates. Despite an understanding of the mechanisms underlying the relationship between climate variation and mosquito-borne disease transmission, few studies have considered the impact of mediating and interacting factors. There is a growing need to understand the joint impact of climate variation and land-use alterations on the spatiotemporal variation of mosquito-borne diseases, in conjunction with socioeconomic factors such as vector control activities. In this thesis, I investigate how climate variation, land-use change and socioeconomic factors affect spatiotemporal disease risk by using an integrated modelling framework. I firstly investigate the joint influence of both climate variation and vector control activities on malaria incidence in a high-risk border region of Ecuador, using a Bayesian hierarchical mixed effects modelling framework to account for multiple risk factors (Chapter 2). I find a difference in both the effectiveness of control measures and the impact of climate variation on the two predominant malaria parasites, with *P. falciparum* demonstrating greater climate sensitivity than *P. vivax* malaria. I then test for the interacting effects of climate and land use on disease risk by investigating the synergistic effects of environmental degradation and climate variation on malaria re-emergence in southern Venezuela in Chapter 3. I show that the effect of temperature on malaria incidence is amplified in areas degraded by mining activity. Further, I demonstrate that the choice of climate data product used to inform climate-disease models has implications for the resulting associations between climatic variables and disease risk (Chapter 4). Finally, in Chapter 5 I investigate differing taxonomic mosquito responses to land-use change using a systematic data search strategy and comparative space-for-time approach. I find strong declines in species richness of both *Aedes* and *Anopheles* mosquitoes in urban environments, in addition to diverging species-specific abundance responses. I additionally discuss how climate-disease research can be intuitively integrated into policy-relevant impact assessments. In this thesis, I demonstrate how multiple components of mosquito-borne disease risk can be attributed to environmental change, advancing knowledge on how climate variation, land-use change and socioeconomic factors synergistically interact to determine mosquito-borne disease risk.

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Glossary of key terms

Annual parasite incidence (API)	Number of confirmed malaria cases per 1,000 people per year.
Bayesian hierarchical model	Statistical models where observations fall into multiple levels (or hierarchies) and model parameters are estimated using a Bayesian approach.
Climate service	A decision aide based on climate information, aimed at reducing vulnerability to climate hazards.
Downscaling	A procedure taking information known at a coarse scale to make predictions at a fine scale.
Earth observations	Atmospheric, oceanic, or terrestrial data collected about the planet, via remote sensing technologies and ground-based techniques such as meteorological stations.
El Niño-Southern Oscillation (ENSO)	Irregular periodic (2-7 years) fluctuation in sea surface temperatures and air pressure over the tropical eastern Pacific Ocean. El Niño refers to the anomalous warming of sea surface temperatures. La Niña refers to episodes of cooler sea surface temperatures.
Extrinsic incubation period (EIP)	The time taken for a pathogen e.g., malaria parasite, to develop inside a vector e.g., a mosquito.
Falciparum malaria	Malaria caused by *Plasmodium falciparum* parasites that can progress to severe illness, and even death.
Indoor residual spraying (IRS)	Application of long-lasting, residual insecticide to potential malaria vector resting surfaces such as internal walls, eaves and ceilings of houses.
Land-use change	Process by which human activities transform the natural landscape, including urbanisation, deforestation and afforestation, and cropland expansion.

Space spraying	The dispersal of a liquid fog of insecticide into an outdoor area to kill adult insects.
Space-for-time approach	Ecological method where spatial patterns in ecological variables are used to model temporal processes.
Ultra-low-volume (ULV) fumigation	Application of minimum effective volume preparations of aerosol insecticide.
Vivax malaria	Malaria caused by *Plasmodium vivax* parasites, characterised by dormant liver stages (hypnozoites) that can persist in the liver and cause relapsing infections. Compared to *P. falciparum*, *P. vivax* is less fatal.

Chapter 1 – Introduction

1.1. Planetary Health – underscoring the interconnectedness of human and environmental health

Humans are having an unequivocal and profound impact on the planet. 75% of the Earth's land surface is subject to widespread human pressures and major drivers of this global environmental change include climate change, pollution, agricultural intensification, and resource scarcity (Whitmee *et al.*, 2015; Venter *et al.*, 2016). Human-induced warming of the Earth's climate system is estimated to have reached approximately 1°C above pre-industrial levels (IPCC, 2021) and one third of natural land has been converted to cropland or pasture (Foley *et al.*, 2007). Since 2000, more than 2.3 million km^2 of primary forest has been cut down (Hansen *et al.*, 2013) and the global population is predicted to peak at 9.73 billion by 2064 (Vollset *et al.*, 2020). Considerable evidence is mounting that these human demands on natural systems are unsustainable, which has widespread consequences not only for global biodiversity (Newbold *et al.*, 2015) but also for services to humanity that underpin our health and wellbeing (Costanza *et al.*, 2014). These changes to the Earth form a distinct footprint that have defined a new geological epoch – the Anthropocene (Lewis and Maslin, 2015) and understanding the impacts of global environmental change during the Anthropocene is one of the most pressing issues of the 21st century.

Planetary health is a rapidly evolving and emerging field with the core message that humans are interconnected with nature, and our health and wellbeing is predicated on the health of the planet's natural systems (Myers, 2017). Planetary Health considers that the environmental impacts of our anthropogenic footprint should be recognised in progress of human health and wellbeing (Horton *et al.*, 2014; Whitmee *et al.*, 2015). The concept embraces 'systems thinking', where humanity is part of a coupled system with nature (Peters, 2014; Steffen *et al.*, 2015). Humans rely heavily on the planet for natural resources that ultimately sustain our health and wellbeing, as well as our social and economic systems (Costanza *et al.*, 2014). For example, the planet provides us with indispensable ecosystem services such as clean air and water, a stable climate and weather system, pollination services, infectious disease regulation, and natural sources of energy, among other things (Costanza *et al.*, 1997; Figure 1.1). In 2005, it was estimated that 60% of ecosystems services are being degraded as a direct result of human pressure on the environment (MEA, 2005). Loss of vital natural resources and changes to ecosystem functioning and flow of ecosystem services, such as disease regulation will ultimately have staggering implications for human health.

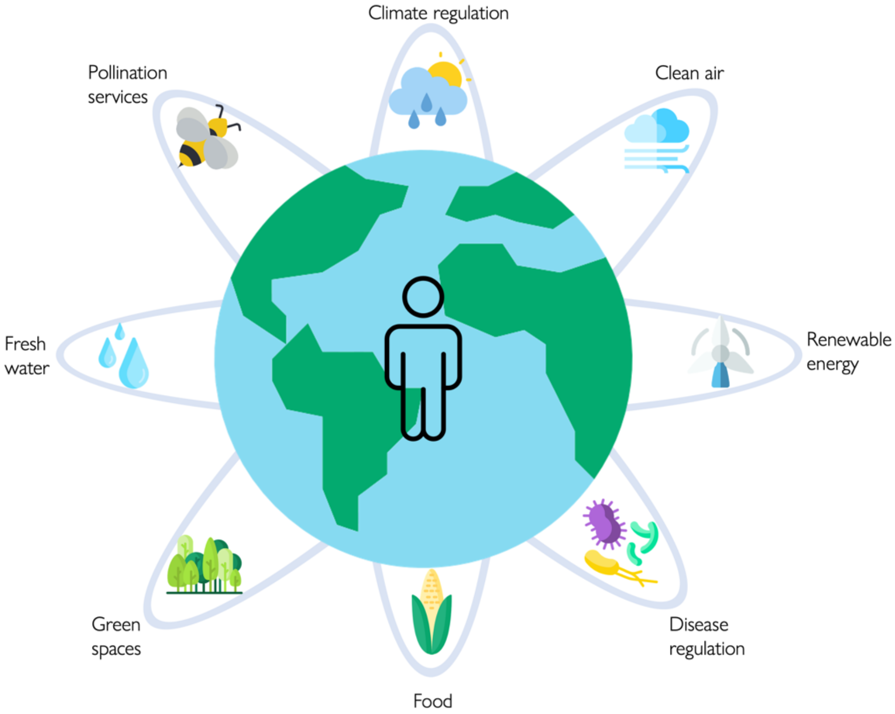


Figure 1.1. Planetary Health: A healthy environment provides the critical foundations for the health and wellbeing of humanity. The concept of Planetary Health is predicated on the idea that the health of the planet and the health of humanity are interlinked. A healthy ecosystem and planet provide a wealth of resources to support sustainable and healthy human living, including suitable climate conditions, green spaces, pollination services, food and clean air and water. This figure has been designed using resources from Flaticon.com.

Placing the concept of Planetary Health in the scope of global environmental change can be a useful approach to advance and progress understanding of how environmental change affects human health. This concept can also be the basis of developing effective and sustainable solutions. Drawing on knowledge from outside the health sector, for example from environmental science, to address important questions about human health in the Anthropocene presents several opportunities. Firstly, adopting a Planetary Health approach to applications in public health provides new scope for transdisciplinary collaboration, and knowledge and skills exchange. Second, research and use of multisource data can be expanded across multiple disciplines including public health, climate science and ecology. Finally, adopting a Planetary Health approach can increase the understanding of the dynamic two-way relationship between people and nature, which can enhance nature’s benefits for a sustainable quality of life (Mace, 2014; Díaz *et al.*, 2018). The causal links between global environmental change and human health are however complex and are often indirect and dependent on modifying factors. What is clear is that despite the opportunities provided by the Planetary Health concept, the overarching complexity of how environmental change impacts human health remains a significant challenge.

1.2. A spotlight on mosquito-borne diseases

There is growing recognition that human alterations to the Earth's natural systems will modify the global burden of disease over the coming century (Whitmee *et al.*, 2015). Mosquito-borne diseases provide a good case study to test the applications of Planetary Health in understanding human health and global environmental change, which is vital to inform disease surveillance and control. Mosquito-borne diseases impose a significant global health burden, with roughly half of the global population at risk (WHO, 2014; Tam *et al.*, 2016). Malaria, dengue, yellow fever, chikungunya, Zika and West Nile virus, among others account for the largest number of cases reported, mortality and disability-adjusted life years (DALYs), of all known vector-borne diseases (WHO, 2018a). Over the past 50 years, incidence of dengue has increased over 30-fold (Bhatt *et al.*, 2013). Although great efforts have been made in reducing malaria cases worldwide, progress is now stalling and outbreaks have increased in both size and frequency since 2014 (WHO, 2020). In addition, 14 million more malaria cases were reported in 2020, compared to 2019 (WHO, 2021c). Mosquito-borne diseases exert a substantial toll on populations, restricting economic development and progress towards achieving global health equity. In 2017, an estimated 2,922,630 DALYs were attributed to global cases of dengue (Zeng *et al.*, 2021) and in 2017 the global cost of *Plasmodium vivax* malaria alone was estimated to be US$359 million (Devine *et al.*, 2021). There is great concern that global environmental change is responsible for the emergence and re-emergence of mosquito-borne diseases (Rocklöv and Dubrow, 2020). A greater understanding of how mosquito-borne diseases are impacted by environmental change, including climate variation and land-use modifications is vital for curbing the devastating impacts these diseases have on populations worldwide.

1.3. Impact of climate variation and change on mosquito-borne diseases

There is already considerable evidence that climate change is influencing the occurrence and distribution of many mosquito-borne diseases. Several diseases once limited to tropical and subtropical areas of the world, are increasingly being observed both in regions previously unaffected, such as temperate regions, and in areas where incidence had dramatically subsided (Kraemer *et al.*, 2015; Leedale *et al.*, 2016; Watts *et al.*, 2021). For example, malaria distribution has expanded to higher elevations in Colombia and the East African highlands (Pascual *et al.*, 2006; Siraj *et al.*, 2014) and transmission is projected to expand further with future climate change (Endo and Eltahir, 2020). Indeed, the number of months suitable for malaria transmission has already increased by 39% in highland areas of the world, between 1950-1959 and 2010-2019 (Romanello *et al.*, 2021). In addition, global climate suitability for the dengue mosquito vector *Aedes albopictus* increased by 15% in 2018, contributing to recent outbreaks in southern Europe (Watts *et al.*, 2021). However, an understanding of how changing climate suitability alongside other drivers of global environmental change such as land use, impact mosquito-borne diseases is limited.

Mosquito-borne diseases are highly sensitive to environmental conditions because of the sensitivity of the life-history traits of disease-causing pathogens and mosquito vectors to climate conditions (Rogers and Randolph, 2006; Ciota *et al.*, 2014). Climate has been shown to be an important predictor of mosquito-borne disease outbreaks (Caldwell *et al.*, 2021). Much of the research up to now on mosquito-borne diseases and climate has focused on quantifying the impact of temperature on disease risk. This evidence has been provided by a combination of modelling and laboratory studies (Nissan *et al.*, 2021). Warmer temperatures increase the development (Bayoh and Lindsay, 2003), oviposition (Rodríguez *et al.*, 2015), vectorial capacity and competence (Tesla *et al.*, 2018; Chu *et al.*, 2019), survivorship (Christiansen-Jucht *et al.*, 2014) and abundance (Beck-Johnson *et al.*, 2013; Marinho *et al.*, 2016) of disease-carrying mosquito vectors for malaria, dengue, chikungunya and Zika. The time taken for the malaria parasite, and dengue and chikungunya viruses to develop inside mosquitoes (the extrinsic incubation period) is also faster at warmer temperatures (Jácome *et al.*, 2019; Winokur *et al.*, 2020).

Temperature by far has been shown to be one of the most important factors in driving transmission of mosquito-borne disease (Mordecai *et al.*, 2017; Shocket *et al.*, 2018; Caldwell *et al.*, 2021). The evidence for the sensitivity of mosquito-borne diseases to temperature is vast and constantly expanding. A recent field study showed that oviposition of the principal vector of dengue, *Aedes aegypti* increased over four times when minimum temperatures were 1°C higher (Gimenez *et al.*, 2020). Similarly, a 1°C increase in minimum temperature was also associated with a 1.07 relative risk of *P. falciparum* malaria in China (Bi *et al.*, 2013). In modelling studies assessing the impact of climate variation on malaria, models are often parameterised solely for the *P. falciparum* malaria parasite (Rodó *et al.*, 2021). In addition, the effect of climate on both *P. falciparum* and *P. vivax* malaria cases is frequently analysed together (Hurtado *et al.*, 2018), despite the two main malaria-causing parasites having different thermal optima. The *P. falciparum* malaria parasite has a minimum thermal limit of 18°C in comparison to 15°C for *P. vivax* malaria (Gilles, 1999; Watts *et al.*, 2019). Based on these differing thermal limits it is plausible that the climate sensitivity of these two types of malaria may differ, yet there has been a limited assessment of this.

In practice, the relationship between temperature and mosquito-borne diseases is complicated and is non-linear. In both Colombia and South Asia, temperatures that are too high negatively affect dengue transmission (Peña-García *et al.*, 2017; Servadio *et al.*, 2018). In general, dengue transmission declines past temperatures of 32°C, where temperature begins to have a negative impact on mosquito development and survival (Mordecai *et al.*, 2017, 2019). For malaria, a similar non-linear relationship has also been demonstrated, where the strongest transmission is observed above 25°C (Laneri *et al.*, 2019) and the optimum temperature is detected at approximately 29°C (Shapiro *et al.*, 2017). In addition to non-linearities complicating the disease-climate relationship, average temperature variation may not be the best determinant of mosquito-borne diseases. Instead, fluctuations in daily, seasonal and diurnal temperatures play an important role in determining mosquito-borne disease risk and could be more reliable and robust predictors (Paaijmans *et al.*, 2010; Mordecai *et al.*, 2013; Beck-Johnson *et al.*, 2017; Huber *et al.*, 2018; Robert *et al.*, 2019). These complicating factors make generalising the effects of temperature on mosquito-borne diseases extremely difficult.

Rainfall is another important and well-studied climatic variable that influences mosquito-borne disease transmission. Rainfall has a crucial impact on mosquito development and is required to complete the water-dependent stages of the mosquito lifecycle (Rejmánková *et al.*, 2013). In general, rainfall expands the availability of mosquito breeding sites leading to increased mosquito larval densities and adult abundance during periods of elevated rainfall (Reiter, 2001). Increased mosquito abundance with rainfall has been demonstrated for *Aedes* and *Anopheles* mosquitoes in the Brazilian Amazon (de Araújo *et al.*, 2020), in northern India

(Baruah and Dutta, 2013), Argentina (Fontanarrosa *et al.*, 2000) and Mexico (Jiménez-Alejo *et al.*, 2017). In Tanzania, drought conditions caused a reduction in the abundance of the malaria vectors *An. arabiensis* and *An. funestus* (Kreppel *et al.*, 2019). Excessive levels of rainfall however can flush out mosquito larvae and subsequently decrease disease transmission (Benedum *et al.*, 2018). Rainfall in Kenya was shown to decrease the nightly loss of the malaria vector *Anopheles gambiae* larvae by up to 18% (Paaijmans *et al.*, 2007). Overfilling of water containers resulting from high rainfall also reduced *Ae. aegypti* eggs in Argentina (Benitez *et al.*, 2021), with every 1 mm increase in rainfall decreasing the number of eggs found by 0.7. Inter-annual variation in climate, such as the El Niño-Southern Oscillation (ENSO) also influences the transmission of mosquito-borne diseases, mainly through altering local-level climate patterns (Kovats, 2000). For example in Venezuela, dengue outbreaks are more prevalent during El Niño years, which generate warmer and drier climate conditions (Vincenti-Gonzalez *et al.*, 2018).

Seasonal rainfall patterns are an important determinant of malaria epidemics in sub-Saharan Africa (White *et al.*, 2011; Gunda *et al.*, 2017; Elsanousi *et al.*, 2018) and in India both dengue and malaria outbreaks are associated with ENSO-linked monsoon rainfall (Dhiman and Sarkar, 2017; Pramanik *et al.*, 2020). As a result, this has enabled the development of malaria and dengue early-warning systems based on predictable rainfall patterns (Thomson *et al.*, 2005, 2006; Pramanik *et al.*, 2020). The relationships between rainfall and mosquito abundance are species-specific (Galardo *et al.*, 2009), representing the distinct niches these mosquito vectors are adapted to. As a result, mosquito species abundance and disease transmission can peak during periods of low rainfall or outside rainy seasons. For example, peak abundance of the riparian malaria vector, *An. darlingi* occurs during the dry season in the Amazon, and during the wet season *An. darlingi* exhibits reduced survival and human biting as a result of decreased breeding (Barros *et al.*, 2011; Moreno *et al.*, 2015; Vezenegho *et al.*, 2015). Similarly, *Aedes* vectors, which transmit arboviruses such as dengue and yellow fever exhibit species-specific variation in their response to rainfall. The abundance of immature *Ae. albopictus* mosquitoes in Malaysia was positively correlated with rainfall, but this was not the case for *Ae. aegypti*, with heavy rainfall causing declines in abundance (Saifur *et al.*, 2012).

There is substantial variation in the response of mosquito-borne diseases to climate variation in different regions of the world. These relationships are often environmentally distinct and vary according to local-level environmental conditions, such as seasonal patterns of rainfall, sanitation infrastructure and level of urbanisation (Santos *et al.*, 2020; Yuan *et al.*, 2020). In north-eastern Brazil, weak associations were observed between temperature and *Ae. aegypti* mosquito oviposition (Moura *et al.*, 2020), whilst another study in southern Brazil, in urban Sao Paulo, demonstrated that dengue incidence was influenced most by temperature (Araujo *et al.*, 2015), highlighting regional differences in climate-disease relationships. Similar local level heterogeneity has been detailed for malaria vectors and transmission. Temperature was not influential in driving transmission dynamics in Panama, owing to the lack of seasonal temperature fluctuations in the study area (Hurtado *et al.*, 2018). In Venezuela, no significant association was found between *Anopheles* mosquito abundance and rainfall (Moreno *et al.*, 2007), although rainfall is a major driver of *Aedes* mosquito abundance across Asia (Wai *et al.*, 2012; Li *et al.*, 2019; Islam *et al.*, 2021). A consideration of the local level variation in the climate responses of mosquito-borne diseases is essential for developing effective and targeted disease control programs that are tailored for specific locations.

Owing to the time taken for climate factors such as temperature and rainfall to impact mosquito risk and subsequent case reporting, climate variables exhibit a temporally lagged relationship with mosquito-borne diseases (Lowe *et al.*, 2018). Seasonal forecasts, which can be produced up to months in advance (Kim *et al.*, 2019), take advantage of this lagged relationship. Time lags between mosquito-borne diseases and climate can be detected from as little as 0-4 weeks (Kakarla *et al.*, 2019) to up to five months for the delayed impact of rainfall on dengue incidence (Kakarla *et al.*, 2019; Yuan *et al.*, 2020). For malaria, the effects of El Niño on transmission have been detected at a time lag of a year and over (Bouma and Dye, 1997; Gagnon *et al.*, 2002; Hurtado *et al.*, 2018). The relationship between climate and mosquito-borne diseases therefore may not be detected if the temporal time lag is not accounted for. Local and regional variation in climate-disease relationships alongside accounting for temporally lagged associations can complicate the understanding and detection of the impact of global environmental change on mosquito-borne diseases.

Despite an understanding of the mechanisms of how climate variation impacts mosquito-borne diseases independently, many studies do not consider the impact of mediating and interacting factors. For example, mosquito inter-species competition can influence the climate response (Day *et al.*, 2021) and accounting for reporting of other co-circulating mosquito-borne diseases can likewise influence climate-based model predictions (Lowe *et al.*, 2017). Detection of a climate-disease relationship can also be complicated or even masked by the impact of interventions and population fluctuations that may determine underlying risk, especially when detecting long-term associations (i.e. over ten years) (Tatem *et al.*, 2013; Metcalf *et al.*, 2017). Allowing for underlying data uncertainties and attribution of these uncertainties to unaccounted factors will be central to disentangle environment-disease relationships.

The problem of accounting for underlying data uncertainties is exemplified by controversy in the attribution of climate warming to the re-emergence of epidemic malaria in the East African highlands (Loevinsohn, 1994; Lindsay and Martens, 1998; Hay, Cox, *et al.*, 2002). Using coarse-level climate data Hay, Rogers, *et al.*, (2002) reasoned that increases in malaria were attributed to vector control activities and widespread chloroquine drug resistance, and not climate change. Subsequent analyses with quality-controlled local-level climate data however established a robust link between long-term warming and increases in epidemic malaria (Pascual *et al.*, 2006; Chaves and Koenraadt, 2010; Omumbo *et al.*, 2011). Although, Chaves *et al.* (2012) found a large degree of heterogeneity in the observed highland malaria trends, which highlights the need for including high-quality and fine-scale data in assessments of local malaria trends and climate warming.

Beyond the issues of accessing quality climate data to detect climate-disease associations the climate-malaria debate exemplifies the importance of not basing long-term associations on extrapolations from laboratory-based findings. In addition, there is the need to consider alternative explanations for rising disease trends such as changes in human behaviour and immunity, and lapses in control activities (Reiter, 2008). Even when increases in malaria cases in Kenya were attributed to warming temperatures from the 1970s to 1990s, other factors including population growth and chloroquine resistance were also shown to enhance the impact of climate change on malaria (Alonso *et al.*, 2011). In addition, climatic changes such as the ‘slowdown’ of climate warming (Kerr, 2009; Rodó *et al.*, 2021) can act synergistically with control activities, facilitating a concurrent slowdown and decrease in seasonal malaria epidemic size (Rodó *et al.*, 2021). Accounting for the impact of mosquito-borne disease interventions, such as vector control, in impact studies is vital for understanding how risk of disease is influenced by global environmental change and for effective planning of disease control programs. Understanding climate variation will become increasingly important as we accelerate progress towards elimination, for example the Global Technical Strategy for Malaria 2016-2030 aims to reduce global incidence and mortality by 90% by 2030 (WHO, 2015a), however any progress could easily be undermined by climatic changes that facilitate malaria transmission.

In addition to the impact of interventions, socioeconomic influences are also important to consider in climate-disease relationships. Measures of poverty, including healthcare, childhood services, and inadequate sanitation, are significant factors explaining higher incidence of dengue, Zika and chikungunya in Colombia, dengue in Bangladesh (Paul *et al.*, 2018; Morgan *et al.*, 2021) and malaria in sub-Saharan Africa (WHO, 2019). Population density contributed nearly 70% to explaining dengue distribution in China (Liu *et al.*, 2020) and in Europe travel patterns accounted for 70% of the variation in imported dengue cases (Salami *et al.*, 2020). As mentioned previously, although dengue risk can peak during periods of high rainfall, disease risk can also vary as a result of climate-induced alterations to human water storage behaviours. In Brazil and Puerto Rico, increased use of water containers due to water shortages become important sources of dengue mosquito production (Barrera *et al.*, 2011), leading to peaks in relative risk of dengue in the four months after onset of drought conditions (Lowe *et al.*, 2021). Attribution of observed changes in mosquito-borne disease risk to non-climatic factors is important to disentangle the effect of multiple global environmental change drivers.

1.4. Impact of land use and change on mosquito-borne diseases

In addition to climate variation, anthropogenic land-use change is another principal driver of global patterns in mosquito-borne disease risk (Gottdenker *et al.*, 2014). Land-use change comprises how humans alter the natural environment and includes urbanisation, agricultural development, deforestation and natural resource extraction. As a result of accelerating human demands on nature, the global land surface is being converted at an unprecedented rate (Popp *et al.*, 2017). By 2030, urban land cover is projected to have increased by 1.2 million km^2 (Seto *et al.*, 2012). Disturbance caused by land-use change causes specific ecosystem changes that undermines the capacity of ecosystems to regulate infectious diseases, which can lead to the emergence and re-emergence of mosquito-borne diseases (Foley *et al.*, 2005). Land-use change primarily affects mosquito-borne disease risk by altering the abundance and behaviour of vectors, the biodiversity of vectors and mosquito predator-prey relationships.

The impact of deforestation on mosquito-borne diseases, particularly on malaria, has been studied extensively. Deforestation is a primary driver of malaria risk in endemic countries

(Brock *et al.*, 2019). Microclimatic and hydrological changes associated with forest clearance, principally an increase in temperature, increased sunlight and pooling of rainwater have been shown to favour the proliferation of populations of *An. darlingi,* the main malaria vector in the Amazon region (Yasuoka and Levins, 2007; Vittor *et al.*, 2009; Burkett-Cadena and Vittor, 2018). This in turn, leads to higher human biting rates, increased vectorial capacity and intensification of malaria transmission at the interface between natural and disturbed environments (Vittor *et al.*, 2006; Barros and Honório, 2015; Sallum *et al.*, 2019). In the Amazon region, deforestation has allowed malaria vectors to invade new ecological niches and expand into undisturbed habitats. These ecological processes have been exacerbated by road construction associated with deforestation, allowing previously inaccessible areas to be colonised by malaria vectors (Póvoa *et al.*, 2001). Increased risk of malaria is commonly observed in areas of extractive harvesting in Brazil and in forest fringe areas close to extractive activities, with high incidence among farmers and agricultural workers (Valle and Clark, 2013; Souza *et al.*, 2019).

Since the principal mechanism by which deforestation affects malaria transmission is through niche invasion, not all malaria vectors are favoured by deforestation. For example, vectors including *An. aquasalis*, a primary vector of *P. vivax* malaria and *An. triannulatus* a vector also implicated in malaria transmission, exhibit higher abundances in protected areas in comparison to forest fragments in southern Amazonian Brazil (Vieira *et al.*, 2020). In Mexico, well-preserved montane cloud forests have significantly higher mosquito abundance, compared to other sites altered by coffee plantations, cattle grazing and urban development, although species richness was lower (Abella-Medrano *et al.*, 2015). In a synthesis of the evidence of deforestation and vector-borne diseases, which included key malaria (*An. darlingi* and *An. gambiae*) and arboviral vectors (*Ae. aegypti*), the net effect of deforestation was shown to favour mosquitoes that are vectors of human disease. Of the mosquito species that are favoured by deforestation, 57% are confirmed vectors of human pathogens (Burkett-Cadena and Vittor, 2018). Contradictory evidence for the effects of deforestation on mosquito-borne diseases, such as malaria, could be due to the simplistic characterisation of the dynamic relationship between deforestation and malaria. Overlooking important confounding factors in analyses of malaria and deforestation, such as human presence, water bodies, time since deforestation and immunity, can mask the true relationship and lead to misinformed conclusions (Tucker Lima *et al.*, 2017).

Complexities in land use-disease relationships have also emerged regarding the spatiotemporal scale of land-use change processes. Socioecological processes associated with land-use alterations can operate at different timescales, occasionally over long periods (e.g. tens of years) to influence disease risk (de Castro *et al.*, 2006; Laporta *et al.*, 2021). This spatiotemporal complexity is exemplified by the frontier malaria phenomenon in the Amazon region, which is associated with land clearance for the expansion of agricultural activities (Sawyer, 1993; Singer and de Castro, 2001; de Castro *et al.*, 2006; Baeza *et al.*, 2017). In the initial frontier phase, when the push towards economic expansion is strong, malaria risk is high (Baeza *et al.*, 2017). During this early stage of land-use change, relatively fast ecosystem transformations such as deforestation, which favour malaria transmission predominate (Baeza *et al.*, 2017; Souza *et al.*, 2019). Subsequently, as forest clearance advances and economic development is substantially increased and as a result of improved infrastructure and healthcare services, malaria risk is reduced on slower, longer timescales. During this transitionary stage, malaria transmission rates may fluctuate, as a result of alterations in the balance between the ecological conditions that drive transmission and socioeconomic factors that provide protection, such as malaria treatment (de Castro *et al.*, 2006; Baeza *et al.*, 2017). In the final endemic stage, malaria transmission is low and stable with effective public health services to deal with outbreaks and provide diagnostics and treatments.

In frontier regions, the time since deforestation and amount of accumulated deforestation are additionally key determinants of malaria risk. At deforested sites with more recent colonisation, areas with intermediate levels (50%) of forest cover that have the greatest frequency of forest fringe habitat have the highest malaria risk. This is because of high vector abundances combined with low levels of socioeconomic mitigation measures (Laporta *et al.*, 2021). Although a realisation of the temporal timescales that land-use alterations operate over has increased understanding of how malaria risk is governed by dynamic socioecological processes, accurately accounting for these processes in disease modelling frameworks remains a challenge.

In gold-mining areas of Venezuela and French Guiana, malaria hotspots sustained by ecological changes associated with forest clearance, contrast with malaria risk in frontier regions. Instead, malaria risk is exacerbated and modulated by socioeconomic factors, primarily human movement and behaviour. Open mining pits that create large bodies of standing water for breeding mosquitoes cause malaria transmission rates to soar (Moreno *et* *al.*, 2007; Grillet *et al.*, 2021). In addition to these fast-acting ecological processes, vector biting rates and malaria transmission are high due to vulnerable non-immune populations that work in the mining camps (Pommier de Santi *et al.*, 2016; Douine *et al.*, 2020). Migration to these artisanal gold mines is driven by socio-political instability and over time malaria transmission rates are not alleviated by improved socioeconomic development as observed in agricultural frontier areas. Instead, these mining areas can remain as important hotspots of transmission, driving regional patterns of disease (Grillet *et al.*, 2021).

By 2050, two-thirds of the global population is predicted to live in urban areas, with the majority of the increase in urban populations occurring in Africa and Asia (UN, 2015). Human population expansion has been linked to increased exposure to mosquito-borne diseases such as dengue and chikungunya, as a result of an expansion of mosquito geographic ranges, facilitated by heightened trade and travel (Weaver, 2013). In the Brazilian Amazon, dengue is expanding from urban centres to neighbouring rural areas and into urbanised forest, due to the establishment of *Aedes* mosquitoes (Lowe *et al.*, 2020). Urban development favours the transmission of *Aedes*-transmitted diseases because these mosquitoes have evolved to become highly adapted to urban environments. Artificial water storage containers, storm drains, discarded tyres and construction materials typically found in urban and peri-urban environments act as significant producers of *Aedes* mosquitoes in Brazil, Colombia, Puerto Rico and in Bangladesh (Barrera *et al.*, 2011; Paploski *et al.*, 2016; Garcia-Sánchez *et al.*, 2017; Paul *et al.*, 2018). Uncontrolled and rapid urbanisation associated with population growth and poverty, which results in substandard housing and water and waste management and therefore breeding sites, creates ideal conditions for dengue epidemics.

Land-use changes, such as urban development can interact with climate variation and change to influence trends in mosquito-borne disease risk. In conjunction with climate change, urbanisation is driving widespread ecological changes in sub-Saharan Africa, favouring a shift from malaria transmitted by *Anopheles* mosquitoes, towards *Aedes*-transmitted arboviruses (Mordecai *et al.*, 2020). Warmer temperatures in urban areas that create heat islands, combined with increased availability of breeding sites act together to favour arbovirus transmission. In contrast to *Aedes* mosquitoes, several important malaria vectors such as *An. gambiae* and *An. darlingi* breed in natural water sources typical of rural areas. In general, urbanisation decreases malaria transmission for this reason (Pond, 2013), although the establishment of the invasive mosquito vector, *An. stephensi* is raising concerns about urban and peri-urban malaria in Africa (Mathanga *et al.*, 2016; Takken and Lindsay, 2019; Sinka *et al.*, 2020).

The diversity in the relationships between land-use change such as deforestation and urbanisation, with mosquito-borne diseases shows the need for a considerate species-specific approach to understanding environmental change and disease risk. Despite evidence of the expansion of new mosquito vectors into urban areas and how malaria-transmitting mosquitoes are favoured by deforestation, there is limited understanding and synthesis of how mosquito vectors respond to land-use change. This need to understand species-specific responses to land-use change in the context of disease is important and a critical research gap that has received little attention. There is an increasing need to link evidence of the ecological processes by which land-use change affects disease risk, for example the preference of *An. darlingi* mosquitoes for deforested landscapes, to empirical evidence demonstrating the hypothesised response to land-use change. An understanding of how vectors respond to land-use change is vital to provide evidence to inform predictions on how mosquito-borne diseases are likely to change in the future.

Multiple components of mosquito-borne disease risk, including climate variation and land-use change are mediated through a complex system of feedback loops and interacting relationships. This complexity makes causal relationships difficult to identify and is further complicated by imperfect observations of each risk component. A major research gap that remains is how best to explicitly account for factors like land-use alterations in environmental change assessments. In addition, there is a limited grasp of how disease risk is influenced by both climate conditions (the hazard) and vector control measures (exposure) and socioeconomic conditions (vulnerability), and whether vector control measures can mask the effect of climate variation on mosquito-borne disease. Further, it is not clear if and how these components of disease risk, namely climate variation and land-use change, interact with each other. Interactions between multiple components of global environmental change is vital to understand how human health may change in areas of the world vulnerable to the combined effects of climatic change and land-use alterations.

1.5. Tools for addressing shortfalls in the understanding of mosquito-borne diseases and environmental change

Statistical spatiotemporal modelling is a method commonly employed to investigate drivers of mosquito-borne diseases (Rouamba *et al.*, 2020; Lowe *et al.*, 2021). Epidemiological data, such as the annual number of cases of malaria per district, are often characterised by a hierarchical structure, which needs to be considered during analysis. Specifying statistical models in a Bayesian framework, is an effective way to incorporate the spatiotemporal structure of the data into a model. In a Bayesian approach multiple uncertainties can be accounted for, such as uncertainty in the parameter estimates, and the capacity to deal with missing data is improved (Blangiardo *et al.*, 2013). The hierarchical structure of disease data can be incorporated in a Bayesian framework using spatial and temporal random effects. For example, the high correlation of case counts from neighbouring regions (autocorrelation) can be accounted for by specifying an Intrinsic Conditional Auto-Regressive (ICAR) model on the spatial random effects (Besag *et al.*, 1991). In addition, the seasonal pattern of mosquito-borne diseases can be included by specifying a first order autoregressive prior on the monthly random effect (Lowe *et al.*, 2017). Furthermore, new methods in Bayesian statistics, such as Integrated Nested Laplace Approximation (INLA) has allowed for quicker and more computationally efficient generation of parameter estimates in spatiotemporal hierarchical models (Blangiardo *et al.*, 2013; Lowe *et al.*, 2017). In contrast to more traditional methods of Bayesian parameter estimation, such as Markov chain Monte Carlo (MCMC), INLA uses a combination of analytical approximation and numerical integration (Blangiardo *et al.*, 2013). As a result, INLA has shorter computation times and generates results that are comparable to MCMC (De Smedt *et al.*, 2015).

Models implemented in INLA are particularly useful for assessing the potential effect of multiple risk factors on disease, as well as explicitly quantifying the risk due to a particular covariate (Blangiardo *et al.*, 2013). By assessing both the spatial and temporal variation in disease risk, there is potential to develop complex spatiotemporal models implemented in INLA, informed by large datasets and multiple data streams that facilitate a greater understanding of the drivers of mosquito-borne disease risk. Multiple health questions can be addressed simultaneously, including detecting strategies that are most effective at reducing disease incidence alongside identifying communities most at risk (Rouamba *et al.*, 2020). Predictive spatiotemporal models can also be developed to assess how mosquito-borne disease risk may change with future climate change and population growth (Colón-González, Sewe, *et* *al.*, 2021). Spatiotemporal models are a valuable tool with great potential to investigate the joint influence of climate variation and socioeconomic factors on disease risk, as well as interactions between factors, including climate and land-use change.

The advent of Earth observations, such as remotely sensed climate variables has brought major advances in understanding the natural world, mapping global water surfaces, forest extent and the climate system. Historically, Earth observations have been frequently employed for a wide range of uses in epidemiological research (Beck, Lobitz and Wood, 2000; Hay, 2000). In particular, remote sensing of the land's surface has commonly been used to model the spatial distribution of malaria vectors and their habitats (Beck *et al.*, 1994; Roberts *et al.*, 1996; Thomson *et al.*, 1996; Garrett *et al.*, 2005). For example, remote sensing of Mexican tropical wetlands identified areas with high rates of anopheline production and was subsequently used to produce mosquito productivity rankings to guide mosquito control (Pope *et al.*, 1994). Earth observations, such as remotely sensed climate variables and vegetation indices can also be integrated with disease surveillance data into models leveraged for outbreak detection and forecasting (Midekisa *et al.*, 2012; Lowe *et al.*, 2013; Nizamuddin *et al.*, 2013).

More recently, Earth observations have also been employed to detect and measure our anthropogenic footprint, such as global forest loss (Hansen *et al.*, 2013) and pesticide application (Maggi *et al.*, 2019). This has allowed for an improved understanding of the complex spatiotemporal dynamics of mosquito borne disease. For example a study in Lao, which used high resolution forest loss data (Hansen *et al.*, 2013) found that deforestation was only associated with short-term (1-2 years) increases in malaria incidence (Rerolle *et al.*, 2021). In addition to tailored Earth observation products, remote sensing also provides a suite of other variables that can be derived and used to make inferences relevant to human health. For example, the Sentinel 2 satellite provides multispectral satellite images that can be used for flood monitoring (Farhadi *et al.*, 2022) and for detecting crop types at a 10 m resolution (Tran *et al.*, 2022). Combining Earth observations, such as remotely sensed data into modelling frameworks is a powerful tool for investigating the environmental drivers of mosquito-borne disease risk. In addition, a consideration of the Planetary Health approach, specifically how environmental health is linked to spatiotemporal patterns of disease, can help identify environmental proxies for disease, therefore increasing the mechanistic understanding of how environmental change influences mosquito borne disease. These proxies, such as vegetation indices and climate variables can be leveraged from Earth observation data and incorporated into modelling frameworks, reconciling shortfalls in ground truth data. An integration of multiple sources of Earth observation data, environmental and socioeconomic, can help address gaps in understanding the complexities of mosquito-borne diseases because it allows for multiple factors to be considered simultaneously.

Earth observations have frequently been used in spatiotemporal models to quantify the associations between climate variables and mosquito-borne diseases. A vast number of studies have combined remotely sensed and local climate observations in modelling frameworks to characterise relationships between climate and malaria, and dengue (Basurko *et al.*, 2011; Lowe *et al.*, 2013; Midekisa *et al.*, 2015; Lowe *et al.*, 2016, 2018; Gunda *et al.*, 2017; Ikeda *et al.*, 2017; Peña-García *et al.*, 2017). Whilst these studies have contributed greatly to understanding the local-level impacts of climate variation on mosquito-borne diseases, diversity in these studies regarding data products and statistical techniques employed has resulted in a lack of consistency in how climate-disease associations are quantified. For example, the impact of climate variation on disease can be quantified by attributing the variation explained by a particular climate variable (Yu *et al.*, 2016). Alternatively, the percentage increase in disease incidence with a unit increase in the value of a climate variable can be quantified (Lee *et al.*, 2017). When global comparisons of the effect of climate variation on mosquito-borne diseases are required, for example for use in the Intergovernmental Panel on Climate Change (IPCC) assessment reports, this lack of reporting consistency can make global evaluations challenging and difficult to interpret.

Earth observations can also be particularly useful for disease mapping, risk analysis and detecting fine-scale variation in ecological predictors of mosquito-borne diseases. For example, drone-acquired imagery has been used to accurately detect *An. darlingi* larval habitats in the Peruvian Amazon (Carrasco-Escobar *et al.*, 2019), and larval habitats in Malawi (Stanton *et al.*, 2021). Furthermore, in southeast Asia drones were also used to characterise both environmental and social risk factors for zoonotic malaria (Fornace *et al.*, 2014). The use of technology such as drones enables data to be obtained quickly, updated routinely and sites of interest to be mapped frequently (Fornace *et al.*, 2014). These techniques may be particularly useful for monitoring relatively fast land-use alterations such as forest clearance, allowing for temporal variations in land-use to be monitored closely.

Earth observations, in particular remotely sensed data from satellites have also been used to map mosquito abundance or disease cases in a predictive manner. Combining observations of environmental variables such as vegetation and climate conditions, with *Ae. aegypti* trap counts in Brazil into a generalised linear model, enabled the development of a predictive temporal model of the mosquito population (Mudele *et al.*, 2021). Similarly, environmental data has been used to forecast *Ae. aegypti* oviposition and infestation (Lorenz *et al.*, 2020), and even detect a dengue outbreak that occurred earlier in the season than usual in Argentina (Estallo *et al.*, 2016). Further, remote sensing can also be used to inform disease surveillance such as the optimal placement of sentinel sites for entomological monitoring (Longbottom *et al.*, 2020). Impressive developments and innovations in computing power and modelling capabilities has enabled predictive models to be integrated directly with disease surveillance and optimise vector control programs.

Despite what the health sector can learn from the application of Earth observations to mosquito-borne diseases, a concern with the use of Earth observations is the limited accessibility to applications in epidemiology (Dlamini *et al.*, 2019). A common challenge is finding environmental data on a spatial scale that matches the spatial scale of the health data, without compromising fine-scale information that represents ecological processes on the ground. A lack of accessibility can also stem from limited integration and communication between health and climate disciplines to co-develop and tailor a particular Earth observation product to a specific health application. An evaluation of data products applied to the health sector, alongside identification of methodological limitations, investigation of how data product choice impacts the health outcome will help enhance integration of environmental data products into the health sector.

The dynamic socioecological processes triggered by environmental changes such as land-use modifications are only recently being understood. These processes remain a challenge for elimination efforts, as each distinct stage requires a targeted set of disease control measures (Baeza *et al.*, 2017; Laporta *et al.*, 2021). The case of frontier malaria and malaria in gold mining areas highlights the complexity of mosquito-borne disease risk. A seemingly straightforward relationship between environmental disturbance and disease emergence is made up of multiple modulating factors, including ecological and anthropogenic processes, all of which must be taken into consideration. Accounting for multiple factors in a Planetary Health approach, across multiple spatiotemporal scales can help address this critical challenge and provide a framework for understanding these complexities. Understanding of the interacting processes that drive disease risk, in emergent and elimination settings, in rapidly changing environments will be required to facilitate public health decision-making.

A critical challenge in addressing how global environmental change impacts mosquito-borne disease, is understanding the vast complexities that exist in a system of multiple interacting socioeconomic and ecological processes. Mosquito-borne disease risk can be conceptualised as a combination of exposure, hazard, and vulnerability (Gibb *et al.*, 2020; Figure 1.2). The risk of mosquito-borne disease is determined by presence of the mosquito vector, e.g., an *Anopheles* mosquito and the pathogen, e.g., the malaria-causing *Plasmodium* parasite (the hazard). The distribution and occurrence of the hazard is driven by climatic conditions, such as optimal temperatures and adequate rainfall. Land use and land cover, including habitat availability for forest-dwelling mosquitoes also determines the local and regional distribution of mosquito vectors. Exposure to the pathogen-transmitting mosquito is influenced by anthropogenic modulators, such as vector control, which can eliminate or reduce occurrence of the hazard. Socioeconomic conditions, such as housing and sanitation infrastructure determine the population exposure to the mosquito hazard. Exposure is further modulated by human population movements such as influx of workers to agricultural frontier regions, which can increase vector-human contact rates. Land-use change itself can also modify human behaviour, driving populations into high-risk environmentally disturbed areas. Finally, disease risk is influenced by the vulnerability of the underlying population. Disease vulnerability is driven predominantly by socioeconomic conditions such as poverty, healthcare accessibility and population immunity, as well as underlying population health. Importantly, exposure and vulnerability are also driven by environmental factors, such as extreme weather events that can compromise access to healthcare and drive population movements.

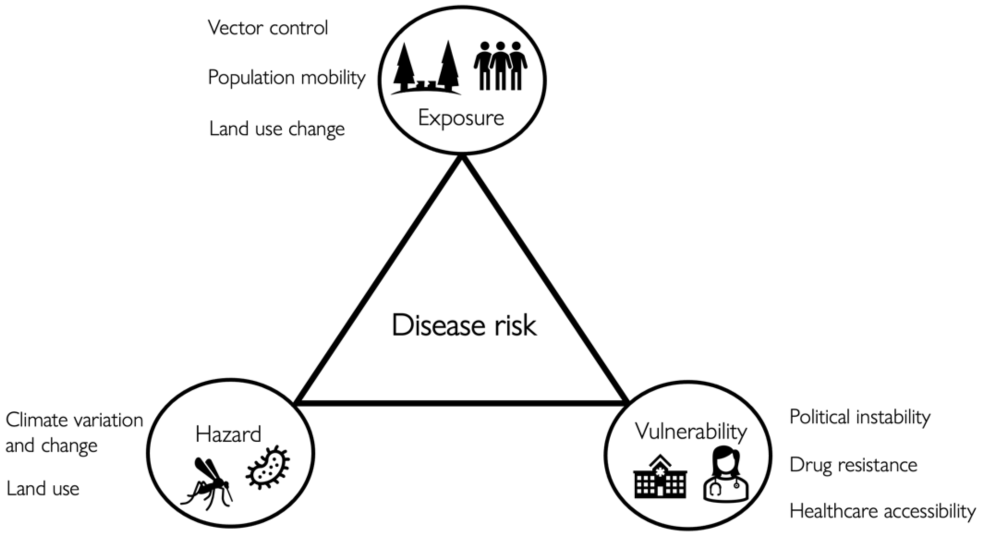


Figure 1.2. Mosquito-borne disease risk framework used to understand the effects of global environmental change. Three elements, hazard, exposure, and vulnerability converge to shape overall mosquito-borne disease risk. The hazard (mosquito and pathogen) is influenced by environmental factors such as climate variation and land use, whilst exposure to the hazard is modulated by factors including vector control in addition to land-use changes, which are driven by socioeconomic influences. Vulnerability to mosquito-borne disease risk is regulated by factors such as healthcare accessibility, which in turn is affected by environmental changes such as extreme weather events.

1.6. Thesis outline

In this thesis, I use the risk framework (Figure 1.2) as a foundation to enhance our understanding of the impacts of environmental change on mosquito borne diseases, by integrating a Planetary Health approach. I consider multiple interacting factors and incorporate concepts from multiple disciplines, including climate, health and ecology exemplified in distinctive case studies of mosquito-borne disease in Latin America and the Caribbean. Latin America is a global hotspot for mosquito-borne disease transmission, where dengue is endemic and arboviruses such as Zika virus have recently emerged in the region. Countries in Latin America and the Caribbean are amongst those with the highest age-standardised incidence rate for dengue in the world (Zeng *et al.*, 2021) and between 2018-2019 Brazil experienced a 600% increase in cases (PAHO, 2019). Malaria also presents a significant public health problem for the region, despite substantial progress (58% case reduction from 2000 to 2020) in countries such as Mexico and Peru (Hotez *et al.*, 2020; WHO, 2021b). Approximately 120 million people in the Americas are at risk of malaria transmission (WHO, 2015b) and malaria deaths in the region occur disproportionately in Venezuela, which accounted for over 70% of deaths in 2019

(WHO, 2020). In addition, some countries in the region that were previously on track towards elimination (Ecuador, Suriname and Costa Rica) have recently showed signs of malaria re-establishment, which is a major threat to ongoing elimination efforts (WHO, 2020).

The Latin American and Caribbean region is battling a growing number of extreme weather events as a result of global climate change, including flooding and severe droughts in the Amazon region following the exceptionally strong 2015-16 El Niño event (Jiménez-Muñoz *et al.*, 2016; Marengo and Espinoza, 2016). Numerous mosquito-borne disease threats, including the expansion of the arbovirus vector *Ae. aegypti* into peri-urban and rural areas (Guagliardo *et al.*, 2014) and ascension of malaria into highland areas (Siraj *et al.*, 2014), makes the region an interesting case study for investigating the impacts of environmental change. Considerable socioeconomic challenges, such as political instability, poverty and human displacement, including the ongoing economic and humanitarian crisis in Venezuela will further complicate efforts to tackle mosquito-borne diseases (UNHCR, 2015). In 2015, 6% of the estimated population in Latin America and the Caribbean lacked access to safe drinking water and 17% lacked proper sanitation facilities (PAHO, 2015). These are optimal conditions for the spread of mosquito-borne diseases, especially in conjunction with urban sprawl and extreme weather events. Strengthening of health systems in the region, by building resilience to the effects of environmental change in conjunction with socioeconomic challenges will be crucial. The Latin American region is experiencing a multitude of dynamic health threats from the combined impacts of environmental change and complex socioeconomic situations, with mosquito-borne diseases posing a particularly formidable challenge.

The overarching goal of this thesis is to investigate the extent to which global environmental change impacts mosquito-borne disease risk through multiple interacting factors, including climate variation, land-use change and socioeconomic influences. The specific objectives are as follows:

1. Develop and test a statistical modelling framework that can be used to explore climate, land use and socioeconomic effects on mosquito-borne diseases.
2. Understand the joint influence of climate variation and elimination efforts on mosquito-borne disease risk, identifying whether a climate signal can still be detected in elimination settings.

3. Test for the interacting effects of land-use change and climate variation on mosquito-borne disease risk.
4. Identify whether choice of climate data product in climate-disease models influences the estimated associations between climate hazards and disease risk.
5. Compile a database of mosquito vector data that can be used to explore the impacts of land-use change on mosquito biodiversity.
6. Explore the response of mosquito vectors to anthropogenic land-use change.

I begin this thesis by assessing how both hazard and exposure combine to influence malaria incidence in a high-risk border region of Ecuador (Chapter 2; Table 1.1). I do this by developing a statistical spatiotemporal modelling framework, which I use to integrate multiple sources of environmental and socioeconomic data, whilst also statistically accounting for unexplained sources of variation in disease incidence. Specifically, I explore the extent to which climate variation impacts the spatiotemporal incidence of malaria in conjunction with elimination efforts, identifying whether a climate-malaria signal can still be detected in an elimination setting. This is an important research gap that is vital to optimise control efforts against the backdrop of a warming climate.

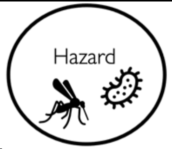
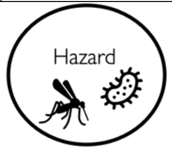
In Chapter 3, I address the interactions between components of the risk framework, specifically testing for the previously unexplored interactions between climate variation and land-use change (Table 1.1). Here, I use a timely case study of malaria re-emergence in southern Venezuela, to investigate the extent to which the impacts of climate variation and land use act synergistically to determine malaria risk. I explore how climate-malaria relationships are altered in areas degraded by mining activity, where both exposure and vulnerability to disease risk is high due to the complex socio-political environment. I then discuss the interacting processes that drive re-emerging disease risk in changing environments.

Given the vast availability and diversity of climate data employed in Chapters 2 and 3, I next explore the data products used to represent the hazard component of the risk framework, using impact-based models for dengue and malaria in Ecuador. In Chapter 4, I summarise methodological differences and uncertainties in climate data products, delivering clarity on how best to integrate environmental data into health impact models. To progress forward with our understanding of environmental change and mosquito borne diseases and take lessons from Planetary Health into the health sector, it is important to identify how new methods and data sources from diverse disciplines can be adopted. I assess the extent to which data product choice in climate-sensitive disease models influences the associations between climate hazards and disease risk. I also discuss how best to move forward with integrating climate and health data for the co-development of an operational climate service (Table 1.1).

Much of epidemiology and health research on mosquito-borne diseases has side-lined ecological information and has instead relied on traditional health approaches, which often neglect the utility of ecological information such as mosquito ecology. For example, in Chapters 2-3, climate variation is used to account for the distribution and occurrence of the mosquito vector (the hazard), although land-use change is also an important determinant. In Chapter 5, I take an ecological hazard-based approach to address gaps in understanding how mosquito vectors respond to anthropogenic land-use change. To do this, I use a comparative mixed-effects modelling framework for mosquito vectors of malaria and dengue, in Latin America and the Caribbean (Table 1.1). Specifically, I test to what extent taxonomic responses in mosquito abundance to land-use change differ, and if species richness in human-dominated landscapes is reduced in comparison to areas not altered by human activity. To conclude, I integrate key findings and insights of this research in Chapter 6, showing how they can be disseminated into public health policy and placing them within the broader context of Planetary Health, highlighting future research directions and policy implications.

Table 1.1. Thesis research questions and how components of the disease risk framework are used to address them. In Chapters 2 and 3, a spatiotemporal modelling framework is employed to investigate incidence of malaria in two contrasting case studies, accounting for the hazard, exposure and vulnerability components of the risk framework. In Chapter 4, I use a case study of impact-based models, and malaria and dengue incidence to show how climate data products (used as a proxy for the hazard) influence the resulting health decision. In Chapter 5 I address the lack of ecological information in mosquito-borne disease research by providing an assessment of how mosquito vectors respond to anthropogenic land-use change.

Overarching research question:
To what extent does global environmental change impact mosquito-borne disease risk through multiple interacting factors, including climate variation, land-use change and socioeconomic influences?

Research question	**Objective**	**Chapter**	**Case study**	**Risk component**
To what extent does climate variation jointly influence mosquito-borne disease risk in conjunction with elimination efforts?	1, 2	2	Malaria elimination in Ecuador	
To what extent do the impacts of climate variation and land use act synergistically to determine mosquito-borne disease risk?	1, 3	3	Malaria re-emergence in a mining hotspot of Venezuela	
To what extent does data product choice in climate-sensitive disease models influence the associations between climate hazards and disease risk?	4	4	Malaria and dengue in southern coastal Ecuador	
To what extent does anthropogenic land-use change facilitate differing taxonomic responses in mosquito abundance and species richness?	5, 6	5	*Aedes* and *Anopheles* mosquito vectors in Latin America and the Caribbean	

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Isabel Fletcher
Principal Supervisor	Rachel Lowe
Thesis Title	Assessing the impact of global environmental change on mosquito-borne disease: A Planetary Health approach

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Frontiers in Environmental Science (see Appendix V)		
When was the work published?	27.08.20		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Author list: **Fletcher IK**, Stewart-Ibarra AM, Sippy R, Carrasco-Escobar G, Silva M, Beltran-Ayala E, Ordoñez T, Adrian J, Sáenz FE, Drakeley C, Jones KE & Lowe R. I lead this study, collated the data, fitted the models, analysed the results and wrote the manuscript.

Student Signature: [redacted] **Date:** 09.09.2021

Supervisor Signature: [redacted] **Date:** 09.09.2021

Chapter 2 - Understanding the combined impact of climate variation and elimination efforts on malaria incidence in a high-risk border region of Ecuador

I begin this thesis by considering multiple components of the disease risk framework to understand the combined impact of climate variation and elimination efforts on malaria. In this chapter, I investigate multiple drivers of the spatiotemporal variation of *Plasmodium falciparum* and *P. vivax* malaria in El Oro, a high-risk border region of southern Ecuador. I do this by developing a spatiotemporal modelling framework that accounts for multiple sources of variation, using a random effects model structure. I assess the relative impact of climate variation (hazard), vector control measures (exposure) and socioeconomic factors (vulnerability) on malaria elimination efforts, exploring the extent to which climate variation jointly influences malaria risk in conjunction with elimination efforts. Disentangling the role of multiple environmental and socioeconomic drivers of disease risk is important for accurately assessing the contribution of climate for use in policy-relevant impact assessments.

Abstract

Malaria is a mosquito-borne disease of significant public health concern and despite the widespread success of many elimination initiatives, efforts in some regions of the world have stalled. Malaria is highly sensitive to climate variation, which represents a substantial barrier to elimination because of shifting climate suitability and strong seasonal impacts. Socioeconomic influences, such as political instability and regional migration also threaten malaria elimination goals. These barriers are particularly relevant in areas where local elimination has been achieved and surveillance and control efforts are dwindling. Understanding how climate variation impacts malaria elimination, in conjunction with control efforts is important to consider when monitoring the threat of disease resurgence. However, there has been limited assessment of how the combination of climate variation, disease interventions and socioeconomic pressures influence long-term trends in malaria incidence. In this study, I used Bayesian hierarchical mixed effects models and malaria case data over a 29-year period to disentangle the influence of climate variation and control efforts on malaria risk in the Ecuadorian province of El Oro. Although local malaria elimination was achieved in 2011, El Oro remains highly vulnerable to resurgence. Here, I found that minimum temperature was a significant driver of malaria seasonality and *Plasmodium falciparum* malaria was more sensitive to climatic conditions than *P. vivax* malaria. A 1°C increase in minimum temperatures was associated with a 146% rise in *P. falciparum* incidence and a smaller 77% increase in *P. vivax* incidence. I also detected shifting patterns of malaria incidence between rural and urban areas, with a relative increase of *P. vivax* malaria in urbanised areas of El Oro. In addition, there was considerable heterogeneity in the impact of three chemical vector control measures on malaria incidence. Whilst indoor residual spraying produced small (8%) reductions in *P. falciparum* incidence, space spraying was associated with a 19% decline in *P. vivax* incidence. These findings have important implications for understanding environmental obstacles to malaria elimination and highlights the importance of sustaining disease control efforts in areas that remain vulnerable to resurgence.

2.1. Introduction

Nearly half of the world's population is at risk of malaria, with an estimated 241 million cases reported in 2020 (WHO, 2021c). Despite global elimination and eradication efforts progress towards elimination is stalling in some endemic countries. In particular, growth in malaria incidence has been observed in some Latin American countries since 2014, including Venezuela, Brazil, Colombia and Ecuador (WHO, 2020). Movement of infected individuals between neighbouring countries in the region has resulted in a resurgence of cases in local populations, threatening progress towards malaria elimination for other countries (Grillet *et al.*, 2019). Malaria is highly sensitive to environmental conditions, including climate variability and land-use alterations (Norris, 2004; Caminade *et al.*, 2014), which along with socioeconomic influences can act as significant barriers to elimination. In addition, lapses in control and surveillance efforts combined with global environmental change also poses a threat to malaria elimination across the Latin American region (Alimi *et al.*, 2015; Conn *et al.*, 2018).

Variation in climate conditions, particularly temperature and rainfall, is an important determinant of the spatiotemporal patterns of malaria (Githeko *et al.*, 2000; Paaijmans *et al.*, 2009; Bennett *et al.*, 2016). Climate variation predominantly influences malaria transmission through its effects on both the life-history traits of the *Plasmodium* parasite and the *Anopheles* vector. Warmer temperatures decrease the extrinsic incubation period (EIP), the time taken for the malaria parasite to complete its development inside the mosquito (Mordecai *et al.*, 2013; Shapiro *et al.*, 2017; Ohm *et al.*, 2018). A shorter EIP increases the transmission intensity of malaria by allowing mosquitoes to become infectious more quickly. The EIP for the *P.*

falciparum malaria parasite, which is most prevalent in Africa, is longer (~10 days) than that for the *P. vivax* parasite (~8 days). Furthermore, the *P. vivax* malaria parasite develops at relatively cooler temperatures (minimum of 15°C), compared to *P. falciparum* (minimum of 18°C) (Patz and Olson, 2006; Watts *et al.*, 2021). Similarly, temperature influences malaria mosquito vectors, by affecting larval and adult survival and longevity (Beck-Johnson *et al.*, 2013), mosquito development (Bayoh and Lindsay, 2003) and vector population dynamics (Beck-Johnson *et al.*, 2013; Wilke *et al.*, 2017). However, the effect of temperature on malaria transmission is non-linear, with the optimal temperature for malaria transmission estimated to be around 25°C (Mordecai *et al.*, 2013). Above 30°C, malaria transmission declines as a result of increased mosquito mortality and reduced vectorial capacity (Paaijmans *et al.*, 2009; Mordecai *et al.*, 2013; Shapiro *et al.*, 2017). Rainfall influences malaria transmission by determining the availability of mosquito breeding habitat and has subsequent effects on mosquito abundance (Abbasi *et al.*, 2020). However, heavy and persistent rainfall can flush out early-stage larvae, diminishing mosquito populations (Paaijmans *et al.*, 2007; Wolfarth-Couto *et al.*, 2019)

Large-scale climate patterns such as the El Niño Southern Oscillation (ENSO), the unusual warming of surface waters in the Pacific, influence the interannual variation of malaria epidemics (Kovats *et al.*, 2003). For example, ENSO-driven flooding events in Peru lead to the proliferation of mosquito vector populations and elevate malaria transmission, whilst in Colombia and Guyana drought conditions favour transmission (Gagnon *et al.*, 2001). Urban development can also influence malaria risk, by eliminating the habitat of mosquitoes that prefer forested areas (Kar *et al.*, 2014; Brown *et al.*, 2020). In other instances, surges in peri-urban malaria are observed as a result of economic migration from rural to urban areas and the creation of novel mosquito breeding habitats, such as drains and pipes (De Silva and Marshall, 2012; Padilla *et al.*, 2015; Takken and Lindsay, 2019). The rising environmental suitability for malaria transmission associated with climatic change and land-use modifications, could compromise global malaria elimination efforts (Recht *et al.*, 2017; Watts *et al.*, 2021). Therefore, a greater understanding of the environmental barriers to elimination efforts and detection of climate-disease relationships against the backdrop of ongoing control measures is warranted.

When assessing the role of climate variation on malaria incidence it is important to simultaneously consider the relative impact of control interventions, especially in elimination settings. Several studies that have evaluated the effectiveness of malaria control programs often consider the influence of environmental factors, most frequently rainfall and vegetation indices (Graves *et al.*, 2008; Gunda *et al.*, 2017; Kipruto *et al.*, 2017). By adjusting for climate conditions in geostatistical models of malaria, the effectiveness of control measures such as indoor residual spraying in sub-Saharan Africa, can be assessed relative to the impact of climate variability (Graves *et al.*, 2008; Giardina *et al.*, 2014). A spatiotemporal study in Pakistan found a positive relationship between temperature and malaria, whilst reductions in incidence of up to 25% were observed with a unit increase in coverage of long-lasting insecticidal nets (Dhimal *et al.*, 2014). However, these findings were based on two separate models of the effects of climate and interventions on malaria incidence, which limits the ability to disentangle the joint impact of climate variation and intervention efforts. Further, climate variables are frequently considered as confounding variables with several studies failing to explicitly apportion variation in malaria incidence to climate (Aregawi *et al.*, 2011; Bennett *et al.*, 2014). There has been a limited assessment of how the combination of environmental factors, elimination efforts and socioeconomic pressures influences long-term trends in malaria, and the route towards elimination. Understanding how malaria elimination efforts might be hindered by climate variation has implications for the targeting of vector control and disease surveillance and is important especially given the possibility of shifting vector distributions and increasing climate suitability across Latin America (Pinault and Hunter, 2012).

According to the Pan-American Health Organization (PAHO), Ecuador is in the malaria pre-elimination phase, but fell short of its target to achieve elimination by 2020 (WHO, 2018b). Since 2016, there has been a surge of malaria cases in the country, mainly in the Amazon region, with more cases detected than expected for a country on the verge of elimination (PAHO, 2017; Sáenz *et al.*, 2017). Malaria cases in Ecuador have been rising since 2014, increasing by 700% between 2014-2020 (WHO, 2021c). Recent surges of malaria in countries in the region, primarily Venezuela, are threatening current elimination efforts in Ecuador due to regional migration (Daniels, 2018; Grillet *et al.*, 2019). In this study I seek to identify local threats to malaria elimination, with a view to prevent lapses in disease control efforts and the re-establishment of malaria in an area currently considered malaria-free, but historically is endemic. I use a case study of the southern province of El Oro, situated in a high-risk border region. Despite local elimination of malaria in 2011, El Oro recently recorded a number of autochthonous cases and is vulnerable to the introduction of infections due to high human mobility associated with its location on a strategic migration route (Jaramillo-Ochoa *et al.*, 2019). Here, I advance the existing knowledge of El Oro's malaria elimination success (Krisher *et al.*, 2016) by quantifying the associations between malaria, climate and control interventions in a region highly vulnerable to resurgence.

2.2. Methods

2.2.1. Study area

El Oro province (latitude: 3°5'45.20"S - 4°11'3.06"S, longitude: -79°43'10.92"W-80°50' 37.96"W) is located in southern Ecuador on the Pacific Coast, sharing a border with the Tumbes region of northern Peru (Figure 2.1A). El Oro covers 5,870 km^2 and is divided into 14 cantons (districts), which range in size from approximately 70 km^2 up to 900 km^2. Population densities per canton range from seven people per km^2 in rural areas and up to 760 people per km^2 in the province capital, Machala. *P. vivax* and *P. falciparum* are the main malaria-causing parasites in the region, with 75% of infections caused by *P. vivax* (WHO, 2021c). The primary mosquito vectors transmitting malaria in El Oro are *An. albimanus* and *An. punctimacula* (Ryan *et al.*, 2017).

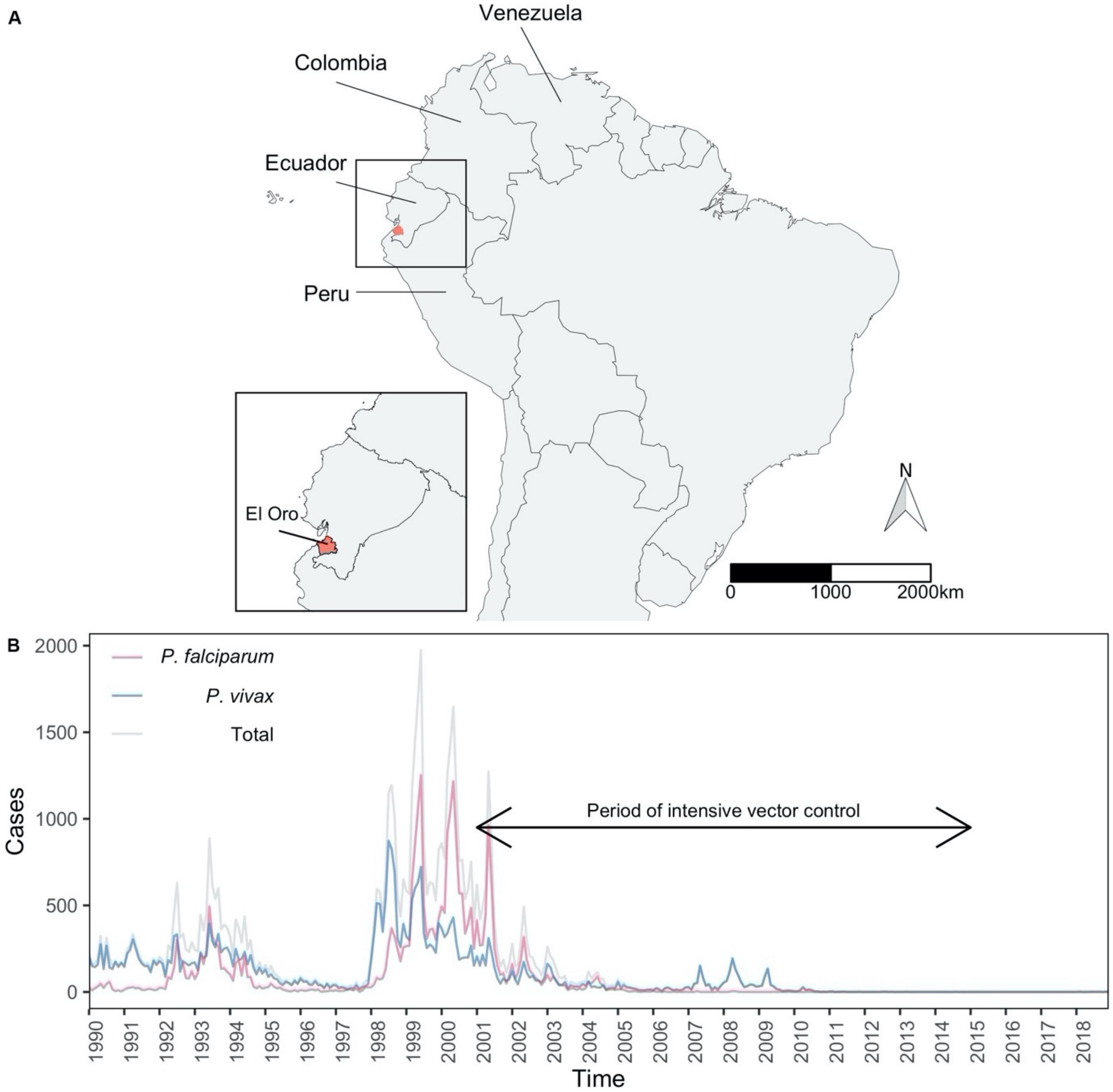

Figure 2.1. Geographical location and cases of malaria in El Oro, southern Ecuador 1990-2018. Location of El Oro province (red), southern Ecuador in relation to neighbouring countries in South America; Colombia, Peru and Venezuela. B) Total number of malaria cases (grey), cases of *P. falciparum* (pink) and *P. vivax* malaria (blue) recorded in El Oro 1990-2018. Arrow indicates a period of intensive vector control implemented in El Oro between 2001-2015.

During the mid-1990s public health authorities in El Oro and neighbouring Tumbes unified to implement an effective binational collaboration to tackle the surge in malaria transmission in the region (Krisher *et al*., 2016). El Oro has been free of locally acquired malaria infections since 2011, although malaria cases have been increasing elsewhere in Ecuador (WHO, 2019). In 2018, seven malaria cases were recorded in El Oro (6/7 were imported cases) during a period of elevated migration of Venezuelan citizens associated with the social and economic crisis in the country (Jaramillo-Ochoa *et al.*, 2019). El Oro's border location, along the Pan American highway, a route used by many migrants, makes it particularly vulnerable to malaria resurgence. In addition, El Oro is one of the most hazardous coastal zones in Latin America and the Caribbean (Calil *et al.*, 2017). Vulnerable populations are susceptible to the effects of ENSO, which intensifies annual flooding events during the rainy season (Lowe *et al.*, 2017; Tauzer *et al.*, 2019). Lapses in surveillance and control efforts alongside reductions in malaria funding following local elimination also means malaria resurgence is highly likely (PAHO, 2017; Sáenz *et al.*, 2017).

2.2.2. Data sources

Monthly counts of blood smear confirmed cases of *P. falciparum* and *P. vivax* malaria for each canton in El Oro, January 1990 – December 2018 (Figure 2.1B), were provided by the Ecuadorian Ministry of Health, where malaria is a mandatory notifiable disease. Cases were recorded at local clinics across El Oro and collated by the Ministry of Health. Population data, available for each canton, were sourced from the national census in Ecuador, from the Instituto Nacional de Estadística y Censos (INEC http://www.ecuadorencifras.gob.ec/institucional/home/) for 1990, 2001 and 2010. Data for 2011-2018 were provided by INEC as annual population projections. Population values between census years (1990, 2001 and 2010) were estimated by interpolating, assuming linear growth to obtain annual population estimates for each canton. To estimate the proportion of the population in poverty per canton in El Oro, Unmet Basic Needs (UBN) were sourced from the 2010 census, an indicator based on measures including housing quality, education and access to water and sanitation. Data from 2010 were used as a spatial socioeconomic covariate in all the models. A complete summary of all data sources and covariates used in the modelling framework is provided in Table S2.1.

Between 2001 and 2015, an intensive period of vector control was carried out across El Oro following a resurgence of malaria cases (Figure 2.1B). Monthly canton-level data for three control measures implemented during this period were available from the Ministry of Health (Figure 2.2). Monthly estimates per canton, of the number of households treated by indoor residual spraying (IRS) with insecticides (deltamethrin 5% concentrated suspension, deltamethrin 2.5%, malathion 50%, alphacypermethrin 10% concentrated suspension and betacipermethrin 2.5%) were collated for January 2001 – September 2013. The number of neighbourhoods in El Oro that were treated with insecticide via ultra-low-volume (ULV) fumigation, which is performed by spraying entire neighbourhoods with 96% malathion from trucks, were collated for January 2004 – May 2015. Finally, the number of households space-sprayed with 2.5% deltamethrin concentrated emulsion, using a backpack fogger that creates a fog insecticide to treat both inside and outside the home, were collated for January 2004 – May 2015. For each control measure, lagged relationships with malaria incidence were tested for, up to three months, in order to account for delays between implementation and impact on malaria cases (Table S2.2). Other malaria control interventions including fumigation with DDT (until banned in 1996), elimination of larval habitats and bed net provisioning occurred during the study period, but no detailed data for control measures were available prior to 2001.

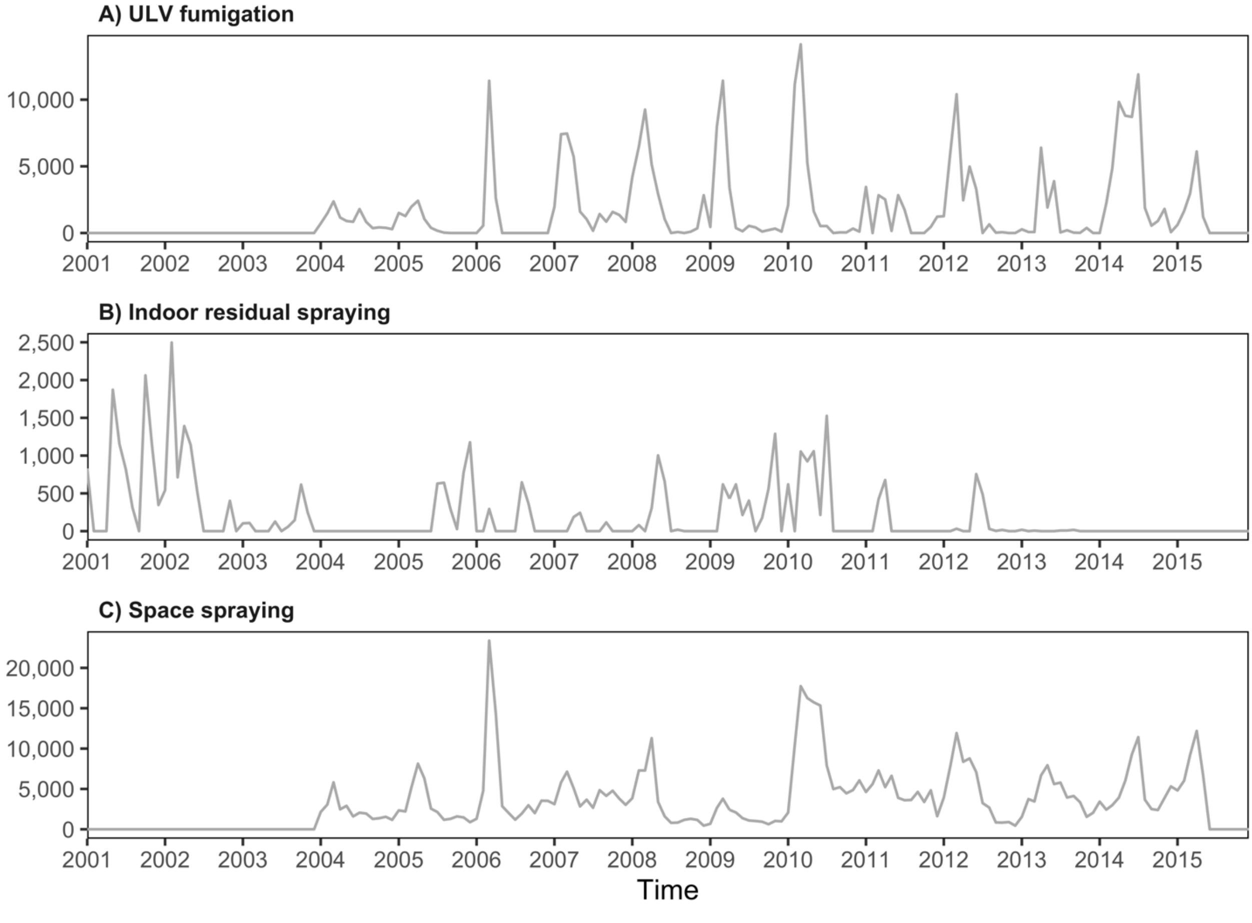

Figure 2.2. Temporal distribution of vector control measures implemented in El Oro 2001-2015. Total number of A) urban blocks fogged by ULV fumigation, B) houses sprayed by indoor residual spraying and C) houses space sprayed, per year.

Monthly climate data, for temperature and precipitation, between January 1990 - December 2018 were sourced from TerraClimate, a high-spatial resolution (~ 4km) gridded dataset that uses climatically aided interpolation (CAI) to produce continuous monthly estimates (Abatzoglou *et al.*, 2018). CAI uses long-term average climate conditions to interpolate variables of interest from weather stations (Willmott and Robeson, 1995). The TerraClimate dataset provides a wide range of climate variables, including maximum and minimum temperature, vapour pressure, precipitation and windspeed. Other hydrological variables such as evapotranspiration and soil moisture are also provided. To obtain climate estimates for each canton in El Oro, TerraClimate variables (temperature and precipitation) were aggregated by taking mean grid cell values across each canton. Annual land cover maps at a 300 m spatial resolution generated by the European Space Agency (ESA) Climate Change Initiative (CCI) were compiled for 1990-2018 (https://www.esa-landcover-cci.org/). Land cover observations from ESA-CCI are interpolated between periods to provide annual estimates. For each annual map, the number of grid cells in each canton that were classified as urban were extracted, and from this the proportion of urban grid cells per canton were calculated to give a continuous spatiotemporal variable of urbanisation (Figure S2.2). All continuous variables were scaled by subtracting the variable mean from each value and dividing this by the standard deviation. This transformation allowed for the direct comparison between variables and enabled their relative importance to be determined in the model.

To assess how climate suitability for malaria transmission has changed in El Oro over the time period (1990-2018), the number of months that had suitable temperature conditions for transmission of each malaria parasite were calculated. As an indicator of suitability, the lower temperature limits for the EIP of each parasite that are considered most suitable for transmission were used. For *P. falciparum* a lower temperature limit of 18°C was used and for *P. vivax* 15°C (Gilles, 1999; Watts *et al.*, 2019).

2.2.3. Statistical analysis

Bayesian hierarchical models are powerful statistical models that can be used to estimate the marginal posterior distributions of covariates, whilst simultaneously accounting for multiple sources of uncertainty that can arise from disease count data. Here, spatiotemporal models were constructed, for each malaria parasite, *P. falciparum* and *P. vivax*, to explore the contributions of climate and vector control measures to variations in monthly malaria incidence in El Oro between January 1990 and December 2018 (348 months).

Zero-inflated negative binomial models were fitted, which account for excess zeros that cannot be explained by a standard negative binomial distribution (Text S2.1). Where μ_{st} is the mean number of malaria cases in each canton ($s = 1,\dots,14$) for each timestep ($t = 1,\dots,348$), the hierarchical spatiotemporal model is defined as:

$$\log(\mu_{st}) = \log(P_{st}) + \log(\rho_{st})$$

Annual population estimates per 1,000 inhabitants for each canton in El Oro, $\log(P_{st})$, were included as an offset in the model to account for canton-level differences in the annual parasite incidence (API). The estimated API, $\log(\rho_{st})$ is then made up of a combination of climate covariates, including mean monthly minimum temperature ($x_{3\mathrm{st}}$) and precipitation ($x_{3\mathrm{st}}$) for each canton. Other explanatory variables included socioeconomic factors (poverty rates, $x_{1\mathrm{s}}$), level of urbanisation ($x_{2\mathrm{st}}$) and vector control interventions (indoor residual spraying, ULV fumigation and space spraying).

To account for the seasonality in malaria incidence, a monthly random effect was introduced using a first order autoregressive prior (m_{t}), which allows malaria in one month to depend on incidence in the previous month (Text S2.2). Independent random effects for each year (y_{t}), 1990-2018, were included to allow for additional sources of variation due to unobserved confounding factors such as variation in healthcare access, case reporting and malaria diagnostics. These independent yearly random effects were also used to capture variation due to other disease control measures, such as bed net usage, which were expected to be implemented during the study period.

Spatially structured random effects, υ_s, were introduced into the model to allow for correlated heterogeneity in malaria incidence across cantons in El Oro. This spatial dependency structure was accounted for by assuming a Gaussian intrinsic conditional autoregressive (CAR) model prior distribution for the spatial effects, which takes into account the neighbourhood structure of the area (Besag *et al.*, 1991). These spatially structured effects allow malaria incidence in one canton to depend on incidence in neighbouring cantons. Spatially unstructured random effects were also included in the model to allow for additional uncorrelated spatial variation across cantons, v_s. The spatially unstructured effects were assigned independent diffuse Gaussian exchangeable prior distributions (Lowe *et al.*, 2016). Separate models were constructed for both *P. falciparum* and *P. vivax* malaria due to their intrinsic differences, which include diagnostic potential, development time inside the mosquito vector (extrinsic incubation period, EIP), the differential impact of vector control on transmission, infection reservoirs of *P. vivax* hypnozoites and the presence of asymptomatic cases. Owing to these differences, it was hypothesised that the influence of climate, along with vector control measures and other covariates in the model would impact *P. falciparum* and *P. vivax* malaria differently.

Detailed data on vector control measures in El Oro were only available for the period January 2001 – December 2015. Therefore, separate sub-models were formulated for each malaria parasite to investigate the relative impact of the control measures implemented between 2001-2015 (see Text S2.3), herein referred to as the 'intervention model'. The intervention model, fitted to data for the period 2001-2015, included the same explanatory variables and random effects as the 'full' models (fitted to data for the period 1990 – 2018) with the addition of the three vector control measures. Differences between the random effect structures for the full models and the intervention models were examined, to see how much variation in malaria due to the vector control measures could be accounted for by random effects in the absence of intervention data for the whole time period. Comparison of the random effects in this way allowed for testing of the influence of the inclusion of detailed intervention data on other parameter estimates and the model posterior distributions.

Posterior distributions of model parameters were estimated using Integrated Nested Laplace approximations (INLA) (Rue *et al.*, 2009). INLA provides a computationally more efficient alternative to Markov Chain Monte Carlo (MCMC) methods, by using numerical approximations of model parameters (see Text S2.2). Covariate time lags and the most parsimonious models were selected using the deviance information criterion (DIC) (Spiegelhalter *et al.*, 2002) and the Watanabe-Akaike information criterion (WAIC) (Watanabe, 2010). DIC and WAIC are Bayesian methods of model comparison that trade off model adequacy against model complexity with lower DIC and WAIC values indicating a more parsimonious model. The logarithmic score was also used to assess model fit, which is based on the conditional predictive ordinate (CPO) leave-one-out cross-validation score, where a smaller value indicates a greater predictive power of the model (Gneiting and Raftery, 2007).

Covariates were added iteratively to the models starting with a baseline model, which included spatial and temporal structured and unstructured random effects. Covariates were retained if model fit was improved, assessed through a decrease in DIC and WAIC. The most appropriate temperature variable, maximum or minimum temperature was also selected using DIC and WAIC (Table S2.3). Various monthly time lags (from zero to three months) were tested to account for the lagged effect of climate factors on malaria transmission (Ikeda *et al.*, 2017), including development time of mosquitoes and parasites as well as the time between malaria diagnosis and case recording (Table S2.3). Non-linear relationships between climate variables and malaria were also tested for, to account for high temperatures and elevated rainfall that may cause a decrease in incidence (Table S2.4). Climate variables were included as nonlinear terms in the models by using a random walk of order 1, using a smooth term to represent nonlinearity. The root mean square error (RMSE) was used to assess the extent to which models of malaria incidence for 2001-2015 were improved by the inclusion of each control measure. RMSE is a measure of the standard deviation of the model residuals, with smaller values indicating better model fit to the observed data.

2.3. Results

2.3.1. Variation in malaria incidence in El Oro 1990-2018

Between 1990-2018, a total of 62,120 cases of malaria were recorded in El Oro. 54% of cases resulted from *P. falciparum* malaria infections and 46% from *P. vivax*. Malaria transmission in El Oro was historically high, reaching up to 2,000 total cases in 1999. An API of 61 cases of *P. falciparum* and 35 *P. vivax* cases per 1,000 people was recorded in Huaquillas canton along the Peruvian border in 1999. Between 1998-2002, large outbreaks of *P. falciparum* malaria occurred across El Oro province before declining to low incidence after a period of more intensive vector control (Figure 2.1B). A small outbreak of *P. vivax* malaria occurred between 2007-2009 before malaria incidence dramatically reduced and remained at a low and stable level between 2010-2018. The highest malaria incidence was concentrated in the western part of the province, along the Peru-Ecuador border (Figure S2.3).

Between 1990-2018 in El Oro, outbreaks of both *P. falciparum* and *P. vivax* malaria occurred concurrently (Figure 2.1B). Prior to the elimination phase (2001-2018), there was a larger difference in *P. falciparum* and *P. vivax* incidence in rural compared to urban areas (Figure 2.3). In rural areas of El Oro between 1990-2000, mean incidence of *P. vivax* was 94% higher than incidence of *P. falciparum*. During the elimination phase, this difference was reduced and in rural areas there was only a marginal difference in the incidence of *P. falciparum* and *P. vivax* malaria. During the elimination phase, malaria incidence in rural areas was reduced more (by 87% for *P. falciparum* and by 94% for *P. vivax*) than in urban areas (by 87% for *P. falciparum* and by 70% for *P. vivax*; Figure 2.3). Overall, between 1990-2000 and the elimination phase (2001-2018), *P. falciparum* was reduced more across El Oro (87% reduction), than *P. vivax* malaria (77% reduction).

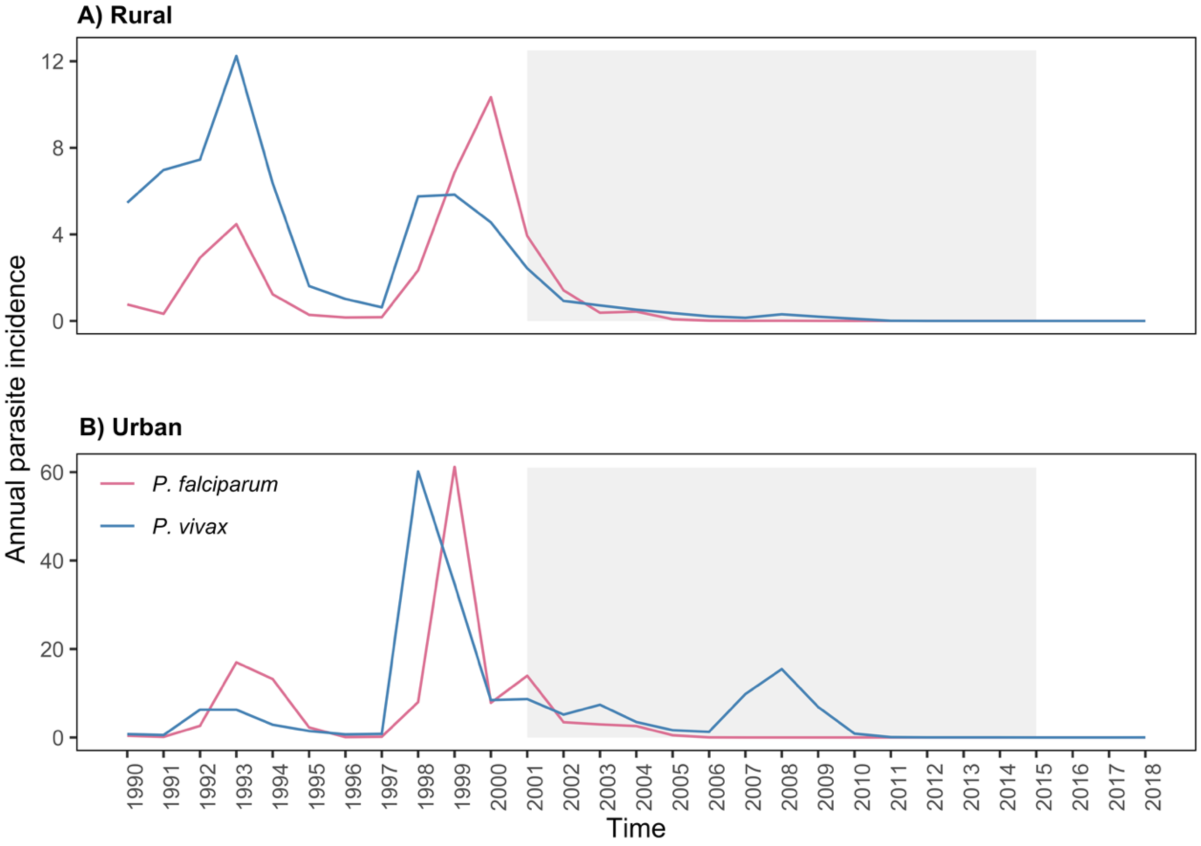

Figure 2.3. Rural and urban malaria in El Oro 1990-2018. Annual parasite incidence (API), per 1,000, of *P. falciparum* (pink) and *P. vivax* incidence (blue) in A) rural and B) urbanised areas. Grey shading represents the period of intensive vector control in El Oro, 2001-2015. Urban areas were defined as cantons that had urban cover above or equal to 5% of total land cover.

In spatiotemporal models of malaria incidence in El Oro between 1990-2018, urban areas were associated with greater incidences of *P. falciparum* (0.23, 95% CI 0.06 - 0.40; Figure 2.4A; Table S2.5), but not *P. vivax* malaria (0.02, 95% CI -0.10 - 0.14; Figure 2.4A; Table S2.5). To examine how the epidemiology of malaria in El Oro had changed during the intervention period 2001-2015, I tested whether there was a difference in the relationship between malaria and level of urbanisation in El Oro, before and after the interventions were implemented. There was a statistically significant interaction between level of urbanisation in El Oro and the intervention period (2001-2015) for *P. vivax* (0.37, 95% CI 0.28 – 0.45) but not *P. falciparum* malaria (-0.01, 95% CI -0.12 – 0.10). Prior to 2001, urban areas of El Oro were associated with lower levels of *P. vivax* malaria, compared to rural areas. After 2001 this relationship reversed, with urbanised areas associated with more *P. vivax* malaria. During the elimination phase (2001-2018) there was also a reduction in the seasonal pattern of both *P. falciparum* and *P. vivax* malaria in El Oro. The reduction was especially evident for *P. vivax* malaria incidence, which ceased to peak between June-July (Figure S2.5). For *P. falciparum* a seasonal peak in incidence during this period was evident between June-July, but less distinct than before 2001.

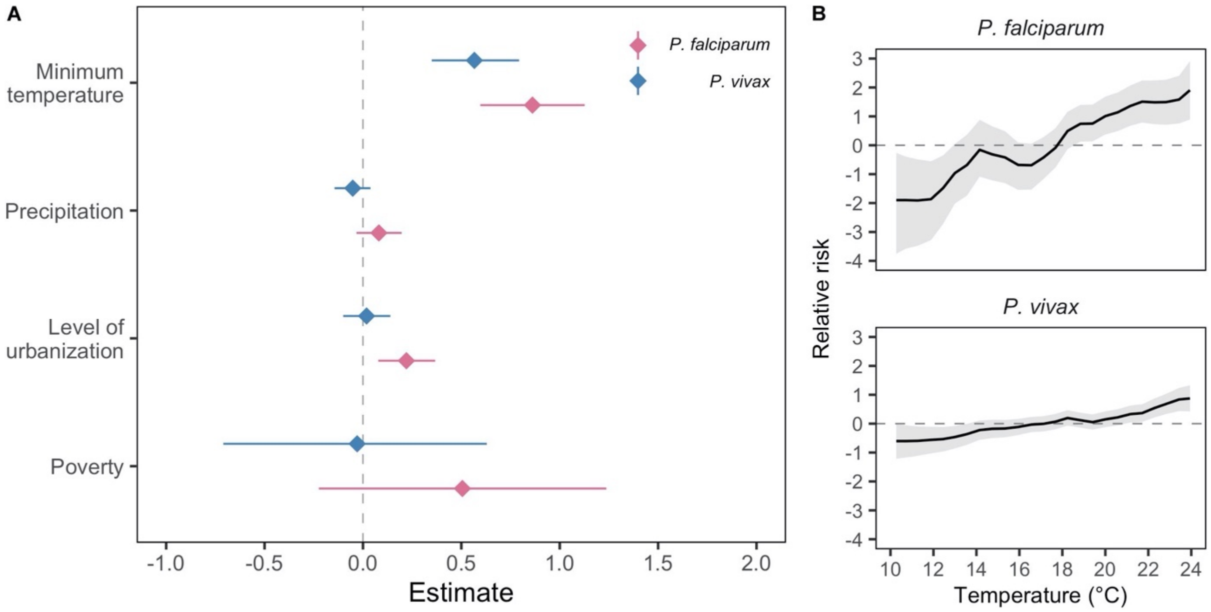

Figure 2.4. Effect of environmental and socioeconomic factors on the spatiotemporal incidence of *P. falciparum* and *P. vivax* malaria in El Oro, Ecuador 1990-2018. A) Posterior mean and 95% credible intervals for minimum temperature and precipitation, included as linear terms, urbanised areas and poverty covariates for *P. falciparum* (pink) and *P. vivax* (blue) malaria. B) Relationships between *P. falciparum* and *P. vivax* relative risk, on the log scale defined as the annual parasite incidence (API) log(ρ_{st}), and minimum temperature, lagged by three months, included in the model as a function to allow for non-linearities.

2.3.2. Climate variability and malaria incidence in El Oro 1990-2018

Minimum temperature was the best fitting temperature variable in the full models of malaria incidence between 1990-2018 (Table S2.3). In the three months prior to case reporting, minimum temperature was an important predictor of the spatiotemporal variation in *P. falciparum* and *P. vivax* malaria in El Oro (Figure 2.4A). Warmer temperatures in El Oro between 1990-2018 were associated with increases in malaria incidence and greater increases in *P. falciparum* (0.90, 95% CI 0.60 - 1.20; Table S2.5) than *P. vivax* (0.57, 95% CI 0.35 - 0.79; Table S2.5) malaria (Figure 2.4A). This result corresponds to a 146% increase in *P. falciparum* and 77% increase in *P. vivax* incidence with a 1°C rise in minimum temperature.

Precipitation, lagged by three months for *P. falciparum* and one month for *P. vivax* were selected as the best time lags. Although, when included in the full model precipitation was not a significant driver of malaria incidence in El Oro (Figure 2.4A; Table S2.5). Introducing a non-linear relationship between malaria and climatic variables improved model fit by decreasing model DIC and RMSE for *P. vivax*, but not for *P. falciparum* malaria incidence (Table 2.1, Figure S2.6). No evidence was found of a non-linear relationship between malaria risk and minimum temperature. Higher temperatures were associated with increases in malaria incidence, which was stronger for *P. falciparum* malaria (Figure 2.4B).

Table 2.1. Model adequacy results for spatiotemporal models of malaria incidence in El Oro, Ecuador 1990-2018. Adequacy results, deviance information criterion (DIC), Watanabe-Akaike Information Criterion (WAIC) and cross-validated log score for full models of *P. falciparum* and *P. vivax* malaria (API, $\log(\rho_{st})$), in El Oro, Ecuador 1990-2018. Covariates were added iteratively, including unstructured yearly effects (y_t) and starting with a baseline model that included structured (ν_s) and unstructured (υ_s) spatial random effects, and a seasonal term (m_t). The proportion of urbanised areas was interacted with a categorical variable ($x_{2st}z_i$) indicating a decline in malaria incidence post 2001. The most parsimonious models included climate variables (temperature x_{3st} and precipitation x_{4st}) as linear terms for *P. falciparum* and as non-linear functions for *P. vivax* malaria.

Model	**Parasite**	**DIC**	**WAIC**	**Log score**
Baseline spatial seasonal $\log(\rho_{st}) = \upsilon_s + \nu_s + m_t$	*P. falciparum* *P. vivax*	12640.97 18745.44	12646.73 18743.44	1.38 2.05
Unstructured yearly random effects $\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t$	*P. falciparum* *P. vivax*	11947.63 17887.75	11970.4 17894.17	1.31 1.96
Socioeconomic effects $\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t + x_{1s}$	*P. falciparum* *P. vivax*	11946.75 17887.61	11970.10 17893.23	1.31 1.96
Urban effects $\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t + x_{1s} + x_{2st}z_i$	*P. falciparum* *P. vivax*	11935.89 17823.38	11958.12 17831.99	1.31 1.95
Temperature effects $\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t + x_{1s} + x_{2st}z_i + x_{3st}$ (linear) $\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t + x_{1s} + x_{2st}z_i + f(x_{3st})$ (non-linear)	*P. falciparum* *P. vivax*	11926.14 17797.49	11941.98 17806.2	1.31 1.95
Precipitation effects $\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t + x_{1s} + x_{2st}z_i + x_{3st} + x_{4st}$ (linear) $\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t + x_{1s} + x_{2st}z_i + f(x_{3st}) + f(x_{4st})$ (non-linear)	*P. falciparum* *P. vivax*	11924.91 17771.48	11941.77 17800.51	1.31 1.95

The influence of minimum temperature on the unexplained variation in *P. falciparum* and *P. vivax* incidence in El Oro between 1990-2018 was also investigated. To do this, the monthly and interannual random effects of models with and without temperature were compared to determine the extent to which temperature accounted for the seasonal and interannual patterns of malaria incidence. The monthly random effects of the model for *P. falciparum* incidence that included minimum temperature were near zero, showing that temperature accounted for all the seasonal variation in *P. falciparum* malaria in El Oro 1990-2018 (Figure 2.5A). In contrast, there was a smaller reduction in the random effects for the *P. vivax* model with minimum temperature, indicating the seasonal pattern was primarily driven by other unmeasured factors, such as control measures (Figure 2.5B).

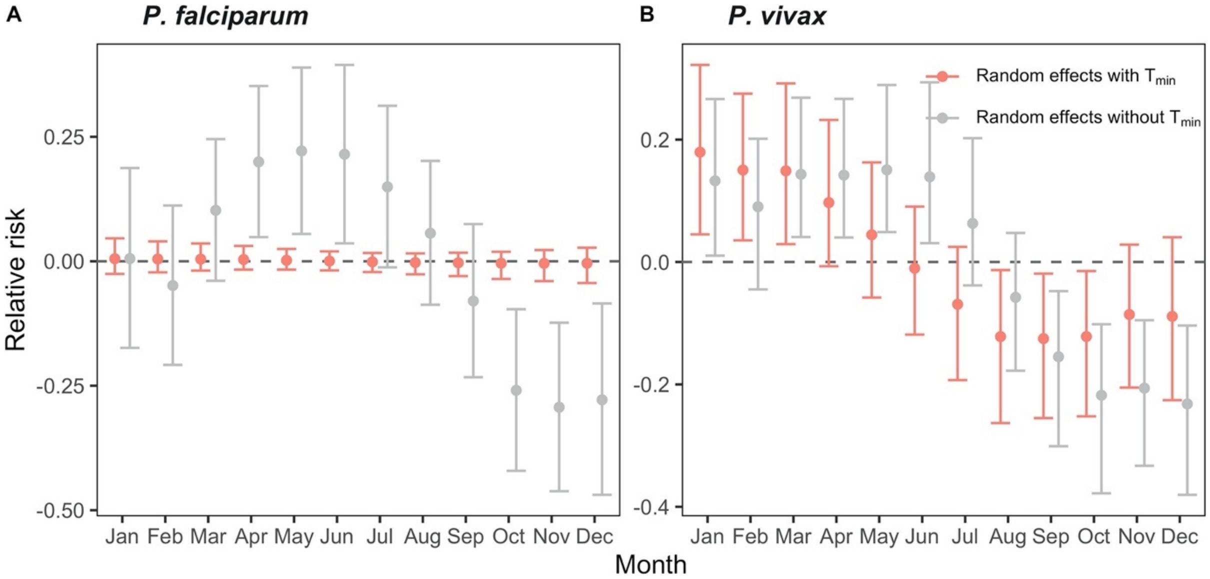

Figure 2.5. Effect of minimum temperature (T_{min}) on the annual cycle of malaria in El Oro, Ecuador 1990-2018. Difference in the monthly random effect marginal posterior distributions for models of A) *P. falciparum* and B) *P. vivax* malaria that include minimum temperature (orange), lagged by three months and models that exclude minimum temperature (grey). Relative risk, on the log scale, is defined as the annual parasite incidence (API), log(ρ_{st}). A reduction in estimates including T_{min} (orange) towards zero indicates that minimum temperature accounts for the seasonal variation in malaria incidence.

In comparison to the seasonal effects, the difference in the interannual random effects of models with and without minimum temperature was marginal (Figure 2.6). This suggests that other interannual signatures as well as temperature, contribute to the interannual variability of malaria in El Oro. For example, for some years the proportion of variation accounted for by the interannual random effects decreased when minimum temperature was included in the models. A reduction in the value of the random effects was observed in 1998 (Figure 2.6), when a strong El Niño event occurred. Reductions were also particularly apparent for *P. falciparum* malaria between 2001-2004 and 2009-2011, suggesting that some additional variation was explained by minimum temperature. For some years there was no reduction, for example in 2008, when an outbreak of *P. vivax* malaria occurred, suggesting the outbreak was not driven by a climate event.

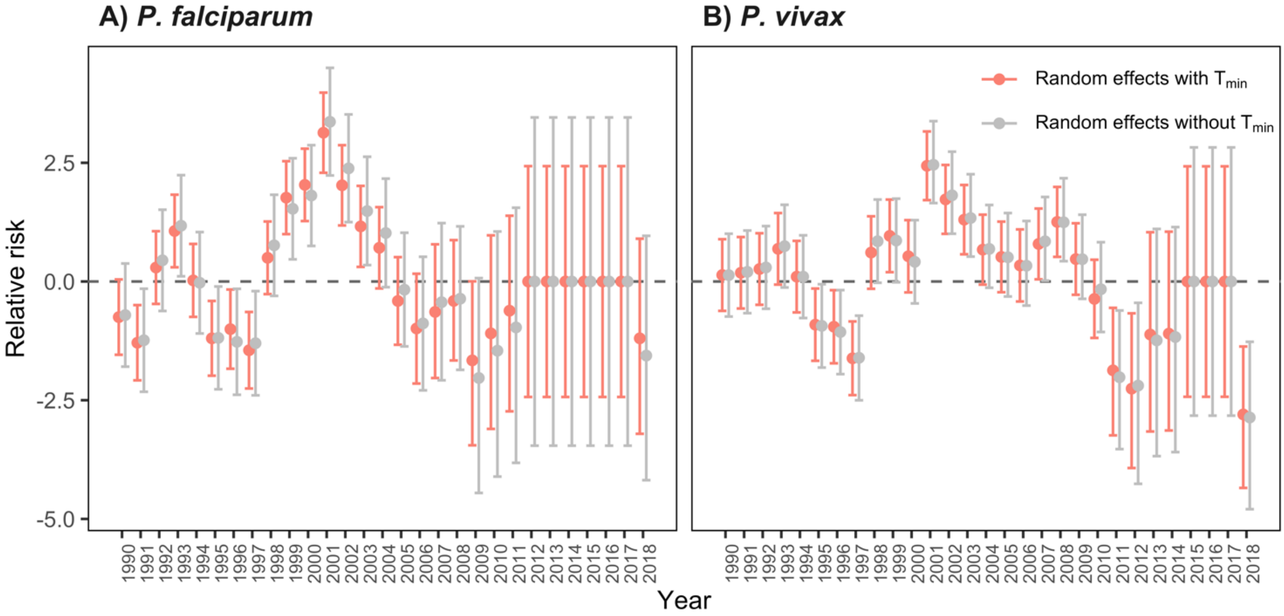

Figure 2.6. Effect of minimum temperature (T_{min}) on the interannual variation of malaria in El Oro 1990-2018. Difference in the interannual random effect marginal posterior distributions for models of A) *P. falciparum* and B) *P. vivax* malaria that include minimum temperature (orange), lagged by three months, and exclude minimum temperature (grey). Relative risk, on the log scale, is defined as the annual parasite incidence (API), $\log(\rho_{st})$.

Between 1990-2018, there was a rise in the number of months with suitable temperatures for *P. falciparum* transmission (Figure 2.7). Noticeable peaks of eight months of suitable temperature conditions occurred between 1997-1998 and 2014-2016. Increasingly suitable temperatures for *P. falciparum* transmission also coincided with consistently warmer seasonal and interannual temperatures in El Oro between 1990-2018 (Figure S2.7). In contrast, temperature conditions for *P. vivax* malaria transmission showed no increasing trend in El Oro between 1990-2018 (Figure 2.7), although similar peaks in suitability were observed in 1997-1998 and in 2015-2016.

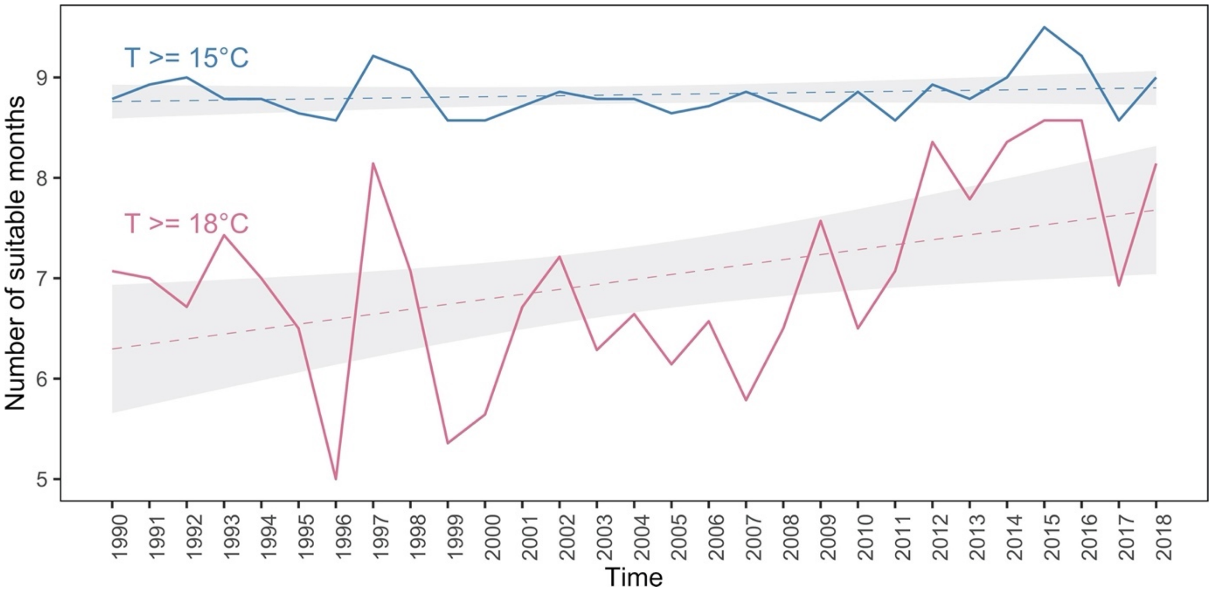

Figure 2.7. Suitable temperature conditions for malaria transmission in El Oro, Ecuador 1990-2018. Mean (solid curve) number of months per year where minimum temperatures exceeded 18°C (i.e. considered suitable for *P. falciparum* malaria transmission; pink) and 15°C (i.e. considered suitable for *P. vivax* malaria transmission; blue), in El Oro 1990-2018. Dashed curve shows logistic regression line and grey shading represents 95% confidence intervals. Suitable temperature thresholds were chosen according to Watts *et al.* (2019).

The most parsimonious models of malaria incidence in El Oro 1990-2018 included minimum temperature and precipitation as linear terms for *P. falciparum*, and as non-linear functions for *P. vivax* malaria. Models also included poverty rates, the proportion of urbanised areas (including an interaction with the period when the vector control measures were implemented), and spatial and temporal random effects (Table 2.1). Although in these models the credible intervals for the precipitation and poverty estimates contained zero, the addition of these covariates to the models slightly decreased DIC values and increased model fit for *P. falciparum* and *P. vivax* malaria incidence. Including climate variables (as linear terms for *P. falciparum* and as non-linear functions for *P. vivax* malaria) decreased the uncertainty of the model posterior distributions, in comparison to distributions from models that excluded climate variables (Figure 2.8). Model uncertainty was reduced more for *P. falciparum* malaria, especially during the large outbreaks that occurred in 1992-1994 and 1998-2002. Interestingly, during the later years of the study period, the model posterior distributions displayed a surge in malaria incidence, particularly for *P. vivax* between 2015-2018.

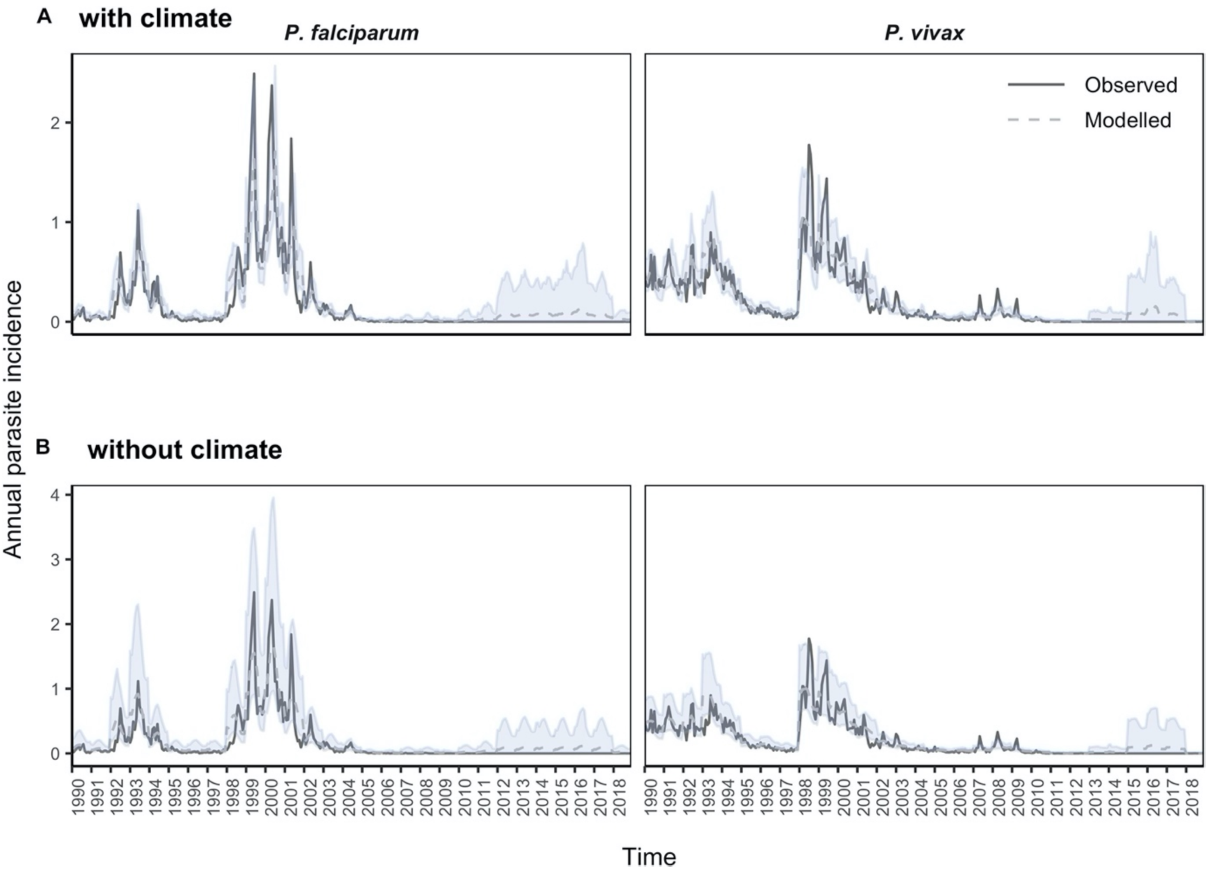

Figure 2.8. Model posterior distributions with and without climate information for *P. falciparum* and *P. vivax* malaria in El Oro, Ecuador 1990-2018. Observed (grey solid line), posterior mean (blue dashed line) and 95% credible intervals (blue shading) for annual parasite incidence (API) for A) models that include minimum temperature, lagged by three months and precipitation, lagged by three months for *P. falciparum* models and one month for *P. vivax* models and B) without climate information. For models of *P. falciparum* malaria, minimum temperature and precipitation were included as linear terms. For *P. vivax* malaria models, model fit was improved when non-linear functions of minimum temperature and precipitation were included.

2.3.3. Vector control measures and malaria incidence in El Oro 2001-2015

To evaluate the impact of the three vector control measures (indoor residual spraying, space spraying and ULV fumigation) that were implemented between 2001-2015, separate sub-models were fitted for *P. falciparum* and *P. vivax* malaria in El Oro (Text S2.3). By comparing the differences in the covariate parameter estimates from the full models for the entire timeseries (1990-2018) and the intervention models for the period 2001-2015, I found that posterior mean estimates were approximately similar across the different models (Figure 2.9, Tables 2.2 & S2.5). However, there was more uncertainty in the estimates for the environmental covariates in the intervention models compared to the 1990-2018 models, particularly for minimum temperature (Figure 2.9; Table S2.5).

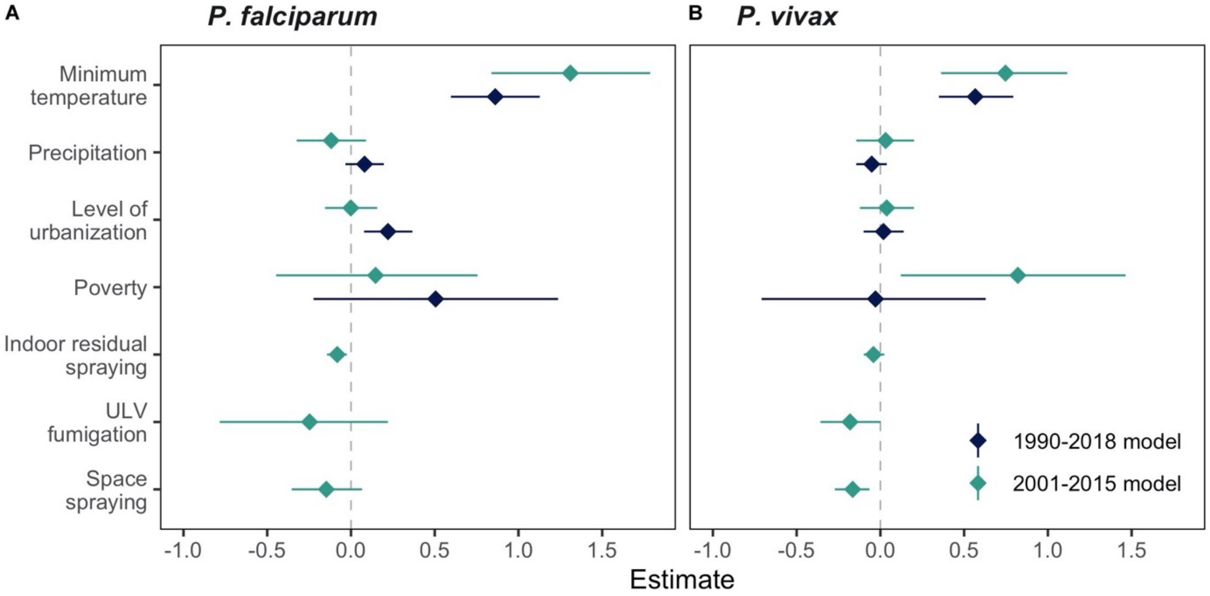

Figure 2.9. Parameter estimates for explanatory variables in spatiotemporal models of *P. falciparum* and *P. vivax* malaria in El Oro, Ecuador 1990-2018 and for models 2001-2015. Posterior mean and 95% credible intervals for environmental, socioeconomic and malaria vector control covariates in models of A) *P. falciparum* and B) *P. vivax* malaria from full models 1990-2018 (dark blue) and intervention models 2001-2015 (green). All vector control covariates were lagged by three months, apart from space spraying in the *P. falciparum* model, which was lagged by two months.

In addition, between 2001-2015 areas in El Oro with higher poverty levels were associated with higher incidences of *P. vivax* malaria (0.82, 95% CI 0.12 - 1.46; Figure 2.9; Table S2.5). In the intervention models, indoor residual spraying implemented in El Oro between 2001-2015, three months prior to case detection was associated with a small decline in *P. falciparum* malaria (-0.08, 95% CI -0.14 to -0.02; Figure 2.9; Table 2.2). This corresponded to an 8% decrease in incidence with every additional household sprayed. In contrast, IRS was not associated with decreases in *P. vivax* malaria (Figure 2.9; Table 2.2). Space spraying was associated with larger decreases in *P. vivax* malaria incidence in the following three months (-0.17, 95% CI -0.27 to -0.06; Figure 2.9; Table 2.2), but not *P. falciparum*. Space spraying every additional household corresponded to a 19% decrease in *P. vivax* incidence. ULV fumigation, also lagged by three months was not statistically significant (i.e., the credible intervals contained zero; Figure 2.9; Table 2.2).

Table 2.2. Parameter estimates for vector control measures in intervention models of malaria incidence in El Oro 2001-2015. Posterior mean estimates, lower (2.5%) and upper (97.5%) credible intervals (CI) for vector control measures from intervention models of *P. falciparum* and *P. vivax* malaria in El Oro between 2001-2015.

Control measure	**Parasite**	**Estimate**	**LCI**	**UCI**
Indoor residual spraying	*P. falciparum*	-0.08	-0.14	-0.02
	P. vivax	-0.04	-0.10	0.02
ULV fumigation	*P. falciparum*	-0.25	-0.78	0.22
	P. vivax	-0.18	-0.36	0.00
Space spraying	*P. falciparum*	-0.15	-0.35	0.07
	P. vivax	-0.17	-0.27	-0.06

I assessed which vector control measure implemented in El Oro between 2001-2015, provided the most valuable information to the intervention models in explaining malaria incidence across El Oro. There was considerable heterogeneity in the model improvement for each control measure, as measured by RMSE difference (Figure 2.10). Indoor residual spraying improved the model (reduced RMSE) for *P. falciparum* malaria in the coastal northwest of El Oro, and in cantons along the Ecuador-Peru border, improved the model by up to 14% in Arenillas canton (Figure 2.10). In contrast, there was little improvement from indoor residual spraying in the model fit for *P. vivax* malaria (maximum model improvement of 2% in Atahualpa canton). Model improvement with space spraying for *P. vivax* (8%) was double the improvement for *P. falciparum* in the province capital Machala (Figure 2.10). ULV fumigation provided minimal or no model improvement for either malaria parasite (Figure 2.10).

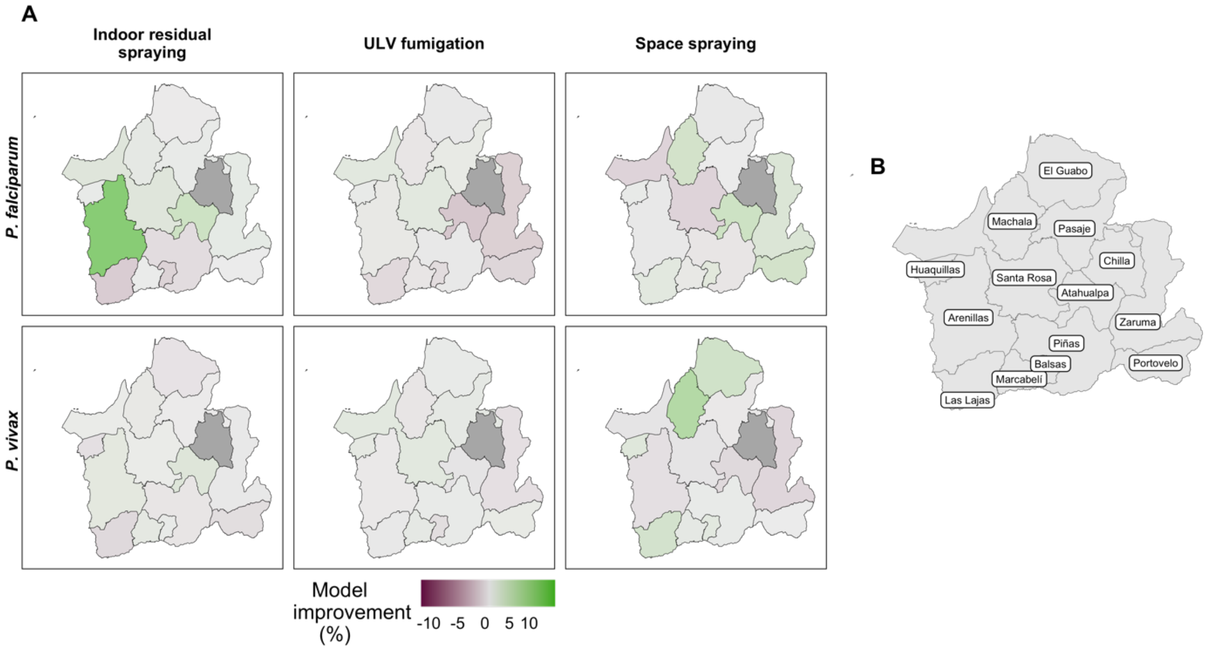

Figure 2.10. Model improvement for vector control measures implemented in El Oro, Ecuador 2001-2015. Model improvement (A), calculated as percentage change in root mean square error (RMSE), between models of *P. falciparum* and *P. vivax* malaria excluding each control measure, indoor residual spraying, ULV fumigation and space spraying, and models including each measure. Positive values (green) show where the addition of the control measure reduces RMSE, and negative values (purple) show where including the control measure does not improve the model. Dark grey areas show missing data. Map (B) shows the location of El Oro's 14 cantons.

Finally, I explored if the variation in malaria incidence in El Oro attributed to the vector control measures in the intervention model could be captured in the random effects structure of the full models. The interannual random effects of the full models (fitted to data from 1990-2018), which did not include intervention data, were compared to the interannual random effects of the intervention models (fitted to data from 2001- 2015). For some years (2001-2003 and 2008) there was a reduction in the magnitude of the random effects in the intervention models (Figure 2.11). This suggests that the control measures accounted for some of the unexplained variation in malaria incidence in the 1990-2018 model during 2001-2015. However, a considerable portion of the random variation was likely due to other unmeasured factors. Between 2012-2015 the random effects of the *P. falciparum* models are close to zero, indicating that variation in malaria incidence for those years was captured well by factors included in the model (Figure 2.11). A similar pattern for *P. vivax* malaria was found, with a reduction in the value of the random effects for the intervention model, compared to the full model during the early years of the interventions 2001-2009. This reduction indicates that the control measures influenced the interannual variation of malaria risk between 2001-2015.

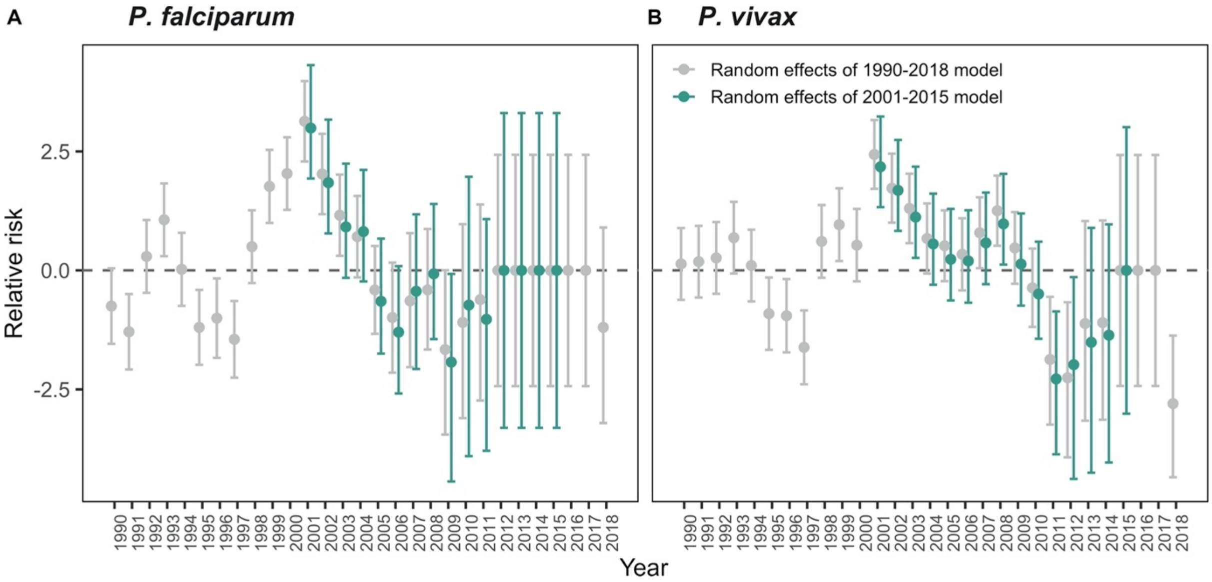

Figure 2.11. Interannual random effects for malaria risk in El Oro, Ecuador 1990-2018. Difference in the interannual random effect marginal posterior distributions for A) *P. falciparum* malaria models and B) *P. vivax* malaria models. Distributions from the intervention model are shown in green, which include intervention data. Distributions from the full model are shown in grey, which does not include intervention data. Relative risk, on the log scale, is defined as the annual parasite incidence (API), $\log(\rho_{st})$.

2.4. Discussion

For regions approaching malaria elimination and where funding and disease surveillance is limited, it is important to understand the drivers of malaria incidence to prevent disease re-establishment and ensure elimination efforts are sustained. In this study, a statistical modelling framework was developed to disentangle the relative role of multiple factors in driving variation in malaria incidence, whilst accounting for unobserved heterogeneity. Minimum temperature was found to be a principal driver of malaria incidence in El Oro, particularly the seasonal variation. Vector control measures implemented also had a differential impact on the incidence of the two malaria parasites. After the intensive period of vector control in El Oro between 2001-2015, malaria incidence in rural areas declined more than malaria in urbanised areas, and *P. vivax* malaria became more dominant. Incidence of *P. falciparum* malaria was also reduced more than *P. vivax* malaria and relatively more *P. vivax* cases were reported in urbanised areas during this time period (2001-2015). The greater reduction observed in *P.*

falciparum malaria is expected given that malaria control measures deployed during this time are primarily designed for use in rural settings and target mosquito vectors that are exophagic such as *An. albimanus*, a dominant malaria vector in El Oro (Ryan *et al.*, 2017).

Indoor residual spraying (IRS) is largely effective in reducing malaria transmission in settings with high prevalence and when applied on a large scale, especially in African countries (Pluess *et al.*, 2010; Sherrard-Smith *et al.*, 2018). In this study, IRS was effective at reducing the incidence of *P. falciparum* malaria in El Oro between 2001-2015, but not *P. vivax* malaria. Conventional control methods are less effective in reducing transmission of *P. vivax* compared to *P. falciparum* malaria because of the ability of *P. vivax* to cause multiple relapsing malaria episodes after the initial infection, caused by the activation of dormant liver stages (hypnozoites) (Price *et al.*, 2007). In addition, the *P. vivax* parasite develops more rapidly in the mosquito vector than *P. falciparum* and control methods such as IRS deployed in El Oro, which aim to shorten the mosquito lifespan, are less effective (Bassat *et al.*, 2016; Mendis *et al.*, 2001). Mosquito vectors can also become infected with *P. vivax* during a pre-symptomatic period, which allows for onward malaria transmission before drug treatment is initiated (White, 2008; McCarthy *et al.*, 2013). The rapid development of the *P. vivax* parasite and the presence of the hypnozoite stage also means that drug treatments, which are often of a longer duration are less effective at reducing transmission. Together these factors complicate the treatment and control of *P. vivax*, which remains a significant challenge to malaria elimination in Latin America (Bassat *et al.*, 2016; Recht *et al.*, 2017).

In this study, only IRS reduced the incidence of *P. falciparum* malaria, and in western cantons of El Oro. IRS, deployed inside homes, is most effective against endophilic mosquitoes, which rest indoors following a blood meal (Sherrard-Smith *et al.*, 2018). The two main malaria vectors in El Oro, *An. albimanus* and *An. punctimacula*, are most commonly observed biting and resting outdoors (Ryan *et al.*, 2017). As a result, IRS and other conventional control methods may not be suitable for reducing malaria transmitted by these mosquitoes. In contrast, space spraying was found to be effective in reducing incidence of *P. vivax* malaria in El Oro by 19%, especially in the province capital, Machala. In contrast, no declines in *P. vivax* incidence were detected with IRS application in El Oro. Evidence for the success of space spraying as a malaria control measure is limited and it is currently only recommended during outbreaks (Pryce and Malone, 2018). In the context of this study, space spraying is possibly targeting outdoor resting mosquitoes, such as *An. albimanus*, especially in peri-urban areas where housing conditions are poor and outdoor exposure is higher.

The *P. vivax* malaria parasite is able to develop at lower temperatures than *P. falciparum* (Nikolaev, 1935; Moshkovsky, 1946; Olliaro *et al.*, 2016; Ohm *et al.*, 2018), enabling its persistence in less favourable environmental conditions, such as colder temperatures (Mendis *et al*., 2001). In this study, a stronger association between minimum temperature and *P. falciparum* malaria compared to *P. vivax* was detected. In addition, all the seasonal variation in *P. falciparum* malaria was explained by temperature. A greater association between minimum temperature and *P. falciparum* malaria compared to *P. vivax* has been previously identified in China (Bi *et al.*, 2013), but to my knowledge this difference has not been previously quantified in Latin America. The differing climate sensitivity of malaria parasites is an important consideration for future elimination efforts in a world with a rapidly changing climate (IPCC, 2021). The greater sensitivity of *P. falciparum* to temperature is due to the greater dependence of *P. falciparum* transmission on the mosquito vector, which is highly susceptible to climate conditions. In contrast, *P. vivax* malaria transmission is less influenced by the mosquito vector and is sustained by unpredictable relapsing infections, which can be explained by other factors such as systemic illness in human populations (White, 2011). Between 2001-2015 areas in El Oro with higher levels of poverty were associated with increased incidence of *P. vivax* malaria, which suggests that socioeconomic conditions, such as limited access to healthcare may have influenced relapsing *P. vivax* infections during this time. However, these results should be interpreted with caution since the socioeconomic effects did little to improve model adequacy and in comparison to other covariates in the model, such as temperature, are not considered main predictors of malaria incidence in El Oro.

Warmer minimum temperatures in El Oro were associated with increases in *P. falciparum* and *P. vivax* malaria incidence three months later. This finding is in agreement with other studies in Latin America that have found a similar relationship between higher temperatures and malaria incidence (Basurko *et al*., 2011; Laneri *et al*., 2019; Poveda *et al*., 2000). This relationship can be attributed to the physiological effects of temperature on both the mosquito vector and parasite that increase transmission. For example, warmer temperatures shorten the development time of the parasite inside the mosquito and increase mosquito larval reproduction (Bayoh and Lindsay, 2003; Blanford *et al.*, 2013; Mordecai *et al.*, 2013). There was also a trend of rising minimum temperatures in El Oro between 1990-2018, with an increase in the number of months that have suitable minimum temperature conditions for *P. falciparum* malaria transmission. This increasing trend suggests a lengthening of the malaria transmission season. Large peaks in the transmission suitability of both *P. falciparum* and *P. vivax* malaria are evident between 1997-1998 and 2014-2016, when major El Niño events occurred. El Niño events bring warmer and wetter conditions to southern Ecuador, which are favourable for malaria transmission and have previously been suggested be the cause of an observed peak in cases (Krisher *et al.*, 2016).

During the later years of the study period, the model posterior distributions for both *P. falciparum* and *P. vivax* malaria incidence increase, despite few or zero cases being reported. This mismatch between observed and modelled incidence between 2015-2017 could possibly be due to warmer temperatures and the large El Niño event that occurred during this time. Increasingly suitable temperature conditions and large-scale climate events such as El Niño pose a real threat for the re-establishment of malaria in El Oro if cases are allowed to return, surveillance is not maintained, and interventions are not deployed appropriately. Moreover, this mismatch between observed and modelled malaria incidence could be problematic for decision makers and make it challenging for interpreting a rise in modelled incidence. In these circumstances, it is crucial to work with stakeholders and decision makers, to identify and discuss potential sources of this variation and how they might influence model results. For example, this can be achieved by performing a sensitivity analysis to identify how variables affect the modelled incidence. This is crucial for building trust with decision makers in the use of spatiotemporal models for assessing the impact of multiple factors on malaria risk.

Rainfall is essential for providing suitable habitats for mosquito breeding (Parham & Michael, 2010; Thomson *et al.*, 2005) and is considered to be a dominant factor in driving malaria transmission. Studies in the Amazon and Argentina have found that rainfall was important in determining variation in malaria incidence (Dantur Juri *et al.*, 2009; Olson *et al.*, 2009). For example in wetland areas of the Amazon, rainfall is associated with up to 80% lower malaria risk as wetland habitats become too deep for mosquito breeding or aquatic habitats are washed out completely (Olson *et al.*, 2009). In this study, rainfall was not a statistically significant explanatory variable for malaria incidence in El Oro and when added to the model only produced a small reduction in DIC and WAIC. This is possibly because ample larval habitat is already available. Two to three months prior to the peak malaria season (March-June), monthly rainfall accumulation reaches 80 mm across El Oro, which is considered more suitable for malaria transmission (Watts *et al.*, 2019), and up to 530 mm rainfall in the southeast of the province. Much of El Oro is rural with extensive mangroves and wetlands in the coastal northwest, which provide habitat suited to *An. albimanus* mosquitoes (Pinault and Hunter, 2012). The results therefore suggest that rainfall is not a significant predictor of malaria incidence in El Oro.

Using the random effects model structure, I was able to probe sources of unexplained variation in malaria incidence in El Oro 1990-2018. For example, I showed that the interannual random effects in the full models accounted for some of the variation due to the control measures that were implemented between 2001-2015. This demonstrates how the random effects model structure can be used to account for additional sources of variation where data may be limited. In addition, increases in the unexplained yearly variation in malaria were observed in 1998, when a large El Niño event occurred that could have elevated malaria risk in El Oro. However, it is expected that the climate variables included in the model will pick up some variation due to climatic anomalies from El Niño events. The Cenepa War, a period of political instability across the Ecuador-Peru border (Krisher *et al.*, 2016) likely hindered malaria control efforts and case reporting during 1995, and there is evidence of reduced malaria risk during this time in the interannual random effects. The reduction in malaria risk is likely explained by diminished case reporting. In addition, the outbreak of *P. vivax* in 2008 was probably not driven by a climatic event and may instead be driven by political instability or lapses in control efforts. Using the random effects structure to identify additional unexplained sources of variation proves valuable when engaging with stakeholders, such as the Ministry of Health and allow for two-way dialogue between stakeholders.

Despite the considerable length of the dataset, there are some study limitations to consider. In Ecuador a high number of malaria cases are asymptomatic. Low levels of parasitaemia, which act as a reservoir of transmission are difficult to diagnose (Sáenz *et al.*, 2017). It is probable that many cases of *P. vivax* malaria were missed and not reported during the study period. In addition, many *P. vivax* cases reported between 1990-2018 are likely to be relapses from the same initial infection, which could mask the true climate-malaria relationship. Urban malaria was approximately 70% higher than incidence of malaria in rural areas of El Oro. However, this may be a product of migration from neighbouring countries and case importation from surrounding rural areas (Gómez *et al.*, 2017). Unfortunately, here it was not possible to quantify the amount of malaria variation explained by migration and border effects owing to the lack of detailed migration data for the study period. Due to El Oro's location on a key migratory route, including for Venezuelan refugees, it is likely that human movements are influential in driving case reporting and subsequent malaria incidence. Likewise, outbreaks along the northern Peruvian border with El Oro also increase the risk of malaria transmission due to human movement (Krisher *et al.*, 2016).

In addition to migratory effects, the passive surveillance data used in this study also likely resulted in an underreporting of malaria cases. In comparison to active malaria surveillance, which may be able to capture more cases especially during local outbreaks, the passive surveillance of cases reported at local health centres, means that many cases would be missed. This is especially true given passive surveillance relies on self-reporting and would not detect those with asymptomatic infections. It is also likely that some reporting of cases occurred at health centres distant to the source of malaria infections.

Although variation in *P. falciparum* and *P. vivax* malaria in El Oro due to socioeconomic influences (poverty) were included in the model, this variable only accounted for spatial effects. Due to the considerable length of the study period (29 years), it is expected that a great deal of socioeconomic development took place in El Oro over this time. Whilst in some areas of El Oro, such as the centre of the capital, Machala, conditions such as housing quality and water infrastructure improved, other more remote areas may have experienced declines in socioeconomic status. Despite this limitation, it is expected that the unstructured yearly effects, as well as urbanisation included in the models were able to account for a proportion of the random variation due to changing socioeconomic conditions over time. Other factors that likely contributed to the spatiotemporal variation in malaria incidence in El Oro that were accounted for using the model random effects structure include variations in case reporting and surveillance, as well as health seeking behaviour.

The incompleteness of the intervention data used is also a limiting factor in this study. I was only able to evaluate the role of the three vector control measures implemented between 2001-2015, although there were other important elimination efforts that were carried out in El Oro between 1990-2018. For example, the use of DDT was widely used up until 1996 and a campaign to distribute insecticide-treated bed nets (ITNs) was initiated in 2004, although no detailed data exist for this in El Oro, or for other forms of personal protection that would have contributed to local elimination. However, by examining the interannual random effects of the models I observed a reduction in *P. falciparum* malaria risk between 2004-2006, which could be attributed to the use of ITNs. In 2005, the Ministry of Health suspended the use of chloroquine for treatment of *P. falciparum* malaria. Instead, the recommended change to artemisinin-based combination therapy (ACT) was adopted amid reports of drug resistance, which local partners suggested led to a major decline in transmission (Krisher *et al.*, 2016). The introduction of ACT in Colombia and Peru around 2005 also contributed to significant reductions in malaria case numbers (Rodríguez *et al.*, 2011; Quispe *et al.*, 2016). ACT introduction is also likely to have contributed to local malaria elimination in El Oro as declining malaria risk was observed during this period, by using the model interannual random effects. At the same time in El Oro (2005), a new shorter treatment regime for *P. vivax* malaria was adopted to ensure patients completed their treatment course, which was also reported to have contributed to declining transmission (Krisher *et al.*, 2016).

In summary, a statistical modelling framework was developed to simultaneously explore multiple environmental and socioeconomic barriers to malaria elimination in a low-transmission setting. I show that accounting for unobserved interannual variation using a random effects model structure is highly valuable for investigating malaria variation where detailed data is lacking. Here, I used available intervention data to explore the relative impact of three vector control measures on *P. falciparum* and *P. vivax* malaria in El Oro. I also provide an assessment of where control measures improved models of *P. falciparum* and *P. vivax* incidence, which will prove useful for targeting future malaria local control efforts in the region. I demonstrated a greater sensitivity of *P. falciparum* malaria to climate conditions, particularly warmer temperatures, which is important to consider in light of global environmental change and increasing climate suitability for malaria transmission (Laporta *et al.*, 2015; Romanello *et al.*, 2021). In addition, with climate warming of 1.5°C above pre-industrial levels it is predicted that southern Ecuador will experience temperatures 2-3°C warmer, and precipitation could increase by up to 20% (Allen *et al.*, 2018), providing conditions that are highly suitable for malaria transmission. *P. vivax* malaria was found to be less sensitive to temperature variation and exhibits more complex transmission patterns dependent on socioeconomic conditions, making it particularly challenging to eliminate

(Feachem *et al.*, 2010). An assessment of the environmental obstacles to elimination efforts in Ecuador is timely and important. Lapses in control efforts should be avoided, especially as it becomes harder to prevent and detect cases due to limited funding for surveillance and control. Recently, indigenous cases of malaria have been detected in El Oro and re-introduction of malaria parasites along with warming temperatures threaten current elimination progress.

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SECTION A – Student Details

Student	Isabel Fletcher
Principal Supervisor	Rachel Lowe
Thesis Title	Assessing the impact of global environmental change on mosquito-borne disease: A Planetary Health approach

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	The Lancet Planetary Health		
When was the work published?	01.09.22		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Author list: **Fletcher IK,** Grillet ME, Moreno JE, Drakeley C, Hernàndez-Villena, Jones KE & Lowe R. I lead this study, collated the data, fitted the models, analysed the results and wrote the manuscript.

Student Signature: [redacted] **Date:** 25.09.2022

Supervisor Signature: [redacted] **Date:** 25.09.2022

Chapter 3 – Synergies between environmental degradation and climate variation on malaria re-emergence in southern Venezuela

In the previous chapter, I showed how multiple components of the risk framework can be accounted for in a spatiotemporal modelling framework to understand the joint influence of climate variation on malaria alongside the combined impact of elimination efforts (Chapter 2). However, the impact of climate variation on disease risk must also be understood in the context of how human activities are altering the environment. The way in which land-use change modulates the impact of climate factors on mosquito-borne diseases has received little attention. However, it is important to understand the synergistic links to improve targeting of interventions and strengthen resilience to climate change in a world increasingly dominated by human activities. To address this gap, I build upon the model framework developed in Chapter 2 and explore the interactions between climate variation and environmental degradation on malaria. In this chapter, I investigate the extent to which the impacts of climate variation and environmental degradation act synergistically to determine mosquito-borne risk. To do this, I integrate multiple sources of environmental data including climate observations and land cover data in a Bayesian hierarchical mixed effects modelling framework, using a case study of rapid malaria re-emergence and mining activity in southern Venezuela. Understanding how both climate variation and environment degradation influence mosquito-borne disease risk will be important to guide policymakers in areas of the world vulnerable to both climate and land-use change.

Abstract

Environmental degradation facilitates emergence of mosquito-borne diseases such as malaria, through changes in the ecological landscape that increase human-vector contacts and proliferate vector habitats. However, the modifying effects of environmental degradation on climate-disease relationships have not been well explored. Here, I investigate the rapid re-emergence of malaria in a transmission hotspot in southern Venezuela and explore the synergistic effects of environmental degradation, specifically mining activity, and climate variation on malaria risk. Monthly cases of *P. falciparum* and *P. vivax* malaria between 1996-2016 were modelled using a Bayesian hierarchical mixed effects model framework for Bolívar state, southern Venezuela, where approximately 60% of national cases occur annually. Using remotely sensed land cover and climate observations, I quantify the variation explained by mining activity before exploring the modifying effects of environmental degradation on

climate-malaria relationships. The presence of mining activities explained almost half of the spatial variation in *P. falciparum* malaria in Bolívar. In addition, the effect of temperature on malaria was exacerbated in areas with mining sites, where the effect size for *P. falciparum* malaria at temperatures of 26.5°C was twice as high as the effect in low mining areas. I show that mining activity in southern Venezuela is associated with hotspots of malaria transmission, which threatens progress towards elimination in the Latin American region. Warmer temperatures exacerbated malaria transmission in mining areas, highlighting the need to consider how environmental degradation modulates climate impacts on disease risk. This is especially important globally, in areas subjected to rapidly rising temperatures and land-use change. These findings are also important for effectively targeting timely treatment programs and vector control activities in high-risk mining areas.

3.1. Introduction

Global increases in land-use alterations alongside climate variability and change are strongly implicated in driving the emergence and re-emergence of infectious diseases (Patz *et al.*, 2003; Myers *et al.*, 2013). Environmental degradation, including deforestation for agriculture or mining activities, can compromise human health by modifying the natural habitat of disease pathogens and their vectors, facilitating increases in human exposure to zoonoses. Malaria is a mosquito-borne disease sensitive to environmental conditions (Parham and Michael, 2010; Gottdenker *et al.*, 2014; Caminade *et al.*, 2019) that imposes widespread global disease burden, with an estimated 241 million cases recorded in 2020 (WHO, 2021c). The links between climate and malaria in endemic regions of the world are well-established, for example seasonal increases in rainfall and temperature are tightly linked to the malaria transmission season across sub-Saharan Africa (Thomson *et al.*, 2006; Macleod *et al.*, 2015). Warmer temperatures and adequate rainfall provide favourable conditions for the development of the *Anopheles* mosquito vector and *Plasmodium* malaria parasite (Bayoh and Lindsay, 2003; Mordecai *et al.*, 2013; Beck-Johnson *et al.*, 2017), thereby enhancing disease transmission.

In addition to climate variation, land-use changes occurring over multiple spatial and temporal scales, can also affect malaria transmission predominantly through the alteration of *Anopheles* vector ecology (Yasuoka and Levins, 2007; Vittor *et al.*, 2009). In the Peruvian Amazon, ecological fragmentation resulting from deforestation favours the primary malaria vector *Anopheles darlingi*. In deforested areas, the availability of *An. darlingi* breeding habitats, characterized by permanent sunlit water bodies and forest edges is increased (Vittor *et al.*, 2009). The relationship between deforestation and malaria however is highly context-dependent and subject to strong socioeconomic feedbacks, such as economic development, which can dampen the effect of increased mosquito breeding habitats on malaria risk (Baeza *et al.*, 2017; MacDonald and Mordecai, 2019; Fornace *et al.*, 2021). Understanding the impact of land-use change on disease risk, alongside other important factors including climate variation will be required to tackle compounding threats in landscapes increasingly dominated by human activities (IPCC, 2021; Winkler *et al.*, 2021).

Despite an understanding of how land-use change and climate variation affect malaria transmission independently, there has been little exploration of how land use modulates the impact of climate variation. Microclimatic changes associated with environmental disturbances including forest clearance result in warmer temperatures compared to intact forest, subsequently enhancing mosquito survivorship and vectorial capacity (Afrane *et al.*, 2005, 2006). As a result, it is expected that land-use change may alter the impact of climate variation on disease transmission (Lindblade *et al.*, 2000). These modifying effects are important to consider in light of increasing trends in global land-use change, ongoing climate variation, in addition to recent plateaus in the global malaria response (WHO, 2020). An assessment of the interacting effects of land use and climate on malaria is of notable concern in politically unstable regions experiencing uncontrolled surges in disease transmission. In particular, Venezuela is a country which is currently experiencing an explosive epidemic growth in malaria cases (WHO, 2020) and is vulnerable to the effects of land-use change and climate variation (Grillet *et al.*, 2021). The dramatic rise of malaria cases in Venezuela is a regional problem, which threatens to reverse malaria elimination progress across the Latin American region (Grillet *et al.*, 2018, 2019).

Malaria transmission in Venezuela is thought to be sustained by disease hotspots in southern areas degraded by mining activity, primarily for gold, which has expanded in the last ten years driven by political instability and economic collapse (Hotez *et al.*, 2017; Grillet *et al.*, 2021). Clustering of malaria cases in mining areas creates source-sink dynamics across Venezuela, bolstering hotspots of transmission in the south of the country (Grillet *et al.*, 2021). High entomological inoculation rates (number of infective bites) and *An. darlingi* abundance have been identified in gold mining areas in Venezuela (Moreno *et al.*, 2007; Jorge E. Moreno *et al.*, 2009). The ecological changes associated with mining activity, primarily the clearance of vegetation and formation of standing bodies of water that create suitable habitat for malaria vectors, provide ideal conditions for malaria transmission and allow for high exposure of vulnerable migrant populations to vectors (Moreno *et al.*, 2009; Abou Orm *et al.*, 2017). Despite local studies providing evidence of how hotspots of malaria transmission are maintained in mining areas, malaria transmission rates in Venezuela continue to rise (WHO, 2020), highlighting the need for a more comprehensive understanding of the spatiotemporal drivers of transmission.

Further work has indirectly linked increasing malaria trends to gold mining activity, not only in Venezuela. For example, increased densities of anopheline vectors documented in illegal gold mining sites in French Guiana have subsequently been linked to malaria outbreaks (Pommier de Santi *et al.*, 2016). Additionally, studies in Peru, Brazil and recently Guyana have linked gold prices (Sanchez *et al.*, 2017; De Salazar *et al.*, 2021) and rates of gold production to malaria (Duarte and Fontes, 2002; Castellanos *et al.*, 2016), and in Colombia 32% of national malaria cases were found to be from gold mining areas (Castellanos *et al.*, 2016). In Suriname, the mobility of mining workers was associated with an increase in the number of imported malaria cases (Douine *et al.*, 2019). Despite these findings, previous research has not yet been able to draw a direct link between mining activity and malaria, and it is unclear to what extent mining activity can explain patterns of malaria incidence. Moreover, previous research has overlooked the impact of climate variation on malaria, considering only the impact of gold mining on malaria independently of other important environmental factors. How environmental degradation caused by mining activity interacts with and modulates the impact of climate on malaria risk, has received limited attention.

In this study, I explore the spatiotemporal drivers of malaria re-emergence in southern Venezuela, investigating the influence of environmental degradation, specifically mining activity, and its modifying effect on climate-malaria relationships. To do this, I use spatiotemporal Bayesian hierarchical mixed effects models to explore monthly patterns of *P. falciparum* and *P. vivax* malaria incidence between 1996-2016 in Bolívar state, an important focal malaria hotspot in southern Venezuela (Figure 3.4A). I integrate multiple sources of environmental data, including remotely sensed land cover and climate observations, to address the lack of ground truth data. Building on previous knowledge of mining and malaria, I provide evidence for the link between mining activity and malaria incidence, and explicitly quantify the variation explained by mining activity. Finally, I use the model to test for the interaction between environmental degradation, caused by mining activity and the nonlinear impacts of temperature and rainfall on malaria risk in Bolívar.

3.2. Methods

3.2.1. Study area

Bolívar state (latitude: 3°36’9.82”N – 8°26’48.39”N, longitude: 67°26’22.47”W – 60°15’45.0”W) is located in south-eastern Venezuela and shares borders with Guyana and Brazil. Bolívar (total area 240,500 km^2) is subdivided into 11 municipalities, which are further divided into 46 parishes (third-level administrative units; Figure 3.1). Parishes in Bolívar vary considerably in geographical size from ~18 km^2 (La Sabanita parish) to ~46,870 km^2 (Barceloneta parish). Most of the population resides in urban centres in the north and east, whilst rural and southern regions of Bolívar are sparsely populated, with limited accessibility and transport networks. The landscape of Bolívar is characterised by lowland forest ecosystem and has a tropical humid climate. Annual temperatures average 24-26°C and there are two main peaks in rainfall per year, the larger occurring from May to July, followed by a smaller rainfall peak from October to November (Grillet *et al.*, 2014).

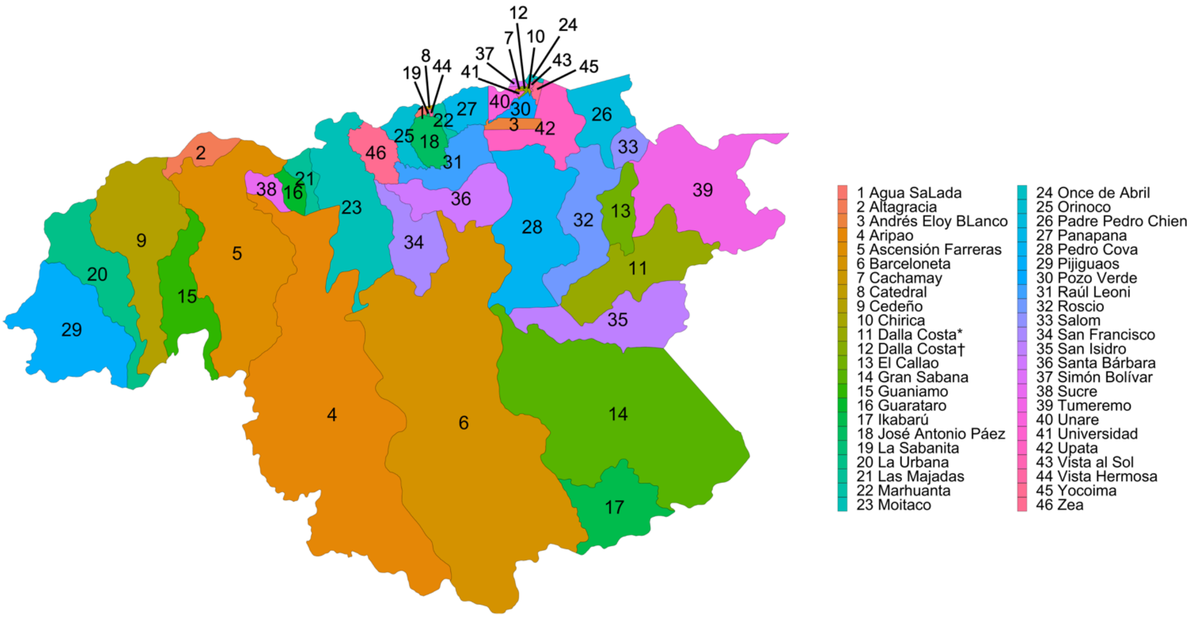

Figure 3.1. Parishes in Bolívar state. Location of the 46 parishes in Bolívar state, Venezuela. *Dalla Costa parish, Sifontes municipality. †Dalla Costa parish, Caroní municipality.

Although malaria was eliminated in approximately 75% of Venezuelan territory in the 1960s, transmission of *P. falciparum* and *P. vivax* has persisted in remote southern regions of the country including Bolívar state, which accounted for 47% of national cases in 2017 (Grillet *et al.*, 2021). More recently local malaria transmission has emerged in new areas of the country, including in the southwest. Recent emergence of malaria transmission has been exacerbated by the political, humanitarian and health crises in the country, which has had a damaging effect on vector control, disease surveillance, as well as access to treatment. Malaria transmission in Bolívar state is highly focal, with local clustering of malaria cases in Sifontes municipality in the northeast, which has sustained high transmission rates (Figure 3.4) (Grillet *et al.*, 2021). The majority of malaria infections in Bolívar result from *P. vivax* (70-80%) and *P. falciparum* (20-30%) parasites and the most important malaria vectors in Bolívar are *Anopheles darlingi* and *Anopheles albitarsis* (Grillet *et al.*, 2021).

3.2.2. Data sources

The number of monthly cases of *P. falciparum* and *P. vivax* malaria reported at local health centres and confirmed by blood smears were provided for each of the 46 parishes in Bolívar state from 1996-2016 by the Ministry of Health. There was no detection of mixed infections or whether cases were due to relapses from previous infections. Annual population estimates per 1,000, per parish between 1996-2016 were also sourced from the Ministry of Health. Monthly estimates of precipitation and mean temperatures for each parish in Bolívar 1996-2016 were obtained from the ERA5-Land dataset, a reanalysis of the European Centre for Medium-Range Weather Forecasts (ECMWF) ERA5 climate model, which combines model data with meteorological observations to provide temporally consistent global data at a resolution of 9 km^2 ('Copernicus Climate Change Service (C3S) (2019): C3S ERA5-Land reanalysis', 2019). Monthly climate variables for each parish in Bolívar were obtained by calculating mean values over each polygon. Monthly climate variables (temperature and precipitation) were included into the models by taking the average climate conditions of the previous three months for each parish. This enabled the capturing of the lagged effect of climate on malaria transmission, which results from the time required for completion of mosquito and parasite life cycles, and the time between malaria diagnosis and reporting (Ikeda *et al.*, 2017; Laneri *et al.*, 2019; Chapter 2).

Monthly anomalies in sea-surface temperatures (SST) for the Niño 3.4 region were obtained from the National Oceanic and Atmospheric Administration (NOAA). Niño 3.4 is an index of the El Niño Southern Oscillation (ENSO), a major climatic phenomenon affecting the north and west coast of South America. The Niño 3.4 index has previously been linked to the interannual variability of malaria across Venezuela, with increased malaria epidemics following ENSO-related droughts (Gagnon *et al.*, 2002; Grillet *et al.*, 2014). The Niño 3.4 anomalies were lagged by eight months (Figure S3.1), which is in broad agreement with previous studies that have associated seasonal malaria with SST anomalies in the Niño 3.4 region with a delay of 9-12 months (Grillet *et al.*, 2014).

The location of suspected mining sites in Bolívar state (n = 2,460) were sourced from the Rede Amazónica de Información Socioambiental Georeferenciada (Amazon Geo-Referenced Socio-Environmental Information Network) (Figure 3.2). This dataset is primarily comprised of sites for gold extraction, which is the main economic activity in the area. The dataset also contains sites where other resources such as bauxite, aluminium, calcite and iron are extracted. Locations of sites from satellite images were captured in 2009, 2017 and 2018 and some smaller sites identified by satellite imagery were verified by local communities. The total number of mining sites per parish in Bolívar were counted, which included all sites that were labelled as inactive under the assumption that the habitat created by land clearance for mines including pools of stagnant water can remain once mining pits are abandoned. The total number of mines per parish was used to best capture the spatial variation in mining activity across Bolívar; many parts of Bolívar are extremely remote with no mines and low population densities whilst others are hotspots of mining activity (Figure 3.2).

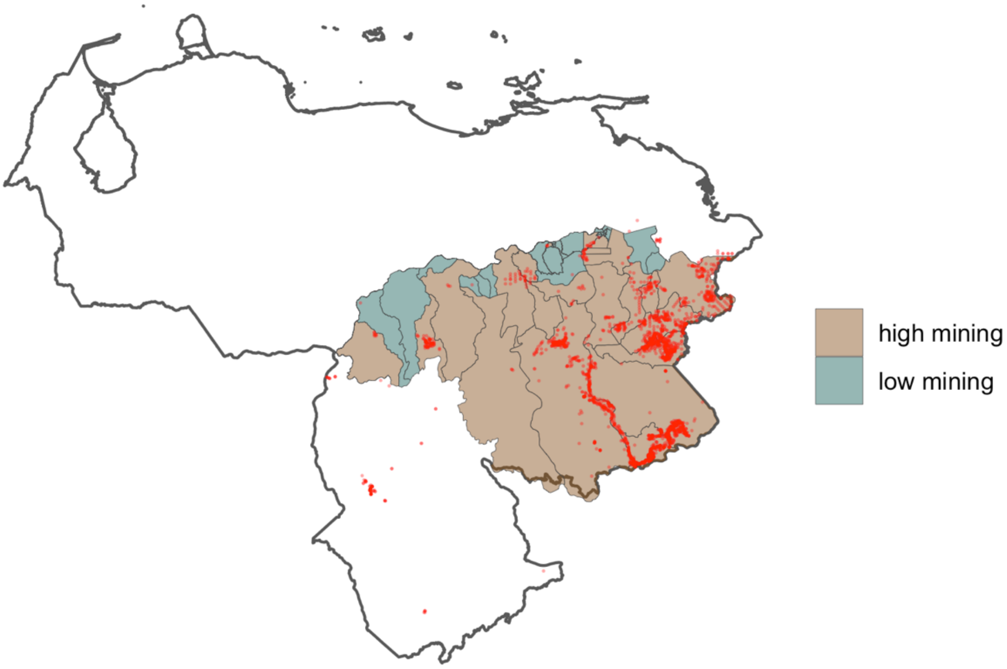

Figure 3.2. Mining activity in Venezuela. Location of mines (red) in Venezuela (n = 2,561) of which the majority are in Bolívar state (n = 2, 460) (inset map). Parishes in Bolívar are classified as having high (brown, n = 22) and low (green, n = 24) levels of mining activity.

To account for healthcare accessibility in Bolívar, the travel time to health centres for each parish was calculated using the global friction surface generated by the Malaria Atlas Project (Hay and Snow, 2006) and georeferenced locations of health sites in Bolívar sourced from the Humanitarian Data Exchange. The friction surface captures land-based travel speed in 2015, based on transportation networks such as roads and railways, as well as rivers and topographic conditions (Weiss *et al.*, 2018). A major advantage of this approach is that it not only captures distance but also cost of and willingness to travel, making it a more useful socioeconomic indicator than simply distance to a health facility. For each parish in Bolívar, the mean travel time (in hours) to the nearest health site was calculated based on the land speeds from the friction surface (Figure 3.3). A summary of all data used is provided in Table S3.1.

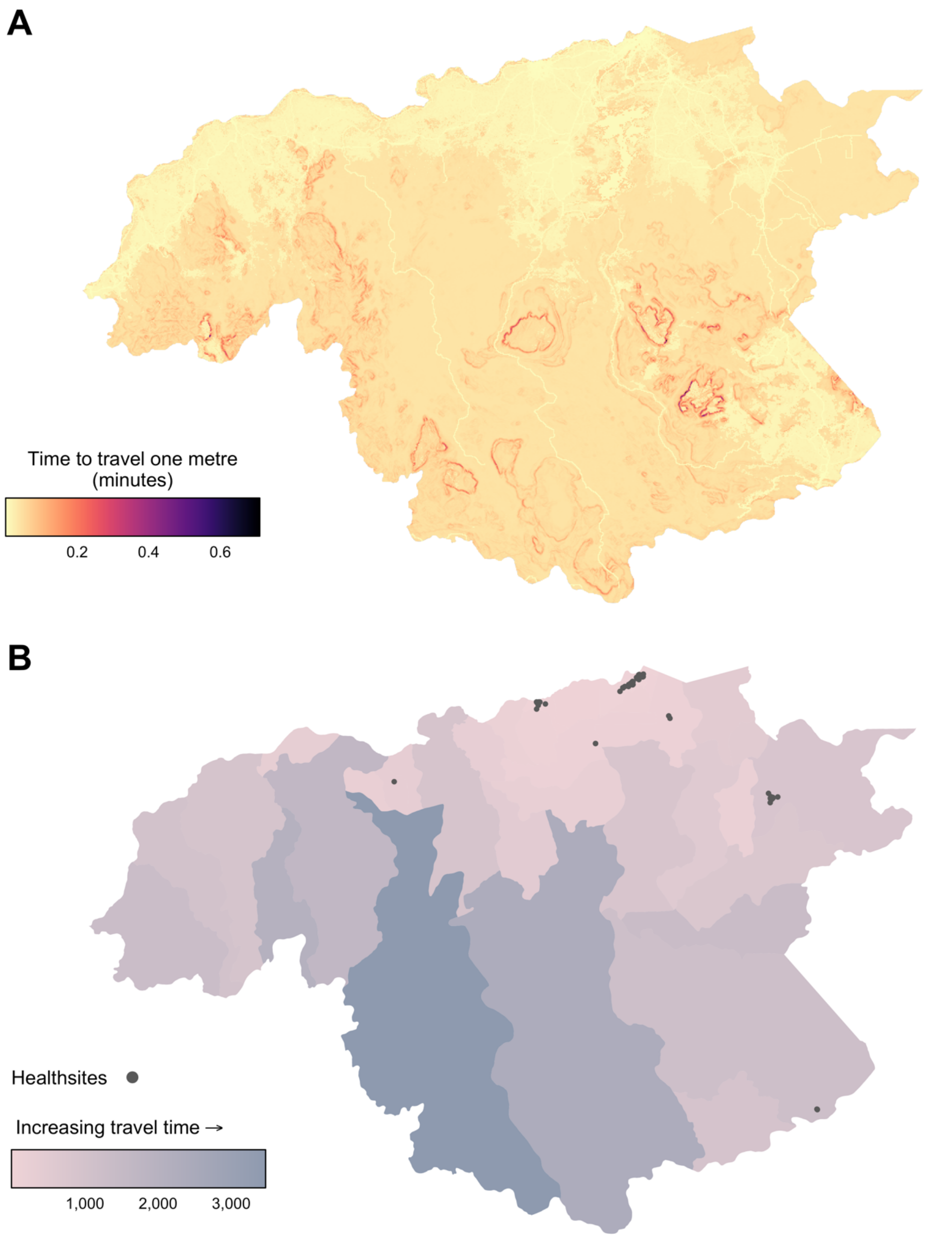

Figure 3.3. Healthcare accessibility in Bolívar state. A) Friction surface of land-based travel speed (minutes required to travel one metre) sourced from the Malaria Atlas Project, used to calculate average travel time to a health facility in Bolívar. Data are for a nominal year 2015. B) Locations of health sites in Bolívar (grey dots) and calculated average travel time (in hours) to the nearest health site for each parish in Bolívar.

3.2.3. Detecting land-use changes in Bolívar using remotely sensed land cover data

In order to investigate land-use changes, specifically forest loss and urbanisation, in Bolívar between 1996-2016 annual land cover maps of 300 m spatial resolution were obtained from the European Space Agency (ESA) Climate Change Initiative (CCI) (https://www.esa-landcover-cci.org/). Annual land cover changes that occurred between 1996-2016 were identified for each parish in Bolívar by first reclassifying the land cover maps. The CCI land cover classes were aggregated into broader categories of interest that included urban areas and forested areas (Table S3.2). To calculate a measure of forest loss, the number of grid cells per parish, that were classed as forest cover for one year and for following years were no longer classed as forest (i.e. a decrease in forest cover), were calculated. These values were summed across each parish in Bolívar to give an annual measure of cumulative forest loss between 1996-2016 (Figure S3.2A). As this measure accounts for annual cumulative changes in forest cover per grid cell, it may also capture areas where forest cover had increased, for example where a grid cell had changed from being classified as non-forest in one year to forest in the following year. The same process was repeated for urban areas to obtain a yearly measure of urbanisation for each parish 1996-2016 (Figure S3.2B). The relationship between deforestation and urbanisation, with mining activity is shown in Figure S3.3, showing some parishes in Bolívar that experience both high levels of mining and deforestation, whilst others are hotspots of mining activity with little deforestation.

3.2.4. Spatiotemporal modelling of *P. falciparum* and *P. vivax* malaria incidence

To explicitly examine how mining activity influences malaria risk, as well as account for the interacting effects of land-use change and climate variation on malaria, spatiotemporal Bayesian hierarchical mixed effects models were developed. Monthly incidence of *P. falciparum* and *P. vivax* malaria was modelled between 1996-2016 in Bolívar. Separate models were constructed for each malaria parasite in order to account for differences between parasites, which include their extrinsic incubation period (EIP), the ability to cause relapsing infections, the effectiveness of vector control and sensitivity to local climate conditions (White, 2011; Chapter 2). A zero-inflated negative binomial model was used to allow for excess zeros present in parishes of Bolívar with low malaria incidence, which are not explained by a standard negative binomial distribution. The mean, μ_{st} number of monthly ($t = 1,\ldots,252$) malaria cases for 21 years (1996-2016) in each parish ($s = 1,\ldots, 46$) in Bolívar were modelled as:

$$\log(\mu_{st}) = \log(P_{st}) + \log(\rho_{st})$$

The monthly annual parasite incidence, API $\log(\rho_{st})$, which is the number of malaria cases per 1,000 individuals, was estimated for *P. falciparum* and *P. vivax* malaria for each parish in Bolívar 1996-2016 using a combination of land use (mining sites, deforestation, urbanisation), climate (mean temperature and total precipitation) and socioeconomic covariates (healthcare accessibility), and spatial and temporal random effects. All covariates in the models were scaled by subtracting the covariate mean from each value and dividing by the covariate standard deviation. Population estimates 1996-2016 for each parish were included as a model offset, $\log(P_{st})$, and to allow for modelling the API $\log(\rho_{st})$, values were transformed by first dividing by 12, then by 1,000.

Spatiotemporal random effects were included in the model framework to account for unobserved confounding factors and capture unknown variability in the models. Extra variability could result from data limitations in the model framework, such as vector control and population movements. For each month in the model m_t, a first-order random walk latent model was introduced, which allowed for malaria incidence in one month to depend on incidence in the previous month to capture any seasonality in malaria incidence in Bolívar. Exchangeable random effects were specified for each year y_t, 1996-2016 in order to allow for additional sources of variability that could not be captured by the model covariates (Lowe *et al.*, 2016).

To allow for spatial correlation in malaria incidence across parishes in Bolívar, conditional intrinsic Gaussian autoregressive (CAR) model priors were assigned to the spatial random effects. Independent diffuse Gaussian exchange priors were also specified for each parish in order to account for any additional uncorrelated variation in malaria incidence across parishes in Bolívar that could not be measured (Besag *et al.*, 1991; Lowe *et al.*, 2016). Models were implemented using Integrated Nested Laplace Approximation (INLA), which in contrast to Markov Chain Monte Carlo methods uses numerical approximations of model parameters and is computationally more efficient and a faster alternative for spatiotemporal disease modelling (Rue *et al.,* 2009).

3.2.5. Model implementation

Spatiotemporal models of *P. falciparum* and *P. vivax* malaria were formulated that included the model covariates (El Niño, mining included as a continuous variable (number of mines per parish), deforestation, urbanisation and healthcare accessibility and nonlinear temperature and rainfall). I investigated how land-use changes modify the effect of local climate conditions on malaria incidence in Bolívar by including an interaction term between level of mining activity, included as a categorical variable (low vs. high mining) and each climate variable (temperature and precipitation, specified as a non-linear term (Table 3.1). Non-linear climate terms were specified as high temperatures above 30°C can limit mosquito and parasite survival and development, and large amounts of rainfall can flush out mosquito larval habitats, leading to a decrease in malaria transmission (Mordecai *et al.*, 2013; Shapiro *et al.*, 2017; Wolfarth-Couto *et al.*, 2019). High levels of mining activity were classified as areas in Bolívar with >2 mines (the median for the dataset) and low levels as ≤2 mines (Figure 3.2).

To assess the relative influence of mining activity on the re-emergence of malaria transmission in Bolívar, a comparison of the model spatial random effects between a model that accounted for mining activity across Bolívar, and a model that did not explicitly account for mining activity was performed. If all the spatial variation in malaria incidence in Bolívar was explained by the model covariates, such as deforestation and mining, then I would see no spatial random variation in malaria incidence, corresponding to a marginal effect of zero. Model fit was assessed using Bayesian methods of model comparison, the deviance information criterion (DIC) (Spiegelhalter *et al.*, 2002) and Watanabe-Akaike information criterion (WAIC) (Watanabe, 2010). These methods trade off model adequacy against model complexity, with lower DIC and WAIC values indicating the more parsimonious models.

3.3. Results

3.3.1. Malaria re-emergence in southern Venezuela

Malaria transmission in Bolívar state, southern Venezuela is highly focal (Figure 3.2A). The majority of malaria incidence is concentrated in the north-east of the region, in Sifontes municipality (Figure 3.4B). Between 1996-2016 a total of 455,461 *P. vivax* and 148,169 *P. falciparum* malaria cases were recorded in Bolívar state, with corresponding increases in cases between 1990-2016 of 2,986% and 1,609%. The unprecedented malaria increase in Bolívar was driven mainly by transmission patterns in Sifontes municipality (San Isidro, Dalla Costa and Tumeremo parishes), a known transmission hotspot (Figure 3.4C). Incidence in Sifontes has been rising since 2005, where 56% and 63% of total *P. vivax* and *P. falciparum* cases were recorded between 1996-2016. The highest annual parasite incidence (API) for *P. vivax* malaria of 3,198 cases per 1,000 was recorded in San Isidro parish in 2016 (Figure 3.4B). 1,074 cases per 1,000 of *P. falciparum* malaria was also recorded in the same year. Malaria re-emergence in Bolívar is heterogeneous – for some municipalities in Bolívar, such as in Sucre and Cedeño, incidence has remained high since the early 2000s, whilst others have experienced a sharp increase in malaria incidence more recently in 2013, such as Raúl Leoni (Figure 3.4C).

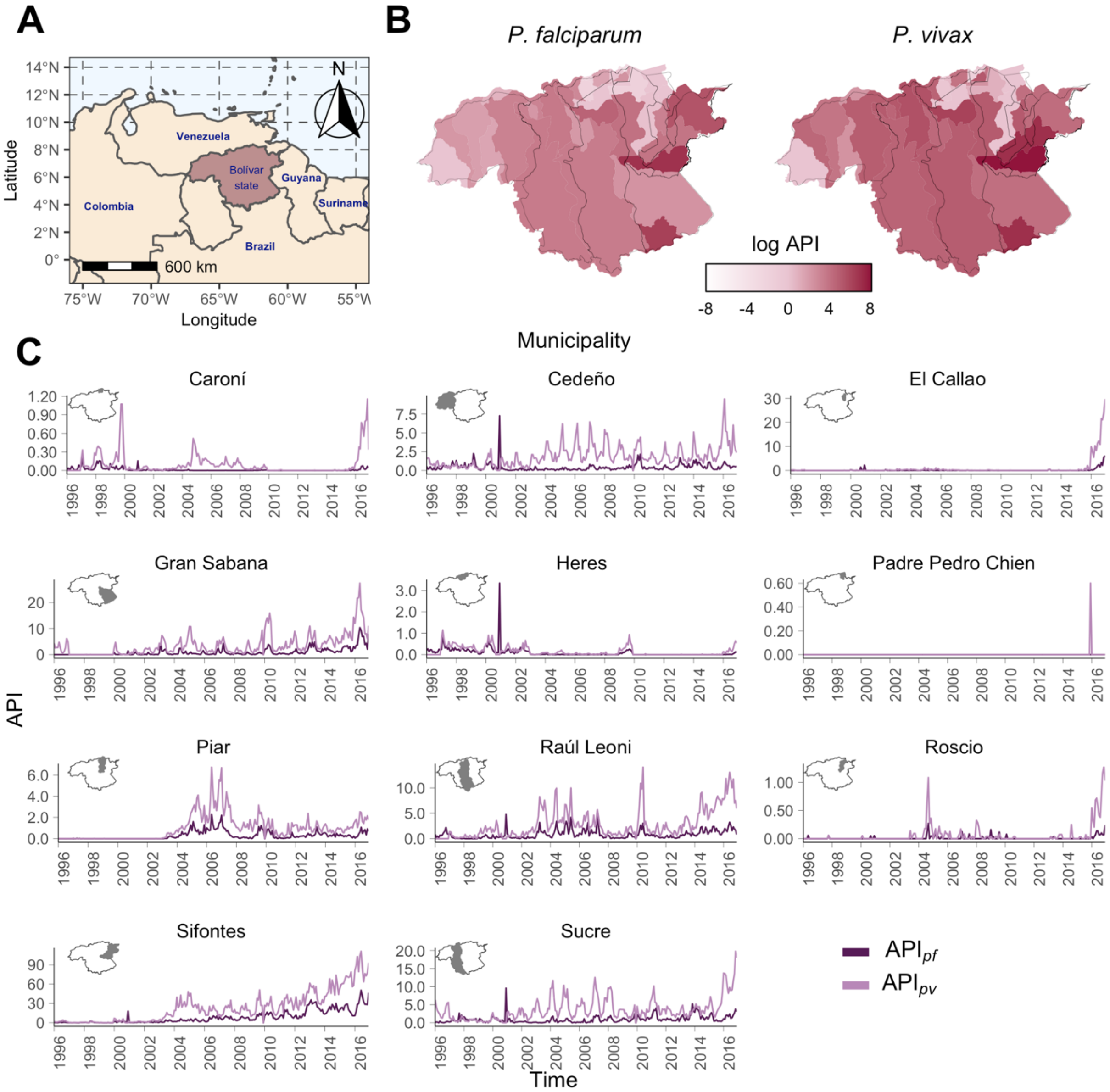

Figure 3.4. Geographic context and spatiotemporal trends of malaria incidence in Bolívar 1996-2016. A) Location of Bolívar state (brown) in southern Venezuela. B) Annual parasite incidence per 1,000 (API), log transformed, of *P. falciparum* (left) and *P. vivax* (right) malaria across Bolívar state, in 2016. Black lines show municipality boundaries. C) Annual parasite incidence, per 1,000 of *P. falciparum* (dark purple) and *P. vivax* (light purple) malaria in the 11 municipalities of Bolívar state between 1996-2016 (black lines). Inset maps show locations of each municipality in Bolívar (grey shading).

3.3.2. Environmental drivers of malaria re-emergence

Using estimates of forest cover loss between 1996-2016 identified from remotely sensed land cover maps, I found that areas in Bolívar with higher malaria incidence experienced greater forest loss than areas with much lower incidence (Figure S3.2). For instance, 46% more forest loss was detected in San Isidro parish (153 km^2 forest loss and API of 3,198 *P. vivax* cases per 1,000 in 2016) compared to Pijiguaos parish, which reported no malaria cases in 2016 and lower forest loss of 83 km^2. I also found extensive forest loss across Bolívar, with most deforestation taking place between 1997-2004 (Figure S3.2), during which peaks in malaria incidence were observed in Caroní, Cedeño and Heres municipalities (Figure 3.4C).

Deforestation, measured as cumulative forest loss between 1996-2016, was associated with increases in *P. vivax* malaria (effect size of 1.3 cases per 1,000, 95% CI 1.2 – 1.4) but not *P. falciparum* malaria (Figure 3.5A). Positive anomalies of the Niño 3.4 index in Bolívar, which bring warmer temperatures to the area and drought conditions to central and eastern Bolívar (Figure S3.4) were associated with slight increases in both *P. falciparum* (1.1 cases per 1,000, 95% CI 1.0– 1.2) and *P. vivax* (1.1 cases per 1,000, 95% CI 1.0 – 1.2) malaria (Figure 3.5A). Although there was a general trend towards decreases in malaria incidence with urban development, the credible intervals for both estimates of *P. falciparum* and *P. vivax* contained zero. I found that areas in Bolívar with limited access to healthcare, measured as the travel time to a nearest health facility (Figure 3.3) were associated with increased incidence of *P. vivax* (1.9 cases per 1,000, 95% CI 1.1– 3.4) but not *P. falciparum* malaria (Figure 3.5A).

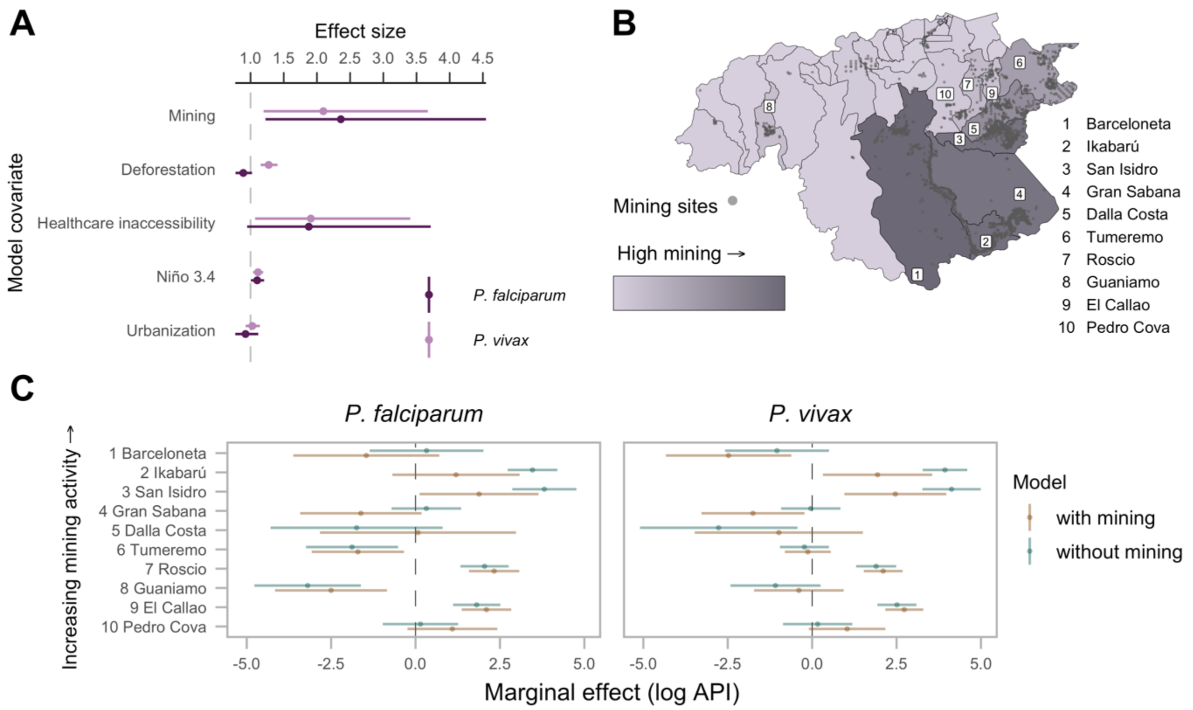

Figure 3.5. Environmental and socioeconomic drivers of malaria in Bolívar. A) Effect size and 95% credible intervals for environmental and socioeconomic covariates in spatiotemporal models of *P. falciparum* (purple bars) and *P. vivax* (pink bars) malaria incidence. The model included an interaction term between high and low levels of mining and nonlinear functions of temperature and rainfall. The model also included random effects, to account for seasonality, interannual variability and spatial dependency structures. B) Locations of mining sites (grey dots) in Bolívar identified through remote sensing and total number of mining sites per parish. Dark purple-grey colours show parishes with a high number of mining sites whilst light purple-grey colours represent areas with few or no mining sites. Labels are shown for the ten parishes with the highest mining activity. C) Variation in malaria incidence explained by mining activity. Marginal effect (mean and 95% credible intervals of the spatial random effect) of log annual parasite incidence (API), of spatiotemporal models for *P. falciparum* (left panel) and *P. vivax* (right panel) malaria that exclude (green) and include (brown) mining activity across Bolívar as a covariate. A reduction in mean estimates towards zero indicates where mining activity explains the spatial variation in malaria incidence. Estimates are shown for the ten parishes in Bolívar with the highest number of mines. The model also included linear effects of mining, deforestation, urbanisation, El Niño, healthcare accessibility, an interaction term between high and low levels of mining and nonlinear functions of temperature and rainfall, as well as random effects, to account for seasonality, interannual variability and spatial dependency structures.

DIC and WAIC values are shown in Table 3.1, for models where each covariate is added iteratively, starting with a baseline spatial seasonal model. Model adequacy was increased, observed through a reduction in DIC and WAIC values, in particular when mining was accounted for (Table 3.1). Other covariates, including temperature and healthcare accessibility increased DIC and WAIC, suggesting that although these covariates were predictors of malaria in Bolívar (Figure 3.5), did not contribute to a parsimonious model.

Table 3.1. Model adequacy results for spatiotemporal models of malaria incidence in Bolívar. Adequacy results, deviance information criterion (DIC) and Watanabe-Akaike Information Criterion (WAIC) for models of *P. falciparum* and *P. vivax* malaria. Covariates were added iteratively, including unstructured yearly effects (y_t) and starting with a baseline model that included structured (ν_s) and unstructured (υ_s) spatial random effects, and a seasonal term (m_t). Temperature $f(x_{1st})$ and precipitation $f(x_{2st})$ included as non-linear terms, El Niño x_{3t}, deforestation x_{4st}, mining, urbanisation x_{6st} and healthcare x_{7s} were then added. Mining was included as both a continuous variable x_{5s}, and as a categorical variable in an interaction term with temperature $f(x_{1st}x_{5is})$ and precipitation $f(x_{2st}x_{5is})$.

Model	**Parasite**	**DIC**	**WAIC**
Baseline spatial seasonal	*P. falciparum*	41355.13	41386.08
$\log(\rho_{st}) = \upsilon_s + \nu_s + m_t$	*P. vivax*	64963.70	64957.98
Unstructured yearly random effects	*P. falciparum*	40875.26	40909.94
$\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t$	*P. vivax*	61827.40	61878.38
Temperature effects (non-linear)	*P. falciparum*	41037.14	41082.26
$\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t + f(x_{1st})$	*P. vivax*	61653.11	61687.68
Precipitation effects (non-linear)	*P. falciparum*	40996.61	41036.45
$\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t + f(x_{1st}) + f(x_{2st})$	*P. vivax*	61640.37	61677.61
El Niño effects	*P. falciparum*	41346.92	41407.98
$\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t + f(x_{1st}) + f(x_{2st}) + x_{3t}$	*P. vivax*	61731.12	61749.56
Deforestation effects	*P. falciparum*	40964.94	41003.05
$\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t + f(x_{1st}) + f(x_{2st}) + x_{3t} + x_{4st}$	*P. vivax*	64630.22	64632.58
Mining effects	*P. falciparum*	40681.46	40728.46
$\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t + f(x_{1st}x_{5is}) +$ $f(x_{2st}x_{5is}) + x_{3t} + x_{4st} + x_{5s}$	*P. vivax*	81853.44	82742.90
Urbanisation effects	*P. falciparum*	40686.93	40729.93
$\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t +$ $f(x_{1st}x_{5is}) + f(x_{2st}x_{5is}) + x_{3t} + x_{4st} + x_{5s} + x_{6st}$	*P. vivax*	61561.05	61621.21
Healthcare effects	*P. falciparum*	40704.95	40741.82
$\log(\rho_{st}) = \upsilon_s + \nu_s + m_t + y_t +$ $f(x_{1st}x_{5is}) + f(x_{2st}x_{5is}) + x_{3t} + x_{4st} + x_{5s} + x_{6st} + x_{7s}$	*P. vivax*	61601.23	61653.46

3.3.3. Importance of mining activity in explaining malaria variation

2,460 mines were identified in Bolívar, representing 96% of mines identified in the whole of Venezuela (Figure 3.2). Parishes in Bolívar with mining activity recorded an average 4,984 cases of *P. falciparum* and 15,081 cases of *P. vivax* malaria between 1996-2016. Parishes with no mines recorded fewer malaria cases, an average of 716 *P. falciparum* cases and 2,541 *P. vivax* cases. In the model, I identified a strong positive association between mining activity and both *P. falciparum* and *P. vivax* malaria (Figure 3.5A). The effect size for mining was 2.4 cases per 1,000 (95% CI 1.2 – 4.5) for *P. falciparum* and 2.1 (95% CI 1.2 – 3.7) for *P. vivax* malaria.

I determined the relative importance of mining activity in sustaining hotspots of malaria transmission in Bolívar by comparing the random effects of a model where I explicitly accounted for mining activity, to a model where I did not (Figure 3.5C; Figure S3.5). For visualization purposes, I looked at the difference in the marginal effect of these models in the ten parishes in Bolívar with the highest mining activity. These parishes saw a reduction in the value of the marginal effect (log API) towards zero when mining activity was explicitly accounted for, indicating that mining accounted for a large proportion of unexplained variation (Figure 3.5C). In San Isidro parish, northeast Bolívar, which accounted for 40% of all malaria cases recorded between 1996-2016, mining activity explained 51% of the additional spatial variation in *P. falciparum* malaria (Figure 3.5C). Less variation (40%) in *P. vivax* malaria was explained by mining activity in San Isidro. Overall, including mining activity in the models reduced the unexplained variation of *P. falciparum* malaria in almost half (48%) of the 46 parishes in Bolívar and in 43% for *P. vivax* malaria (Figure S3.5). In a few parishes the marginal effect did not change considerably, such as in Roscio and El Callao. In other parishes, the magnitude of the marginal effect increased with the addition of mining activity, indicating that unobserved factors contribute to additional variation in malaria incidence. Model adequacy was also compared for models with and without mining (Table 3.2), where both DIC and WAIC values were lower for models including mining activity.

Table 3.2. Model adequacy results for models with and without mining. Deviance information criterion (DIC) and Watanabe-Akaike information criterion (WAIC) for models of *P. falciparum* and *P. vivax* malaria that include and exclude mining activity across Bolívar. The models included linear effects of mining, deforestation, urbanization, El Niño, healthcare accessibility, an interaction term between high and low levels of mining and nonlinear functions of temperature and rainfall, as well as random effects, to account for seasonality, interannual variability and spatial dependency structures.

Parasite	Model	DIC	WAIC
P. falciparum	With mining	40704.95	40741.82
	Without mining	40783.14	40810.69
P. vivax	With mining	61601.23	61653.46
	Without mining	61646.50	61680.51

3.3.4. Interactions between climate variation and mining activity

I explored the potential interaction between environmental degradation and climate variation by examining the impact of climate on malaria transmission in parishes of Bolívar with low and high levels of mining activity. I classified high levels of mining activity as parishes with >2 mines (the median for the dataset) and low levels as ≤2 mines, which resulted in 24 parishes classed as having 'low' and 22 having 'high' mining activity (Figure 3.2). I used non-linear climate and malaria associations in this model, which produced a better model fit (Table S3.3) than linear climate associations (Figure S3.6). Parishes in Bolívar that were classed as having high mining activity (>2 mines) recorded an average API in 2016 of 105 *P. falciparum* and 352 *P. vivax* cases, compared to four *P. falciparum* and 37 *P. vivax* cases per 1,000 in areas with lower levels of mining activity (≤2 mines; Figure 3.6A).

I assessed the impact of climate on *P. falciparum* and *P. vivax* malaria incidence in areas with high mining activity compared to areas with low mining by specifying an interaction term between level of mining and each non-linear climate variable (temperature and precipitation). I found that the impact of temperature on malaria transmission was exacerbated in mining hotspots (Figure 3.6B). In high mining areas, temperatures up to 26.5°C increased incidence of *P. falciparum*, with temperatures above 26.5°C having a negative effect on incidence. At peak temperatures of 26.5°C in high mining areas, the effect size for *P. falciparum* malaria (2.40 cases per 1,000, 95% CI 1.79 – 3.13) was twice as high as that in low mining areas at the same temperature (1.07 cases per 1,000, 95% CI 0.70 – 1.58). For *P. vivax* malaria, the peak in incidence was detected at warmer temperatures of 28.1°C, with temperatures above this point having only a slight negative effect on incidence (Figure 3.6B). At 28.1°C, the effect size for *P. vivax* malaria in high mining areas was 2.1 cases per 1,000 (95% CI 1.61 – 2.81), in contrast to a minimal effect in low mining areas.

Drier conditions with reduced amounts of rainfall in Bolívar were associated with increased malaria incidence only in areas with low levels of mining, whereas in high mining areas the impact of rainfall on malaria transmission was minimal (Figure 3.6D). In low mining areas, dry conditions (2.55 mm rainfall per day) resulted in a peak effect size of 2.5 *P. falciparum* cases per 1,000 (95% CI 1.93 – 3.07). For *P. vivax* malaria, drier conditions (1.84 mm rainfall per day) resulted in a lower peak in effect size of 1.6 cases per 1,000 (95% CI 1.34 – 1.87).

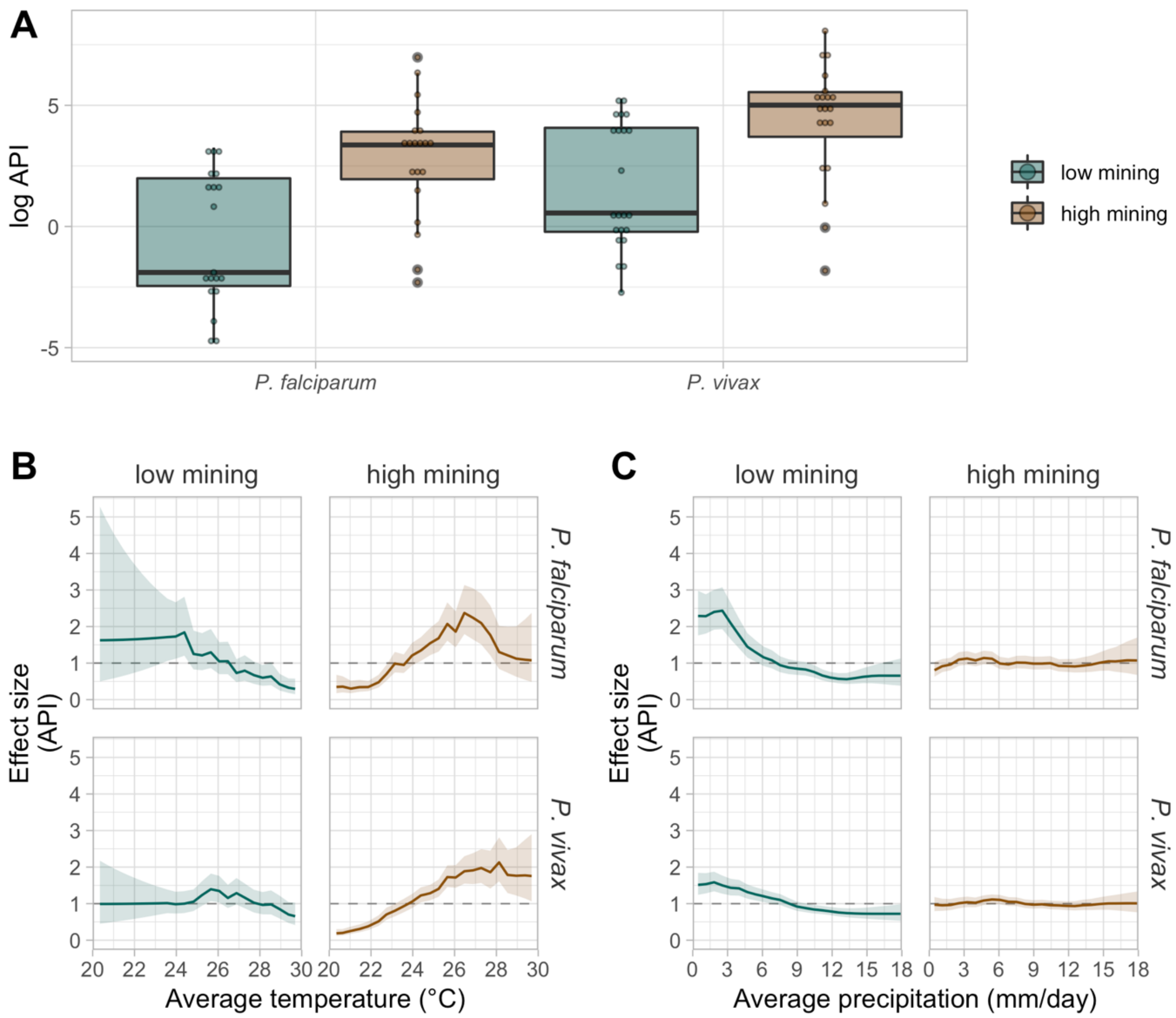

Figure 3.6. Combined impact of level of mining and climate variation on malaria risk in Bolívar. A) Distribution (median, upper and lower quartiles) of annual parasite incidence (API), log transformed in 2016 of *P. falciparum* and *P. vivax* malaria in areas of Bolívar with low (green) and high (brown) levels of mining. Effect size (API; solid line) and 95% credible intervals (shading) for the relationship between mean temperature (B) and precipitation (C) and *P. falciparum* and *P. vivax* incidence at low (green) and high (brown) levels of mining. The model included an interaction term between high and low levels of mining and nonlinear functions of temperature and rainfall. The model also included linear effects of mining, deforestation, urbanisation, El Niño, healthcare accessibility, as well as random effects, to account for seasonality, interannual variability and spatial dependency structures.

3.4. Discussion

Environmental degradation, such as that caused by gold mining activity can facilitate the spread of malaria, by altering the ecological landscape and increasing vector-human contacts (Moreno *et al.*, 2007). Similarly, malaria transmission is also highly influenced by local climatic conditions which determine mosquito and parasite development (Rogers and Randolph, 2006). However, how climate variation influences malaria transmission in areas also undergoing dramatic land-use alterations is not well understood. In this study, I explored the synergistic effects of climate variation and environmental degradation on malaria risk in a vulnerable region of southern Venezuela, demonstrating how the impact of temperature on malaria transmission is amplified in mining areas. I also provided an assessment of how mining activity influences spatial patterns of malaria, explicitly quantifying the variation explained by mining. Understanding how both climate variation and land-use change converge to affect spatiotemporal malaria risk is important to combat continued malaria surges in Venezuela (Grillet *et al.*, 2021).

Here, I found evidence that unregulated mining activity in southern Venezuela was an important determinant of the spatial variation in malaria. In malaria hotspots in Bolívar such as San Isidro parish in the northeast, mining activity accounted for 40% of the unexplained spatial variation in *P. vivax* malaria and 51% of the variation in *P. falciparum* malaria. The ecological changes associated with mining activity, primarily the creation of permanent man-made shallow water bodies promotes increased survival and abundance of *Anopheles* vectors, such as *An. darlingi* and *An. albitarsis,* the most abundant vectors in Sifontes municipality, Bolívar (Moreno *et al.*, 2015; Abou Orm *et al.*, 2017). Migrant worker populations in gold mining areas living in camps and villages with incomplete or no walls, and the highly exophagic (outdoor) biting and resting behavior of vectors generates high rates of vector-human contact (Ache *et al.*, 2002; Moreno *et al.*, 2007). The combination of ecological changes in gold mines that results in increased permanent mosquito breeding habitats and high vector-human contact rates maintains high levels of malaria transmission observed in hotspots in Bolívar. Mining activity explained more variation in *P. falciparum* (48%) in comparison to *P. vivax* malaria (43%) and the mining effect size was greater for *P. falciparum* malaria. In contrast to *P. vivax*, which is characterized by multiple relapses of infection (Beeson *et al.*, 2015) *P. falciparum* malaria is more sensitive to environmental conditions (Chapter 2) and has been shown to be the predominant circulating parasite in mining areas (Douine *et al.*, 2020). However, it is probable that high human mobility of immunologically naïve populations in mining areas contributes to the long-term persistence of *P. vivax* in mining hotspots in Bolívar.

The habitat preference of *An. darlingi* for fragmented landscapes located at the interface between forested and human-dominated environments has been implicated in explaining patterns of malaria transmission in frontier settlements in the Brazilian Amazon (de Castro *et al.*, 2006; Barros and Honório, 2015). Greater frequency of forest fringe habitat resulting from deforestation, which *An. darlingi* has rapidly adapted to, is associated with increased levels of malaria transmission due to the intensified human-vector contact rates that these environments allow (Barros and Honório, 2015; Bourke *et al.*, 2018; Burkett-Cadena and Vittor, 2018; Sallum *et al.*, 2019). Higher abundances of both *An. darlingi* and *An. albitarsis* have been found in open or deforested areas in comparison to more intact forest environments (Laporta *et al.*, 2011, 2021), which can lead to increased vector biting rates in human-dominated landscapes (de Castro *et al.*, 2006). In addition to increased rates of human exposure, deforested areas are associated with increased secondary growth, abundant sunlight and water pools that provide favourable habitat for malaria vectors such as *An. darlingi* and *An. albitarsis* (Vittor *et al.*, 2006; Vittor *et al.*, 2009). Here, I found higher *P. vivax* but not *P. falciparum* malaria incidence, in deforested areas of Bolívar. This result contrasts with previous findings in Chapter 2, where I demonstrated that *P. falciparum* is more sensitive to environmental conditions compared to *P. vivax* malaria. A likely explanation for the positive association between deforestation and *P. vivax* in this study is the predominance of *P. vivax* in the region. The presence of multiple relapsing infections characteristic of *P. vivax* malaria makes a stronger association with deforestation more likely to be detected amongst other unobserved factors. Nonetheless, these results provide important evidence of the differential effect of deforestation on the two circulating malaria parasites in the region. Future work could explore whether other metrics of forest loss, including forest patch size, which has been shown to be a good predictor of malaria incidence in the Brazilian Amazon (Chaves *et al.*, 2018), could account for the effect of forest loss on malaria in Bolívar. Although not explored here, it is also important to consider the interaction between deforestation and mining in Bolívar. It is expected that a proportion of the forest loss accounted for in this study is due to mining activity, although this is likely to be on a local scale. Other drivers of deforestation, such as urban development are also likely to be important in this context.

Multiple environmental factors, including climate variation and environmental degradation, interact in complex socioecological landscapes to determine overall disease risk. Here, I explored how environmental degradation modifies the impact of climate variation on malaria transmission. I found evidence of a synergistic impact of climate on malaria in areas with high mining activity compared to areas with low levels of mining. The positive impact of temperature on malaria transmission was greater in mining areas of Bolívar, compared to areas with minimal mining. In high mining areas, the effect size for both *P. falciparum* and *P. vivax* malaria was twice as high as the effect size in low mining areas. In areas with reduced forest cover, such as open mining pits, temperatures are typically warmer than nearby forests due to increased sunlight reaching the ground (Karlsson, 2000; Wolff *et al.*, 2021). Warmer temperatures and an increased number of stagnant pools of water together establish favourable microclimatic conditions that support *A. darlingi* proliferation and accelerate the development of the *Plasmodium* parasite, and subsequent malaria transmission (Lindblade *et al.*, 2000; Afrane *et al.*, 2005, 2006). In contrast to the stronger relationship that was found between *P. vivax* and deforestation in Bolívar, the synergistic effect of temperature in high mining areas was stronger for *P. falciparum* malaria. Previously in Chapter 2, I showed that *P. falciparum* malaria is more sensitive to climatic conditions including temperature than *P. vivax*, due to the characteristic relapsing infections attributed to *P. vivax* malaria, which supports findings here.

Low rainfall, as well as positive El Niño anomalies (warm and dry conditions) was associated with higher malaria transmission in areas of Bolívar with low levels of mining activity. *An. darlingi* is a riverine species (Rozendaal, 1992) and during transitionary periods after the rainy season, river levels are more stable and consequently mosquito populations are more established (Moreno *et al.*, 2015). Heightened malaria during dry conditions in Bolívar corresponds with other studies in gold mines and in the Amazon region, which demonstrate low *An. darlingi* survival and biting during the rainy season (Vittor *et al.*, 2006; Moreno *et al.*, 2007; de Barros *et al.*, 2011). In addition, higher parous (reproductive) rates have also been reported during the rainfall transition period (Moreno *et al.*, 2007). Here, I found a greater impact of rainfall in minimally degraded landscapes compared to areas with high levels of mining activity. The high abundance of mosquitoes found in mining areas and deforested landscapes (Moreno *et al.*, 2007; Vittor *et al.*, 2009), compared to forested areas (Minakawa *et al.*, 2002) may buffer mosquito populations and subsequent malaria transmission from the effects of rainfall.

Owing to the complex sociopolitical and environmental context of the study, there are several limitations. Firstly, whilst I could account for the presence of mining sites in Bolívar I could not account for the increased susceptibility among populations of mining communities that leads to increased risk of malaria (Recht *et al.*, 2017). In addition, I could not account for population movements amongst mining communities. Mining workers are expected to be highly mobile (Ache *et al.*, 2002; Douine *et al.*, 2020) and not all malaria cases may be recorded by national surveillance systems. I expect further underreporting of cases in the data due to the limited healthcare accessibility in mining camps, thus infections may not be reported where they originated (Douine *et al.*, 2020). There was a lack of temporal variation in the mining data, meaning that I was unable to explore the expansion of mining activities in Bolívar. As a result of the worsening economic situation in Venezuela since 2014, I expect an increased influx of workers to mining areas, as well as an expansion of the number of areas being deforested for mining activities (Grillet *et al.*, 2021). The nature of these small-scale artisanal gold mines, which are often established illegally means that capturing the sheer scale of their impact on malaria risk remains a challenge. Mining activity, particularly for gold remains a critical barrier to malaria elimination in the Latin American region.

In the face of a rapidly changing climate, it is important to understand how environmental degradation, such as mining activity can modify the effect of climatic factors on infectious diseases. Here, I have demonstrated that rapid malaria re-emergence in a vulnerable socioeconomic region was driven by patterns of environmental degradation for mining, that in turn modulate the impact of climate on malaria transmission. Mining activity in southern Venezuela was strongly related to hotspots of malaria transmission and environmental degradation from mining activity amplified the impact of warmer temperatures on malaria transmission. I have shown that under conditions of socioecological change, it is important to consider how environmental factors interact to determine overall disease risk, utilizing Earth observations to make up shortfalls in ground truth data. These findings show that areas undergoing environmental degradation, such as mining areas are at higher risk of malaria transmission and require targeted malaria control activities, such as increased bed net provisioning and surveillance in mining communities. Furthermore, health authorities also need to consider that the impact of climate variation on malaria may differ amongst areas with different levels of environmental disturbance. Areas at risk of both environmental degradation and warming temperatures will require more targeted interventions and improved surveillance.

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SECTION A – Student Details

Student	Isabel Fletcher
Principal Supervisor	Rachel Lowe
Thesis Title	Assessing the impact of global environmental change on mosquito-borne disease: A Planetary Health approach

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Parts of this research were published as a Commentary in Med, Cell Press (see Appendix V) and were re-formulated into a chapter for this thesis		
When was the work published?	09.04.2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	No

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Author list: **Fletcher IK**, Stewart-Ibarra AM, García-Díez M, Shumake-Guillemot J & Lowe R. I lead this study, collated the data, fitted the models, analysed the results and wrote the manuscript.

Student Signature: [redacted] **Date:** 09.09.2021

Supervisor Signature: [redacted] **Date:** 09.09.2021

Chapter 4 – Climate services for health: from global observations to local interventions

In Chapters 2-3, I was able to show using climate observations derived from global products that malaria incidence is sensitive to climate variation alongside elimination efforts and acts synergistically with land-use change to determine malaria risk in environmentally degraded areas. However, during the development of spatiotemporal models in Chapters 2-3, it became apparent that the choice of climate data product used to represent the hazard component could influence the strength of climate-disease relationships estimated from the models. In Chapters 2-3, climate data products were selected based on their availability and accessibility, their fine-scale spatial resolutions and temporal coverage. However, whilst global climate data products are readily available for investigating the impact of climate variation on mosquito-borne diseases (Chapters 2-3), the extent to which product choice might influence climate-disease associations is not well understood. To address this issue, I briefly review the use of different climate data products in impact models using an example of malaria and dengue in southern Ecuador to highlight the importance of data product consideration in a climate-informed impact model. I examine the extent to which choice of data product influences associations between climate and dengue and malaria risk. I compare five different global climate data products, including the two products used in Chapters 2-3, and local meteorological station data. I also discuss the considerations that need to be made when incorporating global climate products into local-level models. These include matching the spatial scales of health and climate data and understanding how large-scale data products are processed, such as through downscaling and bias correction using ground truth data. Additionally, there are challenges related to matching ground truth data i.e., from meteorological stations, to global climate observations. A greater understanding of how climate data are best incorporated into health impact models will improve the robustness of climate services that are developed for the health sector.

Abstract

Climate services, co-developed across health and climate sectors, enable risks posed by climate hazards, including mosquito-borne diseases, to be effectively managed. The rising availability of climate information has led to the integration of data into climate services for the health sector, allowing greater capacity to adapt to changing climate conditions. Despite a wealth of data there is no clear guidance on how to choose the most appropriate data product for health

impact modelling. In particular, there is a great need to provide tailored climate services that address local health needs, which will maximise service value in decision making processes. Moreover, there has been a limited exploration of how data product choice influences the downstream climate-based health decision. Here, I review the use of climate data products in applications of disease modelling and discuss the challenges related to product choice, which include a disconnect and lack of communication between sectors. In addition, there is often a mismatch between ground truth data and global climate products. Using climate-informed impact models for malaria and dengue in southern Ecuador, I demonstrate that different global climate data products have differential impacts on the modelled climate-disease associations and resulting disease risk. Specifically, the modelled impact of temperature on dengue relative risk informed by different global climate products ranged from a 40% to a 68% increase in cases with every 1°C rise in temperature. Additionally, models informed by different climate products showed diverging relationships between rainfall and malaria. Finally, I highlight the importance of considering data biases and co-developing climate services across sectors. These findings provide guidance on how global climate products should be effectively incorporated into health impact models.

4.1. Introduction and review

4.1.1. Climate services

There has been a growing acknowledgement of the impacts of climate on human health and the urgent need to manage the risk from climate variability and change (Costello *et al.*, 2009; Romanello *et al.*, 2021). As a result, the development of and demand for climate services, aimed at reducing human vulnerability to climate hazards has followed (Lowe *et al.*, 2017; Hewitt *et al.*, 2021; Manyuchi *et al.*, 2021). The World Meteorological Organization defines a climate service as a decision aide derived from climate information that assists individuals and organisations in society to make improved ex-ante decision-making (WMO, 2021). For the health sector, climate services can improve communication of climate-related risks to health professionals, identify populations that are most vulnerable, predict when and where climate-associated health risks may be greatest, and effectively design and target interventions (WHO/WMO, 2016). Climate services are crucial for strengthening the resilience of the health sector in a world with increasing frequencies of climate extremes.

For a climate service to be successful, it must be based on credible scientific information, respond to user-requirements and result in timely and relevant information that can be easily incorporated into decision-making (WHO/WMO, 2016). A climate service aimed at managing disease risk can be informed by global climate products that supplement ground truth data (Figure 4.1). Earth observations, such as remotely sensed climate data, provided as global gridded products, often have to be combined with administrative-level epidemiological data such as disease cases per district, for data analysis. Alternatively, epidemiological data can also be provided as a series of geolocated points. Effective collaboration and communication between users and service providers, including climate scientists and public health practitioners, is also a key component of the success of a climate service. Co-production of a climate service, where climate and health sectors continually work together during development can ensure successful delivery of a service that is truly useful for health decision making (Stewart-Ibarra *et al.*, 2019; Figure 4.1). Development of a climate service is a continually iterative process, requiring cross-collaboration at multiple points to achieve the final operational tool.

Climate services can be applied to public health decisions at many levels, from the local to the global scale. For example, a nationwide predictive modelling framework developed ahead of the 2014 FIFA World Cup in Brazil, used seasonal climate forecasts to produce probabilistic dengue predictions (Lowe *et al.*, 2014). Development of the framework drew on an interdisciplinary collaboration between climate scientists, epidemiologists, impact modellers, and the Ministry of Health. In contrast, at the regional level the Epidemic Prognosis Incorporating Disease and Environmental Monitoring for Integrated Assessment (EPIDEMIA) tool was developed in highland areas of Ethiopia with periodic malaria epidemics (Wimberly *et al.*, 2014). EPIDEMIA was designed to enhance integration between climate information and epidemiological surveillance, supporting early warning system development and improving outbreak detection at the regional level. Operational climate services can be developed over multiple spatial scales to better anticipate and mitigate disease risk.

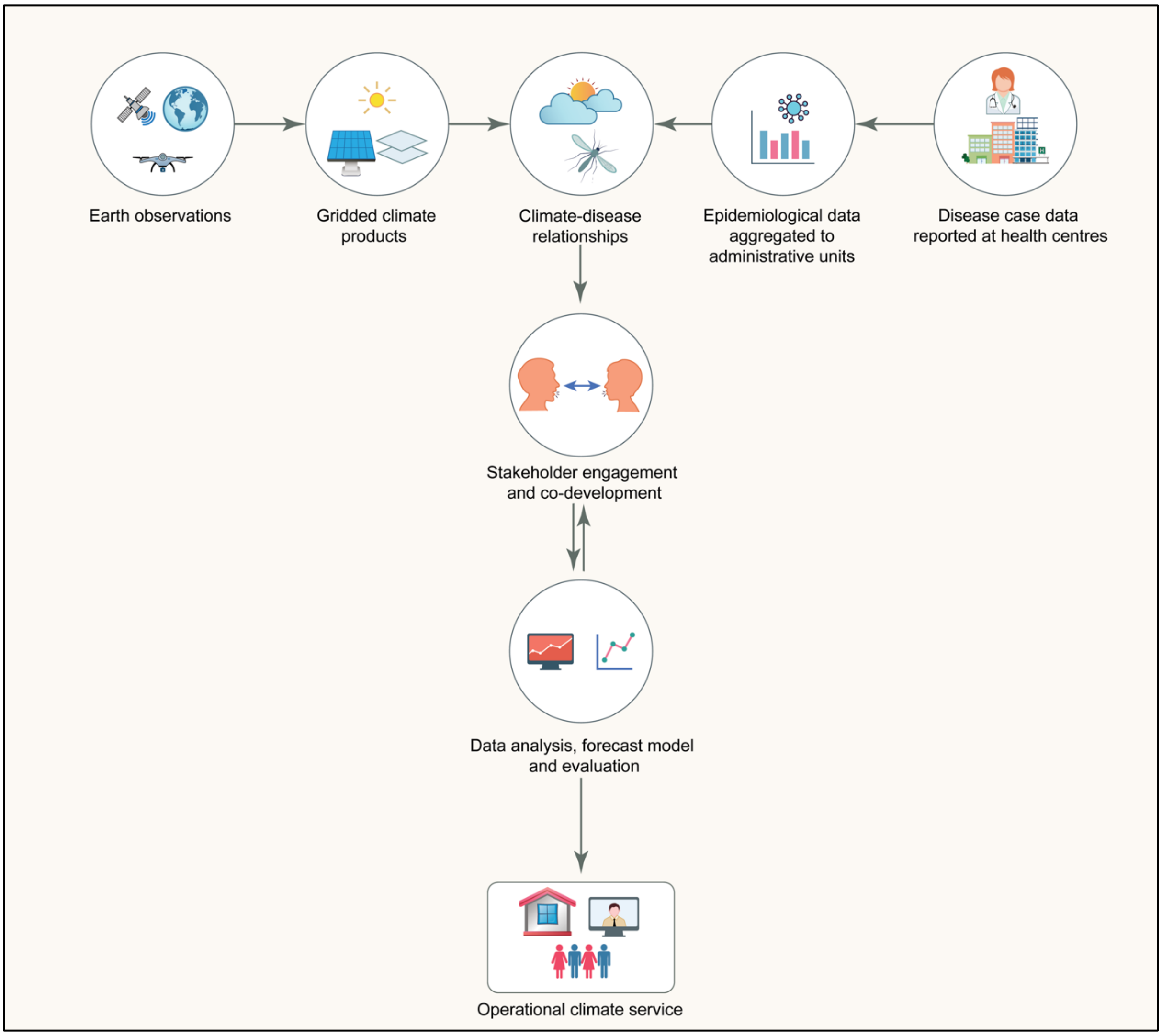

Figure 4.1. Cross-disciplinary processes involved in co-production of an operational climate service. Earth observations, such as remotely sensed climate data provided as gridded products can be combined with epidemiological data to investigate climate-disease relationships that form the basis of a climate service. The development of an operational climate service, such as a climate-sensitive disease-forecasting tool, results from effective cross-collaboration between the climate and health sectors. Source: Fletcher *et al.* (2021).

4.1.2. Earth observations

Earth observations are a critical component of climate services for health (WHO/WMO, 2016). They allow for the timely production and delivery of climate information that can be incorporated alongside epidemiological information to support public health decision-making. Earth observations are atmospheric, oceanic, or terrestrial data and information collected about our planet via *in situ* observations (Group on Earth Observations, 2021). These observations include those obtained from meteorological stations, atmospheric soundings and remote sensing technologies such as satellite imagery. Earth observations provide a valuable and accessible resource for investigating the relationships between the environment and human health, including the impact of climate variation on mosquito-borne disease risk (Beck *et al.*, 2000; Goetz *et al.*, 2000). Earth observations can provide global estimates of land surface temperatures, rainfall and land cover classifications such as forest cover, relevant to the transmission of diseases, including dengue and malaria. Earth observations are desirable for addressing limitations in accessing and using local ground data, particularly for regions with incomplete historical coverage of meteorological stations. For instance, meteorological station data can be complemented with satellite-derived climate products to obtain spatially continuous historical climate observations and fill in data gaps (Schmidt, 2005). This has allowed for the development of disease modelling frameworks used to inform dengue early warning systems (Lowe *et al.*, 2017), the seasonal variation in malaria due to local climate to be determined (Chapter 2), alongside the capacity to track the health impacts of climate change (Watts *et al.*, 2021).

Incorporating globally derived climate information into a functioning and locally relevant climate service can in practice, be challenging (WHO/WMO, 2016). Challenges include the provision of climate information in a suitable format that can be used by the health sector. Climate information is often required at a variety of spatial and temporal scales to suit multiple needs, depending on the climate service (Hewitt *et al.*, 2021). Tailoring global scale products, such as remotely sensed meteorological data, to be interoperable with data for local-level decision-making can be demanding for stakeholders (Figure 4.1). Health and epidemiological data are most often reported by health centres and hospitals to health authorities, and aggregated to administrative levels (i.e., districts and provinces). In order to be integrated into an operational climate service, the climate information needs to be collated at the appropriate spatial and temporal scale to match the epidemiological and health data (Schmidt, 2005; WHO/WMO, 2016). Coarse-resolution gridded climate observations frequently need to be aggregated, downscaled, and bias corrected to be used in a health impact model (van den Hurk *et al.*, 2018). Processing of data over multiple spatial scales to be integrated into a climate service is not a straightforward task, especially in areas with diverse topography.

Global climate products are easily accessible and provide users with a wide range of climatic variables, ranging from land surface temperatures to relative humidity and wind speed. These products have good spatial and temporal coverage, enabling global comparisons across multiple timescales. The resolution of climate products varies from coarse (50 km) to fine-scale resolutions up to 1 km (Table 4.1). For example, the ERA5-Land reanalysis dataset provided by the European Centre for Medium-Range Weather Forecasts (ECMWF) covers the period January 1950 to near real-time. The ERA5-Land dataset provides estimates of meteorological variables that include mean temperature, precipitation, and humidity at a high spatial resolution of 9 km (0.08°) (Table 4.1). In addition, these data are available on an hourly timescale, enabling their use for defining climate indicators for timely disease forecasts. Fine-scale (<0.1°/11 km) spatial climate information can be especially useful to detect microclimatic variations that may be masked in coarser resolution products. For example, topographical variation and the presence of water bodies, can be captured. In contrast to the ERA5-Land dataset, the Climatic Research Unit Time Series (CRU TS) provided by the University of East Anglia has a coarser spatial resolution of 0.5° (55 km). However, CRU TS has the advantage of providing monthly climate information that covers an extensive time period from January 1901 to December 2019, which may be useful for detecting historical and long-term climate impacts on disease risk.

Given the diversity of global climate products available and their differing spatiotemporal resolutions, the purpose of the climate service being developed needs to be considered carefully before selecting the most appropriate source of climate information. For example, a climate product with the ability to detect fine-scale variations in local climate may be useful for predicting differences in disease risk across a highly variable urban landscape. In contrast, long-term climate products with coarser resolution may be more suitable for detecting spatiotemporal associations between disease risk and climate variables over wide geographical areas with large administrative units (e.g., regions or provinces). For instance, when examining the effect of climate change on the global distribution of malaria (Caminade *et al.*, 2014). Whilst the diverse range of climate data products available enables climate services to be tailored to multiple applications, product selection needs to be considered alongside an awareness of data limitations to best match the product to its intended use.

Table 4.1. Selected global climate datasets. Global climate datasets that can be incorporated into a climate service, providing historical timeseries of climate variables, including temperature, precipitation and humidity. Datasets range in the historical timeseries they provide, their spatial and temporal resolution, as well as the format data are provided in. These datasets also vary in the methods used to produce climate information, for example by interpolating from global weather observations (CRU TS) or combining multiple climate model outputs to produce spatially and temporally continuous estimates (TerraClimate). These differing methods have important implications for their use in a climate service.

Source	Description	Temporal resolution	Spatial resolution	Historical coverage	File format	Access
CHELSA	Based on mechanistical statistical downscaling of global reanalysis data (ERA-Interim) or global circulation model output to a high resolution	Monthly	1 km/0.008°	1980-2019	GeoTiff	Karger *et al.*, 2017
CRU TS	Estimates are produced using angular-distance weighting interpolation of climate anomalies from extensive global weather station observations	Monthly	55 km/0.5°	1901-2020	ASCII, NetCDF	Harris *et al.*, 2020
ERA5-Land	A reanalysis dataset based on climate models of land surfaces	Up to hourly	9 km/0.08°	1950-present	GRIB, NetCDF	Muñoz Sabater, 2019
TerraClimate	Uses climatically aided interpolation and combines climatological normals from WorldClim with time-varying anomalies from CRU TS v.4.0 and Japanese 55-year Reanalysis (JRA55)	Monthly	4 km/0.04°	1958-2019	NetCDF	Abatzoglou *et al.*, 2018
WorldClim	Historical estimates of climate variables downscaled from CRU TS v.4.03 and using WorldClim 2.1 for bias correction	Monthly	21 km/0.2°	1960-2018	GeoTiff	Fick and Hijmans, 2017

4.1.4. Methodological differences

In addition to spatiotemporal resolution, global climate products differ in the techniques used to scale products, and the methods used to produce continuous estimates (Fick and Hijmans, 2017; Abatzoglou *et al.*, 2018; Table 4.1). As previously mentioned, epidemiological data are often provided at a scale (i.e. administrative units) that does not allow for easy integration with climate products, which are provided in global gridded formats (WHO/WMO, 2016; Harris *et al.*, 2020; Figure 4.1). Accordingly, the climate information must be reconciled, or downscaled to approximate local climate conditions on the ground. Downscaling and bias correction of climate model output produces data that is more representative of on the ground conditions. In addition, downscaling resolves global data to common spatial units, allowing for use in health impact models at the local, rather than the regional or global level (Ehret *et al.*, 2012; Navarro-Racines *et al.*, 2020). Common downscaling techniques include dynamical and statistical downscaling, which are frequently applied to climate models, such as global circulation models (GCM). Whilst dynamical downscaling can capture fine-scale topographical features, it is computationally expensive and requires a highly detailed physical understanding of the climate system and consequently is impractical for regional studies (Glotter *et al.*, 2014). In contrast, statistical downscaling is computationally less expensive and more workable. It relies on statistical relationships between local climate variables and global-scale predictors, applying these relationships to future GCM outputs (Gutmann *et al.*, 2012; Gebrechorkos *et al.*, 2019). For example, the very high resolution (~1 km) CHELSA global climate data observations are obtained by statistically downscaling the output of global reanalysis data or GCM output. This is performed by using a downscaling algorithm that is applied directly to GCM data, providing a more accurate representation of temperature and precipitation in complex terrain. In addition, to account for small-scale variations in precipitation, the CHELSA dataset also uses wind effect correction to capture orographic events (Karger *et al.*, 2020). Correcting for orographic events that cause fine-scale variations in climate can enable global climate data products to be more representative of ground-truth conditions, meaning these products are more suitable for use in health impact studies that are conducted at a local scale i.e. district-level and for use in areas with large variations in topography.

Systematic deviances from local climate observations, or biases, are common in global climate products. Such biases are caused by a lack of horizontal resolution in the climate model resulting from computational constraints, simplification of physical processes, and inaccuracies in static data such as land cover (Met Office, 2018). Biases in climate information can be addressed using bias correction techniques to ensure that the climate model output produces data that best reflects local climate observations (Hempel *et al.*, 2013). Bias correction methods also include implicit downscaling. Downscaling not only corrects for biases but also downscales global climate model output from coarse to fine spatial scales. Bias correction methods, typically apply a 'change factor' derived from a global climate model to historical observations, which effectively captures local climate observations (Navarro-Racines *et al.*, 2020). Downscaling and bias correction methods differ in their robustness, accuracy and output resolution. Several bias correction methods can even influence the result of climate model simulations, such as the timing of temperature thresholds (Gohar *et al.*, 2017). Bias correction methods have a number of assumptions to be aware of. For instance, biases in climate models are often assumed to remain constant over time and downscaling may mask detailed landscape properties, mis-representing features such as topography in the resulting climate information (Ehret *et al.*, 2012). In addition, statistical downscaling assumes that relationships between local variables and global-scale predictors remains constant over time (Wilby and Wigley, 1997). An understanding of these methodological assumptions during the co-development of a climate service is vital to ensure the robustness of the resulting health decisions.

From a public health perspective, it can be challenging to appreciate the complexities of downscaling and bias correction methods. In the climate science sphere there have been attempts to formulate frameworks, such as the VALUE framework, to validate downscaling methods and their robustness in climate change studies, although this is challenging (Maraun *et al.*, 2015). Representing complex climate processes, understanding simplifications made and the resulting model limitations, is now becoming an interdisciplinary challenge for both climate and health scientists (Lowe *et al.*, 2017; Stewart-Ibarra *et al.*, 2019). Recognising and dealing with uncertainty in global climate information by developing frameworks that allow for robustness assessment, is a step forward in ensuring that climate information can more easily and skilfully be incorporated into an operational climate service.

4.2. Exploring the impact of data product choice on dengue, malaria and climate relationships in southern Ecuador

The impact of climate variation and change on mosquito-borne diseases, including malaria and dengue, is of growing concern (Rogers and Randolph, 2006). Mosquito-borne diseases are especially sensitive to climate conditions, which influence the life history of both the pathogen and the vector to determine the geographical distribution, seasonality, and interannual variation of disease transmission (Githeko *et al.*, 2000; Patz *et al.*, 2003). The availability of fine-scale climate information has led to an improved understanding of local climate impacts on mosquito-borne disease risk, for example how dengue is influenced by drought conditions (Lowe *et al.*, 2021). However, using climate information in a health impact model without due consideration and awareness of inherent data biases and downscaling methods may undermine the appropriateness and reliability of the resulting public health decisions. A significant challenge in the development of climate services is effectively identifying and conveying these methodological differences, their limitations, and the impact they may ultimately have on public health decision making. Despite the wealth of global climate products available, there is no consensus or guidance on the most appropriate data source to use in climate-sensitive disease applications. Even less is understood about the reliability of climate data sources used to inform public health decisions. Furthermore, there has been no direct comparison of climate data sources, how to select the most appropriate product that aligns with the climate service objective, and finally how the use of different products can impact climate-sensitive disease analyses. Here, I address this lack of knowledge and assess how climate product choice affects the outcome of climate-disease models by using temporal models of dengue and malaria as a case study. I also test whether the choice of grid cell influences the model estimates, to assess the extent to which representative climate conditions are captured in global-scale products. I use temporal models, adapted from previous studies (Chapter 2; Lowe *et al.*, 2017), of dengue and malaria for Machala, southern Ecuador, to directly compare climate model estimates informed by different products.

Machala is a midsized port city (population density of 760 people per km^2), located in El Oro province, southern Ecuador. The centre of the city is highly urbanised and has undergone rapid unstructured development, which has created many informal slum settlements on the urban margins. Many of these settlements do not have adequate infrastructure and services, such as piped water. The city is settled on low-lying mangroves and is prone to annual flooding during the rainy season. The city also experiences a substantial amount of human movement, due to the city's proximity to the Ecuador-Peru border, economic activities (mainly agriculture and aquaculture) and its location along the Pan-American highway.

Dengue is hyper-endemic in Machala, which is a key dengue surveillance site. Transmission occurs throughout the year and incidence rates are especially high compared to other locations in Ecuador (Stewart-Ibarra *et al.*, 2018). Historically, Machala had high rates of malaria transmission before local elimination was achieved in 2011 (Krisher *et al.*, 2016; Stewart-Ibarra *et al.*, 2018). In addition, Machala is threatened by the resurgence of malaria from neighbouring countries, the impacts of climate change and has been highlighted as one of the most high-risk coastal cities in Latin America and the Caribbean (Calil *et al.*, 2017; Tauzer *et al.*, 2019). Monthly clinical suspected cases of dengue between 2002-2014 and monthly cases of *Plasmodium vivax* malaria between 1990-2015 (Figure 4.2), were modelled using Bayesian hierarchical mixed effects models developed previously (Chapter 2; Lowe *et al.*, 2017). Here, only cases of *P. vivax* malaria, the most common circulating parasite in both Latin America and Machala were modelled (Chapter 2; Battle *et al.*, 2019).

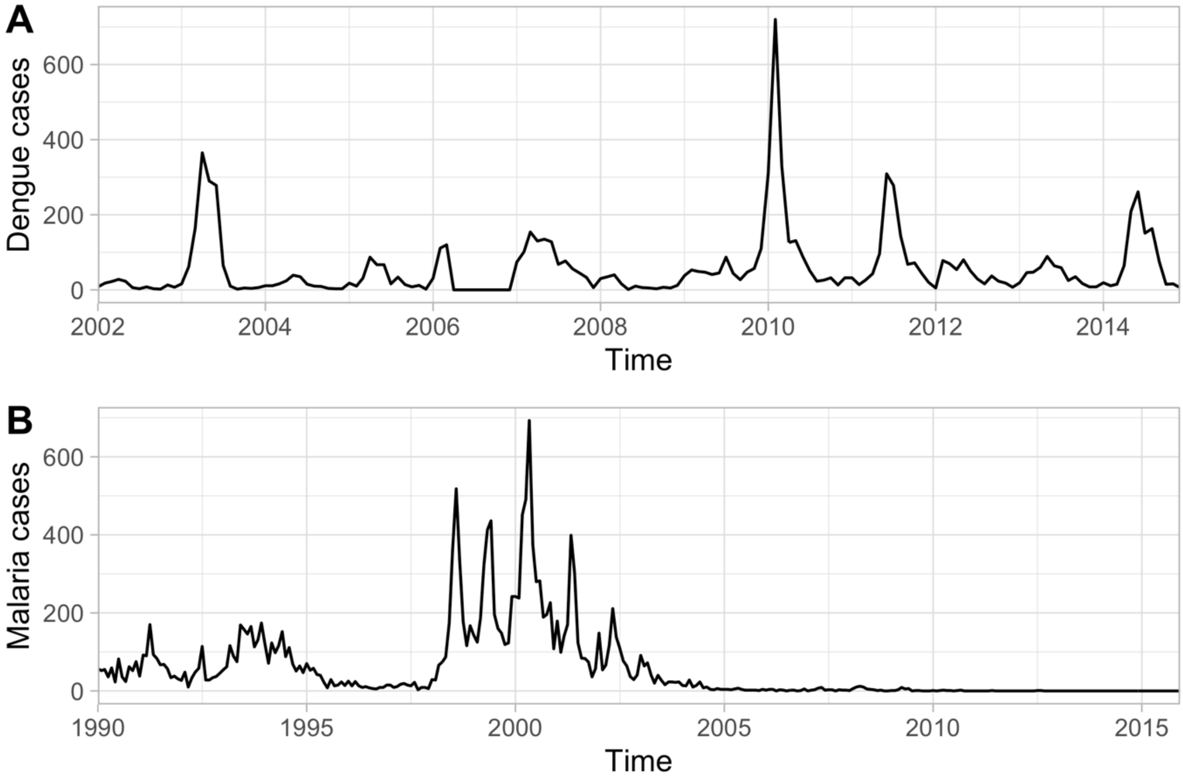

Figure 4.2. Cases of dengue and malaria in Machala, Ecuador. A) Monthly cases of dengue 2002-2014 and B) *P. vivax* malaria cases 1990-2015, in Machala, Ecuador.

Briefly, a negative binomial model for dengue (*d*) and a zero-inflated negative binomial model for malaria (*m*) were fitted to monthly cases reported for both diseases in the city of Machala.

In the model, the log of the mean number of cases of dengue (μ_{dt}) or malaria (μ_{mt}) is equal to the log population per 100,000 (P_{it}), included as an offset in the model, and the log incidence rate (ρ_{it}) for each time point t (12 years for the dengue model and 26 years for the malaria model) (i). The estimated incidence rate for dengue and malaria then includes explanatory climate variables, x_{it} (ii). Here, mean temperature x_{1t} and precipitation x_{2t} were used as climate variables in the model. Temperature and precipitation are most commonly studied in climate-disease modelling, and have been found to have strong associations with malaria and dengue, influencing both the seasonal and interannual variability of both diseases (Laneri *et al.*, 2019; Morgan *et al.*, 2021; Chapter 2).

$$\log(\mu_{it}) = \log(P_{it}) + \log(\rho_{it}) \text{ (i)}$$
$$\log(\rho_{it}) = \alpha + \beta_t + \sum \gamma_t x_{it} + \delta_t \text{ (ii)}$$

A monthly random effect (β_t) was introduced using a first-order autoregressive model to account for seasonal variation in dengue and malaria, and exchangeable non-structured random effects for each year (δ_t). These random effects allow the model to account for interannual changes in disease risk due to unobserved factors, such as interventions and population mobility (Lowe *et al.*, 2017). Posterior distributions of model parameters were estimated using Integrated Nested Laplace approximations (INLA), which provides a computationally quicker alternative for implementing models in a Bayesian statistical framework, in comparison to traditional Markov Chain Monte Carlo (MCMC) methods (Rue *et al.*, 2009). Another advantage is that INLA allows for a quicker model comparison and selection process, which proves highly useful in climate-disease models where the outcome of multiple models is examined.

Five sources of climate data were selected based on available timeseries that matched the malaria and dengue case data (Table 4.3). Data from these five sources were used to formulate malaria and dengue models, facilitating the direct comparison of model parameters informed by each climate dataset. Each dataset was selected to capture a range of spatial and temporal scales as well as bias correction and downscaling methods used to produce fine-scale climate data. Locally observed station data (mean temperature and precipitation) were obtained from the Granja Santa Ines weather station located in Machala (3°17’26” S, 79°54’5” W) to use in a baseline model for comparison with the five global climate datasets. These models, six dengue and six malaria models, were used to assess the impact of mean temperature and precipitation on malaria and dengue cases in Machala and compare estimates informed by each climate dataset.

For each of the five global climate datasets, the value for mean temperature and precipitation of the single grid cell where the Granja Santa Ines weather station is located was extracted. To capture the lagged effect of climate on dengue and malaria risk (Lowe *et al.*, 2018; Kim *et al.*, 2019) the seasonal average temperature and precipitation was calculated by taking a three-month average (0-2 months). Long-term (interannual) and seasonal trends in climate variability were visually compared across the five datasets and meteorological observations and parameter estimates for temperature and precipitation in the resulting models were also directly compared. To investigate the influence of grid cell choice of the global climate datasets the output of dengue and malaria models using different grid cells from the CRU TS data was also compared. Specifically, a model that used the corresponding grid cell for the Granja Santa Ines meteorological station, was compared with a model that used the grid cell adjacent to the meteorological station.

4.2.1. Effect of climate data product choice on modelled estimates of dengue and malaria risk

Mean temperature and precipitation observations from the five selected global sources (Table 4.1) differed when compared with observations from the local meteorological station (Figure 4.3A-B). In particular, mean temperatures from the CRU and ERA5-Land datasets were much cooler (up to 5°C lower) than those from the meteorological station. Furthermore, seasonal dips in temperature observed in the CHELSA dataset were much warmer than station observations (Figure 4.3A: Figure S4.1). The five global climate products were however able to capture peaks in rainfall picked up by the local meteorological observations, although up to 40 mm more rainfall per day was recorded by the ERA5-Land dataset (Figure 4.3B; Figure S4.1).

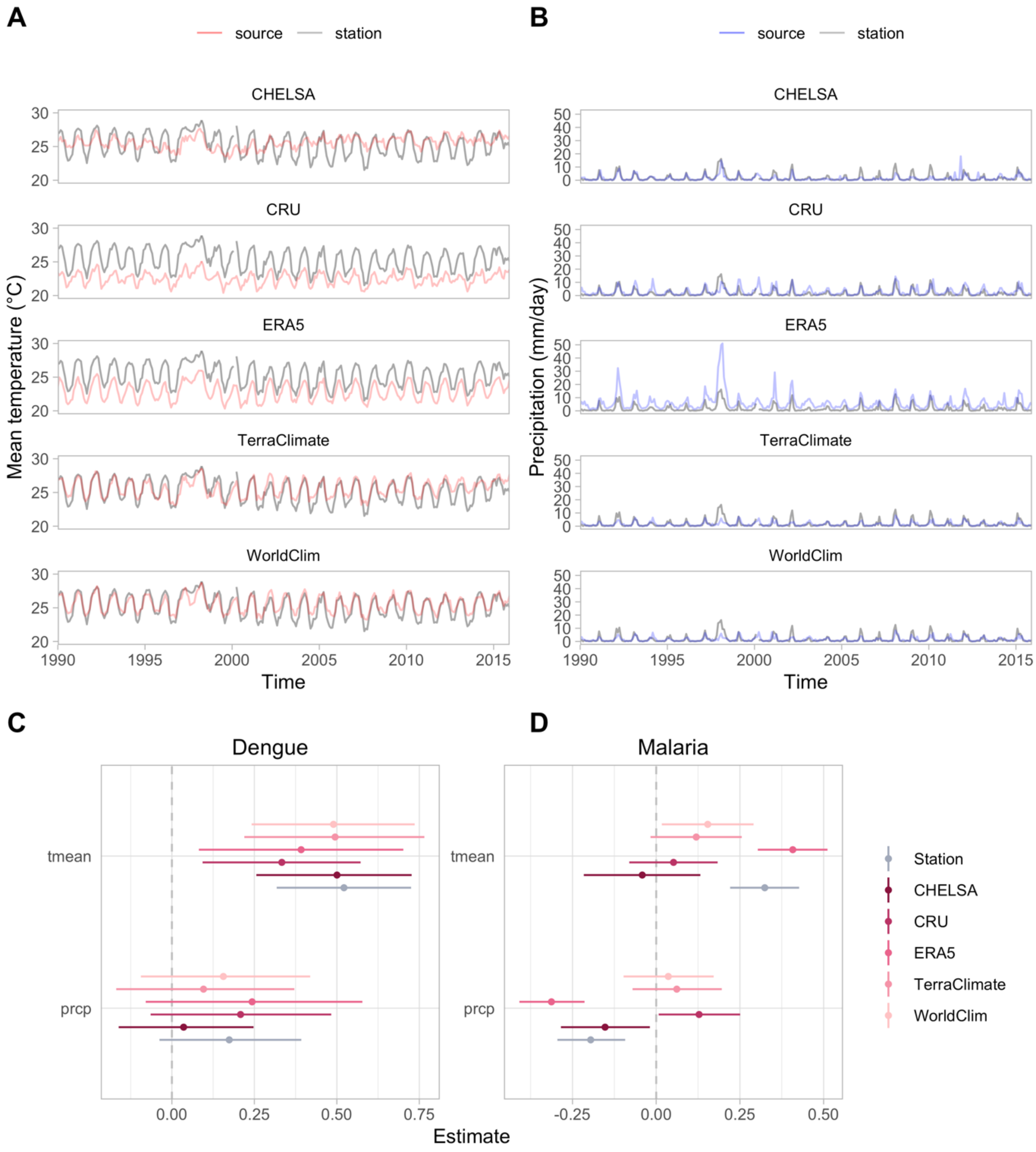

Figure 4.3. Climate observations from different global climate data datasets, and their impact on parameter estimates in climate-sensitive disease models. Monthly mean (A) temperature (°C) and (B) precipitation (mm/day) from the Granja Santa Ines meteorological station in Machala, Ecuador, and corresponding estimates from five global climate datasets: CHELSA timeseries, CRU TS, ERA5-Land, TerraClimate, and WorldClim historical timeseries. Posterior mean and 95% credible intervals of mean temperature (tmean) and precipitation (prcp) variables, in temporal models of monthly (C) dengue cases 2002–2014 and (D) malaria cases 1990–2015 in Machala. Estimates in grey are for models using climate data from the Granja Santa Ines meteorological station and estimates in shades of pink are for

models using climate data from five global climate datasets: CHELSA timeseries, CRU TS, ERA5-Land, TerraClimate, and WorldClim historical timeseries.

Comparison of model parameter estimates revealed fundamental differences in the modelled impact of climate on disease risk (Figure 4.4C-D). All six climate models demonstrated a greater risk of dengue with warmer temperatures, however the estimates from the models differed substantially. The largest temperature estimate (0.52, 95% CI 0.32-0.73; Table S4.1) was from the model using the local meteorological station observations, corresponding to a 68% increase in dengue cases with every 1°C rise in temperature. This contrasted with the lowest estimate, which was from the CRU model (0.33, 95% CI 0.09-0.57; Table S4.1), demonstrating a 40% increase in cases with every 1°C temperature increase. The temperature estimates from the WorldClim, TerraClimate and CHELSA models were all similar in magnitude to the local meteorological station model, whilst the ERA-5 Land model estimate was more in line with the lower estimate from the CRU model. In comparison to the dengue model informed by the local station data, the TerraClimate model had only a slightly larger DIC and WAIC, and even though the CRU temperature estimate was lower than that for the station model, DIC and WAIC values were only slightly larger (Table 4.2). The largest difference in DIC (7.4) from the local meteorological station model was for the WorldClim model. Based on these results, it would be recommended that either CRU or TerraClimate be the best climate products to explore dengue and climate relationships.

Table 4.2. Model adequacy results for models of dengue and malaria using climate observations from different global climate datasets. Deviance information criterion (DIC) and Watanabe-Akaike Information Criterion (WAIC) for models of dengue cases 2002-2014 and malaria cases 1990-2015 in Machala.

Model	Source	DIC	WAIC
Dengue	Station	1460.53	1462.01
	CHELSA	1465.30	1467.18
	CRU	1461.76	1464.07
	ERA5	1465.41	1466.83
	TerraClimate	1461.10	1463.77
	WorldClim	1467.93	1469.45
Malaria	Station	2072.11	2077.02
	CHELSA	2074.94	2079.83
	CRU	2088.96	2092.17
	ERA5	2051.72	2055.55
	TerraClimate	2088.53	2092.03
	WorldClim	2086.16	2089.38

In contrast to the dengue models, there was a divergence in the impact of climate on malaria between the six models (Figure 4.2D; Table S4.2). The ERA5-Land model exhibited the greatest association (0.41, 95% CI 0.30 - 0.51) between malaria and temperature, with every 1°C rise leading to a 50% increase in cases. This result was similar for the model with the local meteorological observations, although the other four models showed dissimilar results. The credible intervals for the estimates of the CHELSA, CRU and TerraClimate models contained zero. If these climate data products were to be used in a health impact model, this could lead to the conclusion that variation in temperature does not have a significant impact on malaria risk, even though temperature has been previously demonstrated to be an important factor explaining malaria seasonality and interannual variability in southern Ecuador (Chapter 2). Additionally, contrary to the dengue models the most parsimonious malaria model was not the local meteorological station model (Table 4.2). Instead, the ERA5 model had the lowest DIC and WAIC values and the CRU model having the highest. In this context, climate observations from ERA5 may be best to use to explore the effects of climate on malaria.

In all the dengue models, and in the WorldClim and TerraClimate malaria models, the credible intervals for the precipitation estimates contained zero (Figure 4.4; Tables S4.1-2). In contrast, the local meteorological station, CHELSA and ERA5-Land models showed negative associations between rainfall and malaria risk. The ERA5-Land model showed the strongest negative association (-0.31, 95% CI -0.41 to -0.21; Table S4.2), corresponding to a 37%

reduction in malaria cases with every 1 mm of rainfall. Conversely, the CRU model showed a slight positive association. These contrasting findings could be due to inherent biases in the underlying climate data and methods used to produce monthly precipitation estimates. Stagnant water bodies are required for completion of the aquatic stages of mosquito development, so increased rainfall is expected to increase rates of malaria transmission (Krefis *et al.*, 2011; Nissan *et al.*, 2021). However, large quantities of rainfall can flush out and destroy mosquito habitats and in riverine areas rainfall can decrease the stability of mosquito populations (Tompkins and Ermert, 2013; Moreno *et al.*, 2015). In turn, this can decrease malaria transmission. Whilst studies across Brazil have demonstrated increased malaria risk with rainfall (de Barros and Honorio, 2007), others have shown elevated risk during dry conditions (de Barros *et al.*, 2011; Chapter 3). Here, the non-linear relationship between rainfall and malaria could explain the diverging impact of rainfall on malaria observed in the different climate models.

4.2.2. Effect of grid cell choice on modelled estimates of dengue and malaria risk

In addition to the issue of selecting the most appropriate climate product to best capture local climate variation on the ground, selection of the most representative grid cell is likewise of great importance. In this analysis, for each model I selected the data value (temperature and precipitation) of the grid cell corresponding to the location of the Granja Santa Ines meteorological station in Machala. However, in climate-disease models it is often not known how well the corresponding grid cell captures local on the ground climate observations. In a previously developed predictive dengue model for Machala, the climate conditions of the grid cell adjacent to the reference Granja Santa Ines meteorological station were found to be more representative of the local climate than the grid cell within which the station was located, despite this grid cell mostly encompassing ocean (Lowe *et al.*, 2017). In this particular case, temperatures for the grid cell corresponding to the location of the meteorological station were consistently colder than the actual station observations. Consequently, ensemble climate forecasts for the grid cell adjacent to the meteorological station were used as a simple bias correction in a model to predict the evolution of the 2016 dengue season in Machala (Lowe *et al.*, 2017).

Here, I compared the monthly mean temperature values between 1990-2015 of the CRU grid cell corresponding to the location of the Granja Santa Ines meteorological station (Figure 4.4A-B, cell 1), with the temperature values corresponding to the adjacent grid cell (Figure 4.4A-B, cell 2). Temperatures recorded in the grid cell adjacent to the Granja Santa Ines station (cell 2) were consistently warmer than that of the corresponding grid cell (cell 1). Temperatures from the adjacent grid cell (cell 2) were more aligned with the local observations than the temperature values from the corresponding grid cell, which were not able to capture the local climate variation (cell 1: Figure 4.4A). Despite the difference in recorded climate values from each grid cell, estimates from climate models informed by each of these grid cells show minimal differences (Figure 4.4C). For dengue, climate models using different grid cell values resulted in increased dengue with temperature and no effect of rainfall. Using the grid cell corresponding to the location of the meteorological station (cell 1), which covers a topographically diverse area that includes the Andean foothills, every 1°C increase in mean temperature would result in a 40% rise in dengue cases. In contrast, using the adjacent grid cell (cell 2), which is 4°C warmer, would result in an increase of 46%. Despite such a small difference in model estimates, this translates into a noticeable effect on disease risk.

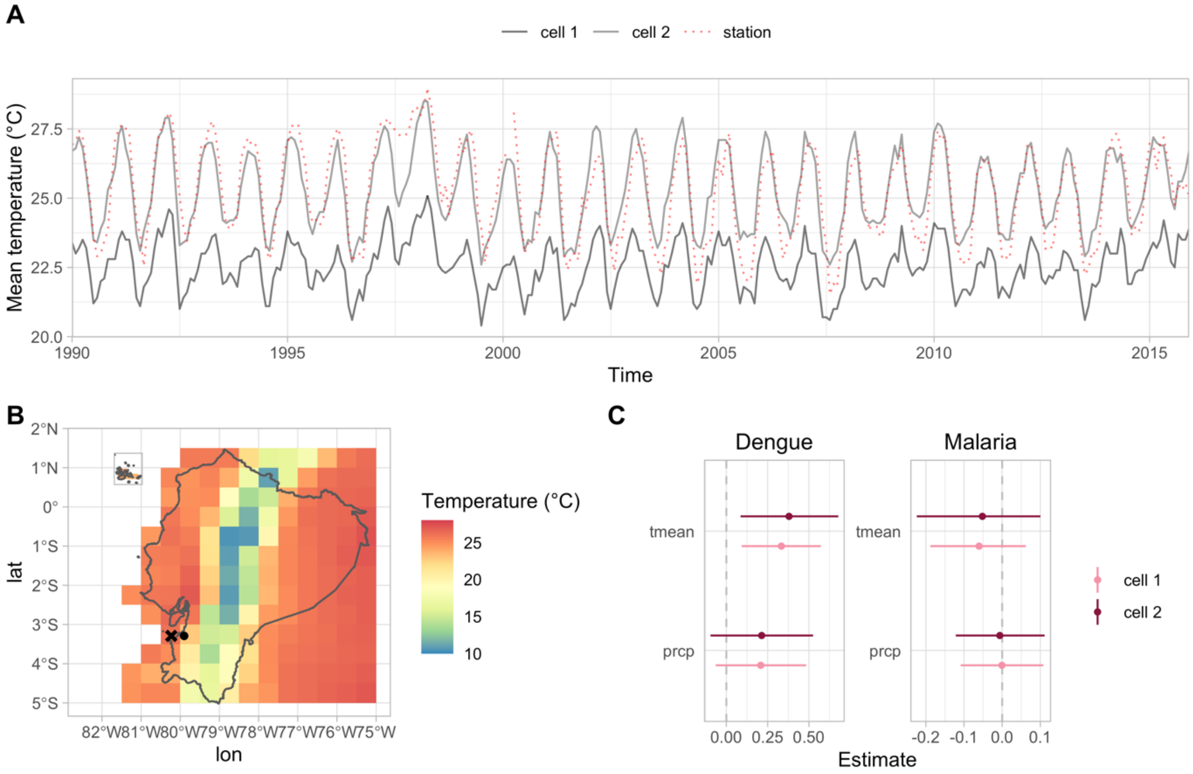

Figure 4.4. Influence of grid cell choice on climate variables and model results. A) Mean temperatures between 1990-2015 extracted from the CRU TS dataset corresponding to the grid cell matching the location of the Granja Santa Ines meteorological station, Machala (solid black line, cell 1), values for the adjacent grid cell (solid grey line, cell 2) and the observations from the meteorological

station (dotted red line). B) Location of the Granja Santa Ines meteorological station (black circle, cell 1) and adjacent grid cell (black cross, cell 2). C) Mean posterior estimates and 95% credible intervals of climate variables (mean temperature and precipitation) in models of dengue and malaria cases in Machala using CRU TS climate data for the corresponding grid cell (cell 1) and the adjacent grid cell (cell 2).

In summary, I found that modelled estimates of climate-disease associations differed depending on the source of data used to inform the model. The modelled impact of temperature on dengue relative risk informed by different global climate products ranged from a 40% to a 68% increase in cases with every 1°C rise in temperature. A differential relationship between rainfall and malaria was also detected with models informed by different climate data products. In addition, I also highlight the issue of selecting grid cells from global climate products that are most representative of local climate conditions, which also had a measurable influence on modelled disease risk. This case exemplifies a single specific problem for one location that will not be universal across other applications. In some instances, models using global climate datasets may not align with ground truth conditions in areas with incomplete meteorological station coverage. Machala is located on the coast of Ecuador, with the Andes mountains situated to the east. Orographic events mean that the climate variables from the corresponding grid cell may not reflect the actual conditions in the coastal city, where the Granja Santa Ines meteorological station is located and the majority of mosquito-borne disease transmission occurs. These findings have important implications for the health sector, as public health practitioners face decisions about how and when to respond to climate-associated health risks. For example, a misinformed conclusion about climate-malaria relationships forming the basis of an early warning system reliant on climate predictors, may give incorrect information about when and where to distribute bed nets. Consequently, a misaligned health outcome could lead to a misallocation of precious resources. I have highlighted that simple off-the-shelf usage of climate products, without thorough understanding and interrogation of methodological and scale issues can lead to misinformed and potentially damaging conclusions.

4.3. Guidance for selecting climate data products for health impact modelling

Here, I have demonstrated that climate data product choice can influence the outcome of health impact models. For example, in models of dengue in Machala, Ecuador, the modelled impact of temperature ranged from a 40-68% increase in cases with a 1°C rise in temperature. Given these findings, it is important therefore to consider more carefully the source of climate observations used and the implications of using one product over another.

Below I list a set of recommendations that researchers can use to guide their choice of global climate data product in health impact modelling and the development of a climate service. I outline the necessary steps to take during analysis to ensure that any conclusions made are well-informed.

1. **Identify multiple climate sources for analysis**

Prior to starting formal analysis for health impact modelling, at least three climate data sources that can be compared should be selected. To enable a representative comparison, a diverse set of sources that use a variety of methods to obtain spatiotemporally continuous estimates should be selected, i.e. global reanalysis datasets (e.g. ERA5-Land) and downscaled datasets (e.g. CHELSA). Where possible, local station data for the area of interest should be obtained.

2. **Consult with a climate scientist on potential sources of bias in data sources**

To understand why sources of climate observations may differ, consultation with climate scientists should occur. This can help identify sources of bias for example, methods used to produce continuous estimates, such as downscaling may contribute to bias. At this stage, consultation may help identify data products that are not suitable for the proposed analysis. For example, global products with a coarse spatial scale (~55 km) will not be suitable for fine-scale analysis of malaria and climate at the village level.

3. **Compare climate observations across selected sources**

Compare climate observations from different sources, which can be performed visually or by using summary metrics. This can help identify climate variation that data sources are able or not able to capture. For example, estimates from CRU may be consistently warmer than other sources and therefore may not be suitable for capturing temperature variation in regions where there is only a small difference in minimum and maximum temperatures.

4. **Consider grid cell choice**

When performing analyses for a single-point location i.e. a city, it is important to explore whether the climate conditions for the corresponding grid cell are adequately capturing ground-truth climate conditions. Here, it may be useful to explore whether the corresponding grid cell is the most representative or if any bias-corrections needs to be made.

5. Compare health impact models informed by different data sources

Formulate health impact models informed by multiple different data sources and compare the modelled relationship between climate and the health outcome. How does it differ and by how much? A model informed by local station data, if available, can be used as a baseline to make comparisons. The most appropriate global climate data source can then be selected based on a combination of model adequacy metrics (e.g. DIC), how close the modelled estimate is to that of a model informed by local station data and the comparison of climate observations. Final product selection should be made in collaboration with relevant stakeholders, including climate scientists.

6. Transparent results dissemination

When reporting results to decision makers the climate service development process should be as transparent as possible. For example, consider how sources of bias can be visualised or communicated to policymakers and if relevant, whether climate-sensitive health outcomes differ substantially based on the data sources used to inform the models. This will enable trust-building between sectors and ultimately result in a climate service that is most useful for decision makers.

4.4. Conclusions

Earth observations and forecasts are helping to reduce society's vulnerability to climate hazards, through the development of tailored climate products and services for the health sector. The availability of and access to global sources of climate data have allowed for gaps in local meteorological station data to be supplemented with global observations. Global climate sources can provide estimates of environmental conditions in areas lacking locally observed data, which is especially useful for developing early warning systems at the local level, or in remote areas. However, as illustrated using examples for two climate-sensitive diseases, dengue and malaria, the choice of climate data product can have considerable downstream implications for interpreting the importance of climate predictors of disease risk. It is therefore important to compare remotely derived data with ground truth data, if available. Geographical sources of local climate variation in the absence of ground truth data, must also be considered when choosing the most suitable climate data product. These considerations can be achieved through close collaboration between experts from the health and climate sectors, enabling local biases in climate information to be detected and corrected for before incorporation into health decision-making tools. Co-production of climate services is vital to ensure that a climate service is truly useful for decision-making by health practitioners. A strong partnership and interdisciplinary collaboration between the health and climate sectors that facilitates appropriate climate data selection, fosters continued sharing of information and skills, will also contribute to a highly effective climate service. In addition, the importance of interdisciplinary knowledge exchange, such as that with climate scientists, is vital to ensure that trustworthy relationships between researchers and decision makers are maintained. An open and collaborative approach to designing and building climate services with increased transparency will secure their use in decision making processes. Improved communication of methods used to produce global products with guidance for users on their appropriate use and limitations, is needed to enhance the uptake of these products and avoid misuse.

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SECTION A – Student Details

Student	Isabel Fletcher
Principal Supervisor	Rachel Lowe
Thesis Title	Assessing the impact of global environmental change on mosquito-borne disease: A Planetary Health approach

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Proceedings of the Royal Society B: Biological Sciences
Please list the paper's authors in the intended authorship order:	**Fletcher IK**, Gibb R, Lowe R & Jones K
Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I lead this study, conducted the systematic data search, collected the data, fitted the models, analysed the results and wrote the manuscript.

Student Signature: [redacted] **Date:** 25.09.2022

Supervisor Signature: [redacted] **Date:** 25.09.2022

Chapter 5 – Differing taxonomic responses of mosquito vectors to anthropogenic land-use change in Latin America and the Caribbean

Up to now, this thesis has used climate variation to inform the underlying hazard component (the mosquito vector) of the disease risk framework. Previously, I showed how climate variation jointly influences malaria risk relative to the impact of elimination efforts (Chapter 2), how the impact of climate on disease is amplified in environmentally degraded areas (Chapter 3) and when accounting for the hazard component using climate data, product choice needs to be considered in impact models (Chapter 4). However, mosquito vectors are also highly influenced by land-use change although much less is understood about the mechanisms underlying the relationship between land-use change and vector ecology. An understanding of how mosquito vectors of disease are affected by anthropogenic change is vital for informing future assessments of disease risk and to prepare effective risk-reduction strategies, such as targeted vector control. In this final chapter, I expand focus to the Latin American and Caribbean region (LAC). I assess the response of *Aedes* mosquitoes, which transmit dengue and other arboviruses including yellow fever, chikungunya and Zika, and *Anopheles* mosquitoes, which transmit malaria, to anthropogenic land-use change. By compiling a dataset of published mosquito abundance records in LAC, across multiple land-use types and using a comparative space-for-time approach, I test for differing taxonomic responses in mosquito abundance to land-use change whilst also testing for reductions in species richness in human-dominated landscapes. This final chapter draws on ecological knowledge to inform how the hazard component of the risk framework (the mosquito vector) is affected by land-use change, building on knowledge of how mosquito-borne diseases studied in Chapters 2-4 are affected by multiple components of environmental change.

Abstract

Anthropogenic land-use change such as agricultural expansion and urban development, dramatically transforms natural environments. These modifications can affect the emergence and re-emergence of mosquito-borne diseases, including dengue and malaria, by creating more favourable habitat conditions for vectors. However, there has been a limited assessment of how mosquito vectors respond to land-use changes, specifically if responses differ among species and are consistent across geographic regions. An improved understanding of vector responses to anthropogenic land use is crucial for developing optimal control strategies. Here, I compile an extensive dataset of 10,004 *Aedes* and *Anopheles* mosquito abundance records across multiple land-use types at 632 sites in Latin America and the Caribbean. Using a Bayesian mixed effects modelling framework to account for between-study differences such as sampling methodologies and mosquito developmental stages sampled, I examine how mosquito biodiversity, specifically abundance and species richness, varies across different land-use types including minimally disturbed primary vegetation, and managed and urban sites. I found strong declines in species richness of *Aedes* (-26%) and *Anopheles* (-37%) mosquitoes in urban environments, in addition to diverging species-specific abundance responses. Additionally, abundance of the arbovirus vector *Ae. aegypti* was higher in managed landscapes, as was *Ae. albopictus* abundance in primary and secondary vegetation sites with higher use intensity. Combined with increasing climate suitability for these vectors, these results demonstrate a major threat of mosquito-borne disease risk in anthropogenic environments. An important secondary malaria vector, *An. albitarsis*, increased in abundance in managed landscapes, suggesting agricultural land-use practices favouring secondary vectors pose a substantial risk of disease emergence in Latin America and the Caribbean. When the mosquito biodiversity dataset was combined with fine-scale remotely sensed deforestation data, I found a 31% increase in abundance of the dominant Amazonian malaria vector, *An. darlingi* with every 1% increase in forest loss. These results suggest that overall biodiversity loss from anthropogenic disturbance can result in the emergence of synanthropic mosquito vector species. The identification of diverging mosquito responses to land-use change has implications for designing species-specific control programs, as well as informing predictions on how mosquito-borne diseases are likely to be shaped in human-dominated landscapes.

5.1. Introduction

The global land system is facing mounting pressure from anthropogenic activities, including the conversion of natural environments for agricultural practices and urban development (Popp *et al.*, 2017). Globally, 75% of land surface area has been transformed by anthropogenic activities, with global net loss of forest cover and expansion of global agriculture predominating (Arneth *et al.*, 2019; Winkler *et al.*, 2021). Disruption of ecosystems has devastating consequences for global biodiversity (Newbold *et al.*, 2015) and similarly influences the incidence and emergence of infectious diseases (Daszak *et al.*, 2001; Keesing *et al.*, 2010; Gottdenker *et al.*, 2014; Gibb *et al.*, 2020).

Mosquito-borne diseases are particularly sensitive to ecological alterations resulting from land-use transformations, including changes in vector habitat availability and vector-human contact rates (Burkett-Cadena and Vittor, 2018; Chapter 3). However, knowledge of how anthropogenic land-use change alters vector biodiversity and consequently influences mosquito-borne disease is lacking. Whilst there is an understanding of how trends in global terrestrial biodiversity (Newbold *et al.*, 2015) and zoonotic hosts respond to land-use change (Gibb *et al.*, 2020), as well as other functional taxa such as pollinators (Millard *et al.*, 2021), there has been limited assessment of how mosquitoes are responding and will respond to anthropogenic modifications. Climate change is increasing the climate suitability for some notable mosquitoes such as the arboviral vectors *Aedes aegypti* and *Ae. albopictus* (Romanello *et al.*, 2021) and malaria epidemics are shifting to regions that previously saw little to no transmission (Siraj *et al.*, 2014). An improved understanding of how important mosquito vectors of disease are impacted by land-use alterations is essential given current trends in global land-use change and intensifying climatic changes (IPCC, 2021), and the interactions between these two factors (Chapter 3).

Variation in climate conditions and shifts in mosquito habitat availability with local environmental alterations have revealed important mechanisms by which disease risk is influenced by land use. For example, environmental degradation caused by mining activity can facilitate increases in malaria risk by amplifying the effect of temperature on transmission (Chapter 3). Furthermore, ecological changes caused by deforestation facilitate increased abundance and biting of the principal malaria vector in the Amazon, *Anopheles darlingi* (Vittor *et al.*, 2006, 2009). At intermediate levels of deforestation in agricultural frontier regions, greater amounts of forest edge habitat provide suitable conditions for the proliferation of *An. darlingi* mosquitoes. Subsequently this elevates malaria risk in the early stages of land-use alterations (Barros *et al.*, 2011; Laporta *et al.*, 2021; Oliveira *et al.*, 2021). In addition to facilitating increases in habitat suitability for mosquito vectors, land-use change such as agricultural development also increases human exposure to pathogen-carrying mosquitoes (de Castro *et al.*, 2006). These local-scale studies have demonstrated how land-use change can alter disease risk through modification of vector habitats. However, there is limited understanding of whether consistent mosquito responses can be detected at regional scales. An assessment of how important vectors respond to land-use change and ecological alterations such as deforestation, will be useful for designing control strategies that can be implemented at scale.

Given the distinct life-history characteristics and diversity of mosquito species (over 3,600 recognised Culicidae species (Harbach, 2020)), it is likely that species will respond differently to land-use change. Urbanisation negatively impacts terrestrial biodiversity (Newbold *et al.*, 2015) and allows for synanthropic mosquitoes, which live in or near human dwellings, to persist in novel environments (Wilke *et al.*, 2021). This is due to the diverse range of aquatic habitats for mosquito breeding in urban environments, such as water-storage containers and drains (Paploski *et al.*, 2016). Increased provisioning of vector habitats in addition to the availability of human hosts have enabled synanthropic mosquitoes, such as the dengue vector *Ae. aegypti* and malaria vector *An. stephensi* to flourish in urban environments (de Carvalho *et al.*, 2017; Wilke *et al.*, 2019, 2020; Sinka *et al.*, 2020). In contrast, mosquito biodiversity is higher in rural, forested landscapes (Loaiza *et al.*, 2017; Câmara *et al.*, 2020), with some mosquitoes exhibiting a preference for preserved forested habitats (Abella-Medrano *et al.*, 2015; Reiskind *et al.*, 2017). Despite this understanding of species' habitat preferences, there is a limited understanding of whether mosquito species respond differentially to anthropogenic land-use change. In addition, several local-level studies have provided an increased mechanistic understanding of how habitat alterations such as deforestation favour important disease vectors (Vittor *et al.*, 2009). However, there has been limited assessment of whether consistent responses to deforestation can be detected regionally, and how the nature of these responses compares among mosquito species. Such assessments will be useful for developing effective mosquito control strategies that can be tailored to species behaviour, such as feeding and resting patterns. This is important for assessing disease risk posed by a wide range of competent vectors and developing interventions that can be targeted at certain mosquito species.

Mosquito-borne diseases are a dynamic public health threat for the Latin American and Caribbean region (LAC), influenced by both climate variation and patterns of environmental degradation (Chapters 2-3). Diversity of mosquito genera is high in Latin America (Foley *et al.*, 2007), with *Aedes* and *Anopheles* mosquitoes imposing a high burden of disease. Approximately five million dengue cases were reported in LAC in 2020 (Du *et al.*, 2021), 145 million people in the Americas are at risk of malaria and cases of yellow fever occur in 13 countries across the region, including Peru, Bolivia and Brazil (PAHO, 2021). Malaria burden is disproportionately high in Amazonian countries, driven by agricultural development that creates disease hotspots at the interface between human-dominated and natural landscapes (Souza *et al.*, 2019). Globally, the Amazon rainforest is the largest reservoir of arboviruses

(Vasconcelos *et al.*, 2001) and is subject to intensifying human pressures, including the development of land for pasture and deforestation for soybean production (Macedo *et al.*, 2012; Winkler *et al.*, 2021). Alterations to natural landscapes have resulted in the rapid expansion of mosquito-borne diseases, including dengue and yellow fever (Wilcox and Ellis, 2006; Lowe *et al.*, 2020), and the rapid re-emergence of malaria in Venezuela (Chapter 3). Disease expansion has been linked to a combination of interacting factors, including global trade and travel, climate variation, as well as increases in habitat suitability resulting from human encroachment into relatively pristine environments (Mayer *et al.*, 2017; Chapter 3). The increasing intensity of extreme weather events and warming temperatures as a result of climate change (IPCC, 2021), which may already be facilitating adaptive behaviour of key mosquito vectors in human-dominated landscapes, poses further disease risk (Chadee and Martinez, 2016).

Understanding how anthropogenic land-use change mediates mosquito-borne disease risk underscores the need to develop highly effective vector control programs. However, there is a limited understanding of mosquito species responses to land-use change. A unified assessment of how mosquito vectors respond to land-use change, identifying variation in species responses is vital. Here, I provide a regional framework for assessing the response of *Aedes* and *Anopheles* mosquitoes to land-use change across Latin America and the Caribbean. Specifically, I test to what extent taxonomic responses in mosquito abundance to anthropogenic land-use change differ and if species richness in human-dominated landscapes is reduced, in comparison to areas not altered by human activity. Additionally, I investigate differences in mosquito species responses to deforestation, harmonising findings from local-level studies. I do this by employing a systematic data search strategy to compile an extensive dataset of mosquito abundance records before using a comparative space-for-time approach, in which sites with varying levels of disturbance are in land-use changes are used as a proxy for ecological timeseries, to identify taxonomic responses to anthropogenic land-use change.

5.2. Methods

5.2.1. Systematic data search strategy

A systematic review approach was employed to find and extract relevant data on mosquito biodiversity across multiple land-use types in LAC. I focused on mosquitoes of the genus *Anopheles* and *Aedes* due to the high burden of disease these vectors have in the region and the large diversity of mosquito genera, enabling the capture of broad-scale mosquito community trends. A systematic literature search was performed on 5th July 2021 across three databases (Medline, Scopus, and Web of Science; Figure S5.1). Country- and region-specific search terms were used to capture studies within geographical boundaries of LAC, alongside a combination of mosquito-specific e.g., *Aedes* and *Anopheles*, and land use specific search terms e.g., deforestation and agriculture (complete search term details are provided in Table S5.1). Results from each database search were combined and duplicates removed. Studies were firstly screened by title and abstract to remove irrelevant studies such as epidemiological interventions and laboratory-based analyses. The full texts of potentially relevant studies were then reviewed for inclusion. To qualify for inclusion, studies had to contain available abundance data (either in the main text or supplementary) for one or more *Anopheles* or *Aedes* mosquito species and include samples across multiple land-use types. If a study included data on at least one mosquito vector, (judged if there was evidence from the published literature linking the mosquito to at least one human disease), then all *Aedes* and *Anopheles* data from that study were collected. Studies were excluded if there was an insufficient description of the land use of the sampled site, or if the description was too crude. For example, studies describing sites as ‘wild’ or ‘peridomestic’ were excluded. Studies were also excluded if only one land-use type was sampled and if the sampling methodology was not adequately described, for example if the study did not include sampling effort.

5.2.2. Mosquito biodiversity dataset construction and assignment of land-use categories

Here, I use a space-for-time approach to compare mosquito biodiversity across different land-use types. In this approach, spatially-separated sites with varying land use were compared, under the assumption that these land use gradients represent the ecological time-series of land development (Pickett, 1989; Wogan and Wang, 2017). A dataset of *Aedes* and *Anopheles* mosquito species in LAC across multiple land-use types was built by extracting information from each study identified in the systematic data search (Table S5.2), following the methodology in Hudson *et al.* (2014) for the PREDICTS database (a global compilation of site-level ecological data across different land uses and land-use intensities). Species- and site-specific abundance data were extracted for each included study and information collated on the sampling methodology, the study area and site descriptions (Table S5.2). As with the PREDICTS database each study site was nested, such that variation due to sampling methodology could be accounted for. Specifically, each record was assigned a study number (a unique paper), site number (a geographic location at which mosquito abundance was sampled), study block (a collection of sites within a distinct spatial cluster, to account for spatial autocorrelation within a study) and study sample (a sample with consistent sampling methodology, such as capture method and sample month) (Table S5.2).

Each sample site was assigned a land-use type (primary vegetation, secondary vegetation, managed or urban) and use intensity (minimal or substantial), adapted following criteria in Hudson *et al.* (2014) and Gibb *et al.* (2020) (Table 5.1). Sites were labelled according to the predominant land-use type as detailed in the site description within each study and use intensity was assigned based on how heavily sites were used. For example, sites sampled near or in buildings, or small rural villages, located in a biological reserve, research station or forested area, were labelled as primary vegetation with minimal or substantial use. Managed sites included those with plantations, pasture or cropland (Gibb *et al.*, 2020). For sites to be classified as urban, sites must have paved roads and significant impervious surface area. For analysis, land-use type and intensity were combined into a categorical variable. Minimal and substantial use intensities were retained for primary vegetation sites and due to a lack of data representation, use intensities for secondary vegetation, managed and urban sites were combined into a single category. This resulted in a categorical variable with five levels; primary vegetation-minimal, primary vegetation-substantial, secondary vegetation-combined, managed-combined and urban-combined (Table S5.3).

Table 5.1. Land-use categories used in the dataset. Description of land-use types used to classify sample sites in the dataset. Categories were adapted following Hudson *et al.* (2014) and Gibb *et al.* (2020).

Land-use category	Description
Primary vegetation	Natural vegetation with no evidence of previous destruction
Secondary vegetation	Vegetation that is recovering after removal of the natural vegetation
Managed	Agricultural land used for plantations (cultivation of woody crops, such as oil-palm, rubber, fruit, coffee, or timber), cropland (cultivation of herbaceous crops, including fodder for livestock), and pasture (livestock grazing)
Urban	Areas of human habitation and buildings, from small green spaces, through to villages and cities

5.2.3. Modelling the effects of land-use change on mosquito abundance and species richness

Bayesian mixed-effects models were constructed to assess mosquito biodiversity (abundance and species richness) across different land-use types (Table S5.4-5). Where a study reported sampling effort, which varied across sample sites within a study, raw species-level abundance measurements were effort-corrected. Raw abundance measurements were subsequently divided by sampling effort to give an effort-corrected abundance measurement (Newbold *et al.*, 2015; De Palma *et al.*, 2016; Millard *et al.*, 2021). Due to the high number of zero observations site-level species abundance measurements were overdispersed, so were log-transformed and subsequently modelled with a Gaussian likelihood. Site-level species richness (the number of uniquely named species sampled at each site) was modelled using a Poisson likelihood (Newbold *et al.*, 2015; Gibb *et al.*, 2020). Models were constructed for *Aedes* species abundance, *Anopheles* species and both species (all *Aedes* and *Anopheles* combined). Species-specific responses in abundance to land use were also examined, by building separate models for four mosquito species per genus. The most represented (highest number of records) *Aedes* and *Anopheles* mosquito species in the dataset were selected (Table S5.6), whilst ensuring the selected species are implicated in transmission of at least one human disease (Sinka *et al.*, 2010; Kraemer *et al.*, 2015). To ensure mosquito responses were not confounded by mosquito habitat preferences and ranges, the models for each species only included studies where the species was detected. A summary of the main fitted models is provided in Table S5.4.

All models included a random intercept term for each study to account for variation between studies, including reporting methods and sampling methodologies e.g., outdoor vs. indoor sampling and trapping method (Table S5.4). A random effect for each study site was included to account for overdispersion due to site-level differences (Hudson *et al.*, 2014). Abundance models also included a random intercept for each unique species. This allowed for species-specific variation in abundance that could result from differences in feeding and resting behaviour, meaning some species were easier to sample than others. Other random effects considered in the model structure included study block, used to account for spatial autocorrelation between sites within a study and study sample. Ecoregion, reflecting habitat types taken from WWF (2021) was also included as a random effect to account for the confounding effect of climate and habitat (Hudson *et al.*, 2014). The best-fitting random effects structure was selected by formulating iterative models of each response (abundance and richness) with the addition of each random effect (Table S5.7-8).

Model adequacy was then assessed using the Bayesian metrics, the deviance information criterion (DIC) (Spiegelhalter *et al.*, 2002) and the Watanabe-Akaike information criterion (WAIC) (Watanabe, 2010). Random effects were retained in the final model structure if the model was improved (assessed by a reduction in DIC and WAIC) with the addition of each random effect, although ecoregion was retained in all models to avoid the potential confounding influence of climate and habitat. Model fit was also assessed through visual inspection of fitted versus observed values (Figure S5.2). All models were implemented in a Bayesian framework, using R-INLA (Blangiardo *et al.*, 2013).

Species richness and abundance models were cross-validated by testing the sensitivity of the fixed effects estimates to geographical and random subsampling. For geographical subsampling, models were fitted holding out data from Brazil, where data coverage was highest. Models were also fitted that excluded data from each ecoregion (n=6) at a time. Finally, for the random subsampling eight models were fitted excluding 12.5% of the data at a time.

5.2.4. Modelling the impact of deforestation on mosquito biodiversity

To test for and compare species-specific mosquito responses to deforestation, abundance records were combined with remotely-sensed deforestation data (Hansen *et al.*, 2013). Specifically, mosquito records from primary and secondary vegetation sites in the dataset were used to explore differences in both the *Aedes* and *Anopheles* species richness and abundance responses to deforestation. The Hansen dataset consists of spatially continuous annual estimates of forest loss derived from Landsat images, between 2000-2019 (Hansen *et al.*, 2013). For each unique primary and secondary vegetation site in the dataset, the percentage of forest loss within a 320 m buffer around each site was extracted. A 320 m buffer was used as an approximation of mosquito flight distance, which can range between 50 m and 50 km. Average *Aedes* and *Anopheles* flight distances range between 89 – 542 m (Verdonschot and Besse-Lototskaya, 2014) so the mean of these values was used. Since the time since deforestation greatly influences mosquito dynamics and subsequent disease risk (Laporta *et al.*, 2021), the deforestation data was temporally matched with site-level mosquito abundance and richness records. An estimate of recent forest loss was obtained by using estimates from the last five years since the sampling start date at each site. Bayesian mixed-effects models for *Aedes* and *Anopheles* mosquito species richness and abundance were formulated including site-level proportional deforestation as a linear covariate. As with the land-use models, random effects for study number, site number, study sample and terrestrial ecoregion were also included (Table S5.9). Eight species-specific abundance models selected based on data representation were also formulated to test for individual responses to deforestation.

5.3. Results

5.3.1. Dataset of mosquito biodiversity and land use

The final mosquito abundance dataset comprised 10,004 records across 632 sites, from 93 studies identified in the systematic data search (Figure 5.1A). Most sampled sites were primary vegetation (46%, n=292; Figure 5.1A), which represented 37% of total records in the dataset (n=3,739). The dataset spanned 13 countries across the LAC region (Figure 5.1A; Figure S5.3) and coverage was highest in Brazil (69% of records, n=6,870), and in biodiversity hotspots such as the Amazon basin (68% of total sites, n=431; Figure 5.1B) and Atlantic Forest (18% of total sites, n=111; Figure 5.1A). The dataset spanned six terrestrial ecoregions (Figure S5.6), the majority of which were in the Amazon and were forested ecoregions (89% of total sites, n=564; Figure 5.1B). The dataset was comprised of 91 species (Table S5.10), 64% (n=58) of which were *Anopheles* species and 36% (n=33) were *Aedes* species (Figure 5.1C).

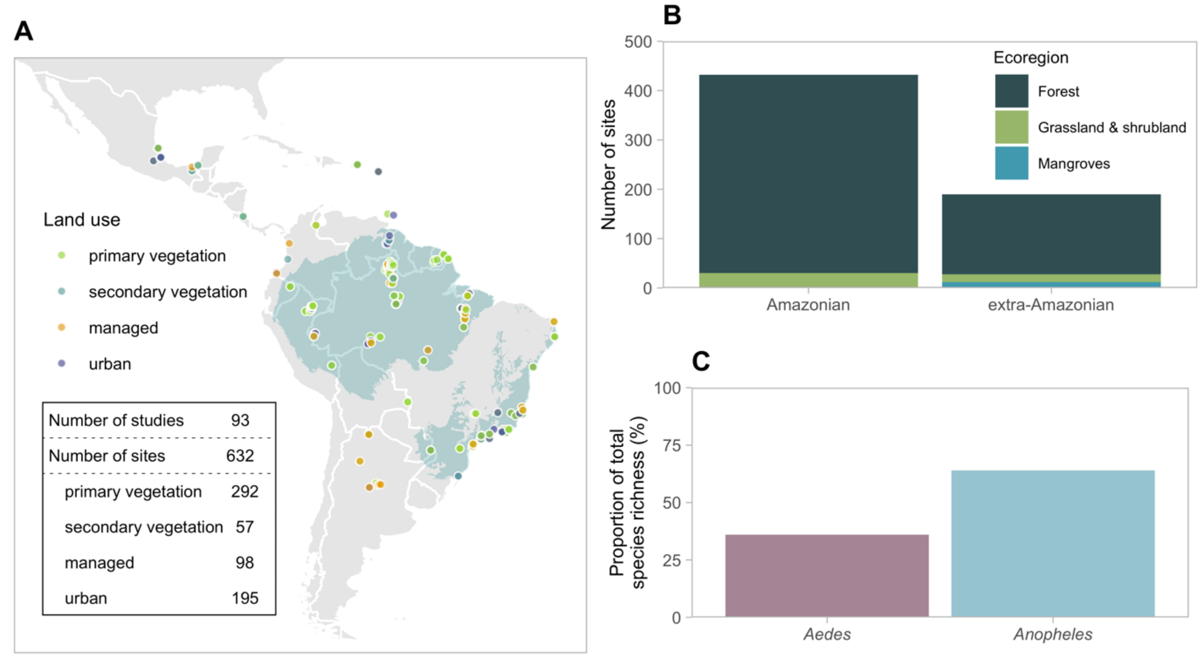

Figure 5.1. Dataset of *Aedes* and *Anopheles* mosquito biodiversity in Latin America and the Caribbean. Geographical location (points) of surveyed sites (n=632) and their predominant land-use type across 93 collated studies (A). Colours represent the four land-use types: primary vegetation (green), secondary vegetation (blue), managed (orange) and urban (purple). Green shading on the map shows the Amazon basin and Atlantic Forest. The number of surveyed sites across broadly defined terrestrial ecoregions (forests, grassland and shrubland, and mangroves) are shown for Amazonian and extra-Amazonian regions (the remaining LAC region) (B). Proportion (%) of unique species (species richness) across total species richness in the dataset (C).

5.3.2. Effect of land-use change on mosquito species richness and abundance

A strong and significant response of mosquito species richness to human disturbance was detected (Figure 5.2A; Figure S5.4A; Table S5.11). *Aedes* mosquito species richness was reduced by 26% in urban areas, compared to the primary vegetation minimal use baseline (95% CI: -42.7% to -5.2%; Figure 5.2A). *Anopheles* mosquito species richness demonstrated a larger 37% decline in richness (95% CI: -50.8% to -20.6%) and there was a trend towards increased *Anopheles* richness in managed areas, although this was not significant (Figure 5.2A). Relative to primary vegetation, *Anopheles* mosquitoes in urban sites experienced a significant 13% (95% CI: -22.4% to -2.1%) reduction in abundance and there was also a trend towards decreased *Aedes* abundance in urban sites (Figure 5.2B; Table S5.12). In contrast, abundance of *Anopheles* mosquitoes increased by 11% in managed sites (95% CI: 0.3% - 24.0%). There was a minimal effect of other land-use types on *Aedes* and *Anopheles* abundance. Total *Aedes* and *Anopheles* mosquito species richness was 37% lower in urban landscapes (95% CI: -50.8% to -20.6%), and there was no significant effect of land-use type on total mosquito abundance (Figure S5.4B).

Both species richness and abundance models were broadly robust to geographical subsampling, although there were higher levels of uncertainty in abundance and richness estimates when data from Brazil were excluded from the models (Figure S5.5). Urban estimates were particularly sensitive to holding out data from Brazil. I also found that both the abundance and species richness models were highly influenced by sites from tropical rainforests, highlighting the need for more representative sampling outside this ecoregion (Figure S5.6). Finally, abundance and species richness responses were robust to random subsampling, where 12.5% of the data was held out at a time from the models (Figure S5.7).

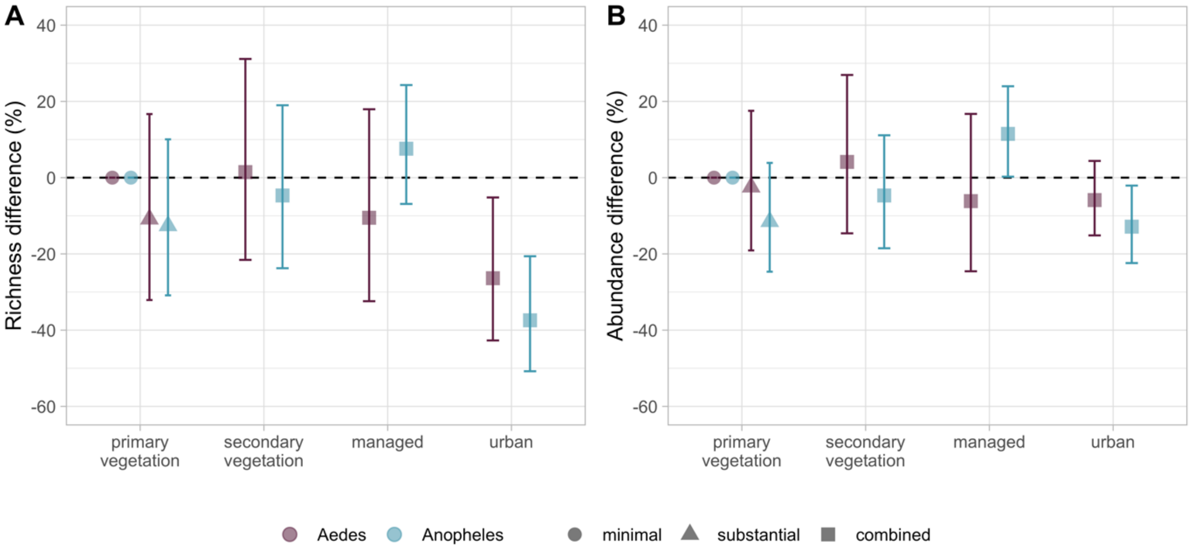

Figure 5.2. Responses of mosquito species richness and abundance to land-use type and intensity. *Aedes* (purple) and *Anopheles* (blue) mosquito species richness (A) and abundance (B) responses to land-use types with minimal (circles), substantial (triangles) and combined (squares) use intensities. Effect sizes were adjusted to a percentage by expressing each mean fixed effect and 95% credible intervals as a percentage of the baseline (primary vegetation minimal use, shown as zero). Intensity levels for secondary vegetation, managed and urban land uses were aggregated due to a lack of data representation.

5.3.3. Species-specific mosquito abundance responses to land-use change

I investigated species-specific variation in responses to land use, by analysing the mean land use effects on species-level abundance for four *Aedes* and four *Anopheles* mosquito species that were most represented in the dataset (Table S5.6). I found that there was a high degree of divergence in the response of mosquito species to land use (Figure 5.3; Table S5.13). *Ae. aegypti* and *Ae. albopictus* diverged in their responses to substantial use intensity at primary vegetation sites, and at secondary vegetation sites (Figure 5.3). Whilst *Ae. aegypti* demonstrated a negative abundance response (-55%, 95% CI: -73.8% to -24.3%) at secondary vegetation sites, *Ae. albopictus* showed elevated abundance at both substantial use primary vegetation (94%, 95% CI: 26.1% – 198.9%) and secondary vegetation sites (68%, 95% CI: 4.7% - 167.3%). *Ae. aegypti* demonstrated the largest abundance response among the eight species, with a 207% increase in abundance at managed sites (95% CI: 75.7% - 435.4%), although there was a high degree of uncertainty associated with this estimate. Both *Ae. aegypti* and *Ae. albopictus* demonstrated an increased abundance trend at urban sites, although this was not significant. In contrast to *Ae. albopictus*, *Ae. scapularis* demonstrated reduced abundance in primary vegetation sites with substantial use intensity (-44%, 95% CI: -57.5% to -27.1%). Similarly, *Ae. serratus* abundance was reduced by 61% at primary vegetation sites with substantial use (95% CI: -75.5% to -36.6%) and by 66% in managed sites (95% CI: -79.3% to -44.5%).

The response of *Anopheles* mosquito abundance to land-use change in contrast to *Aedes* was less marked (Figure 5.3). Only the abundance of *An. albitarsis* mosquitoes was altered in comparison to the primary vegetation baseline. At managed sites, *An. albitarsis* abundance was 163% higher (95% CI: 34.8% - 422.2%). I detected a minimal impact of land-use change on *An. albimanus* and *An. nuneztovari* abundance and although the credible intervals crossed zero there was evidence of a trend towards higher *An. darlingi* abundance at secondary vegetation sites. Holding out influential mosquito species records from genus-level abundance models overall did not markedly change the response to land use (Figure S5.8). However, models holding out *Ae. albopictus* records were sensitive to exclusion of data, as were estimates for managed land-use types.

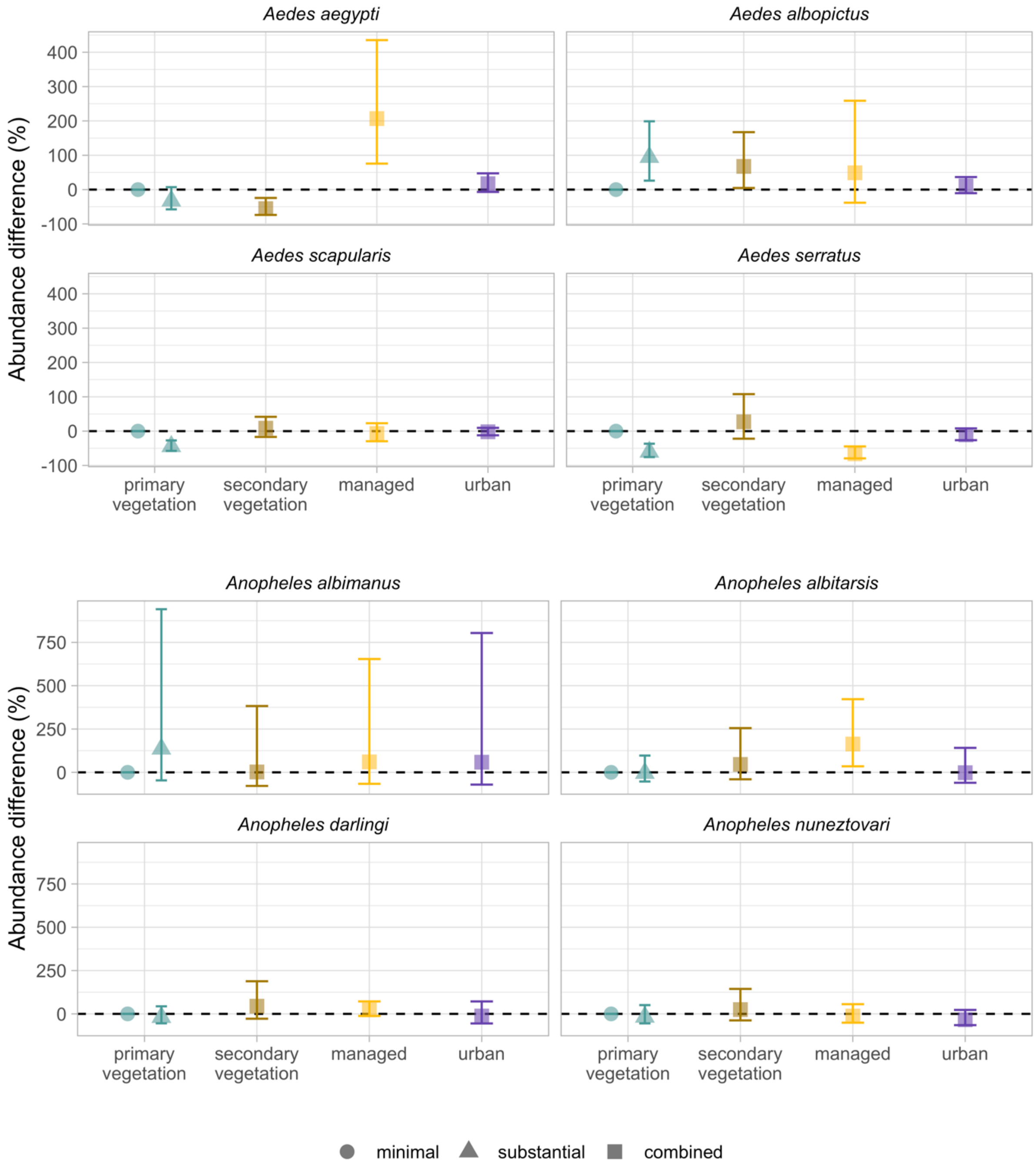

Figure 5.3. **Species-specific mosquito abundance responses to land-use type and intensity.** *Aedes* and *Anopheles* mosquito species abundance responses to land-use types with minimal (circles), substantial (triangles) and combined (squares) use intensities. For each genus, the four most represented species in the dataset were selected. Effect sizes were adjusted to a percentage by expressing each mean fixed effect and 95% credible intervals as a percentage of the baseline (primary vegetation minimal use, shown as zero). Intensity levels for secondary vegetation, managed and urban land uses were aggregated due to a lack of data representation. For *An. albimanus*, urban sites were excluded due to high uncertainty in the credible interval ranges and sparse sampling (only three sites).

5.3.4. Influence of deforestation on mosquito biodiversity

I found that recent deforestation (in the last five years) was associated with higher *Anopheles* species richness (mean estimate 0.13, 95% CI: 0.03 - 0.23; Figure 5.4A). This result corresponded to a 14% increase in richness with every 1% increase in forest loss. Although not significant, there was also a trend towards increased abundance of *Anopheles* mosquitoes (Figure 5.4A). In contrast, I detected a minimal impact of deforestation on *Aedes* mosquito abundance and species richness. Furthermore, I found evidence of species-specific responses to deforestation. Whilst two *Anopheles* species responded positively to deforestation, there was a minimal impact of deforestation on the abundance of *Aedes* species (Figure 5.4B). *An. darlingi* demonstrated the largest increase in abundance with deforestation (mean estimate 0.28, 95% CI: 0.07 - 0.48; Figure 5.4B), followed by *An. albitarsis* (mean estimate 0.10, 95% CI: 0.05 - 0.16; Figure 5.4B). This corresponded to a 32% increase in *An. darlingi* abundance and 11% increase for *An. albitarsis* with every 1% unit increase in forest loss.

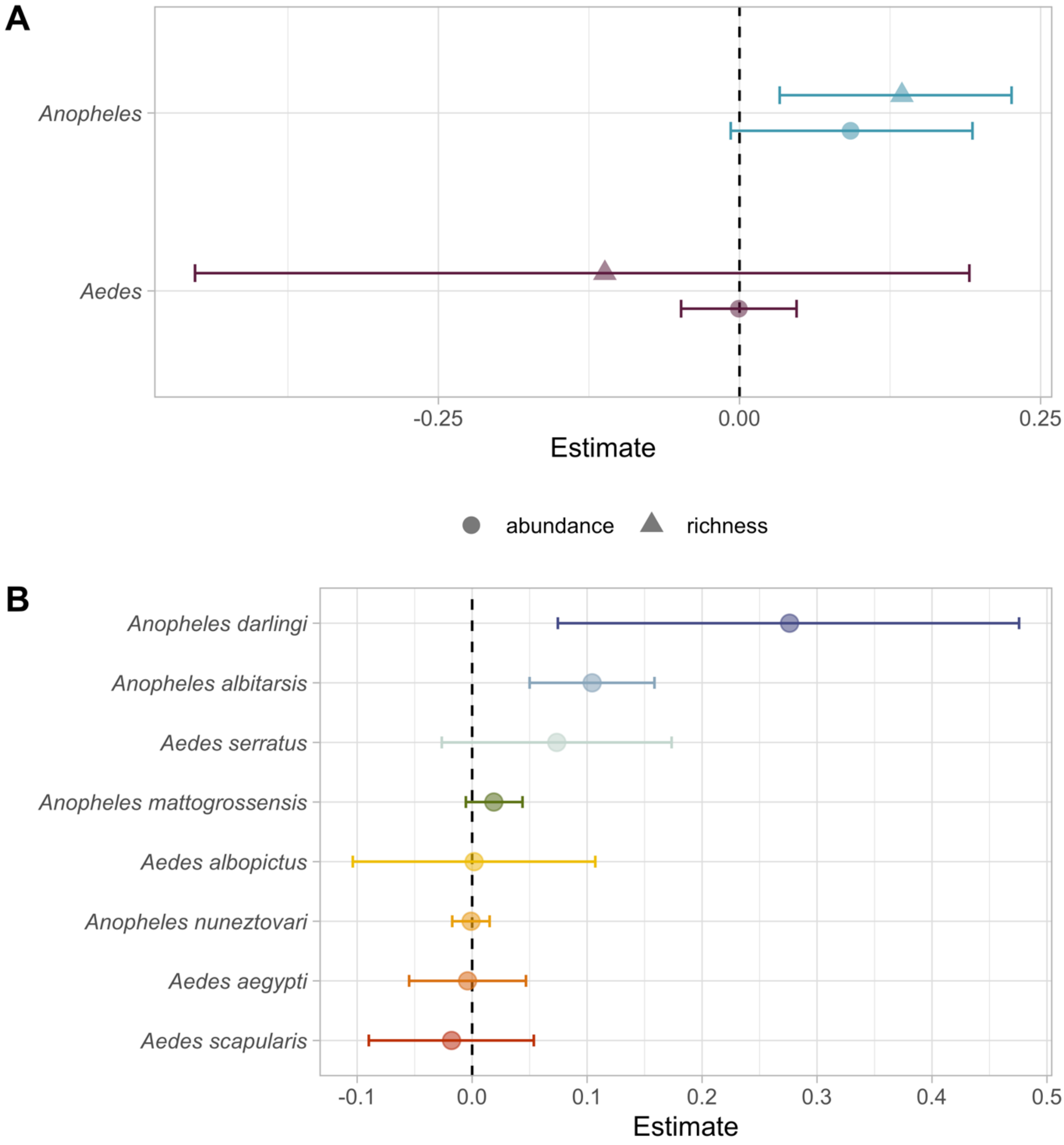

Figure 5.4. Impact of deforestation on mosquito species richness and abundance. Influence of recent deforestation on *Aedes* (purple) and *Anopheles* (blue) mosquito abundance (circles) and species richness (triangles; A). Abundance responses of eight mosquito species to recent deforestation (in the last five years; B). Points and bars for A and B show posterior mean and 95% credible intervals for linear fixed effects estimates of recent deforestation, calculated as proportional forest loss within the last five years of the sample start date for each site-level record.

5.4. Discussion

Here, using a space-for-time approach I provide an improved understanding of the nature of the response of *Aedes* and *Anopheles* mosquitoes to land-use change. Despite local-level studies providing evidence of how specific land-use changes, such as deforestation alter mosquito vector abundance, there has been limited assessment of the broader-scale responses and whether responses differ between mosquito species. I detected geographically consistent trends in mosquito species abundance and richness across differing land-use types in Latin America and the Caribbean. Both *Aedes* and *Anopheles* mosquito species richness was reduced in urban environments and abundance of several synanthropic arboviral (*Ae. aegypti* and *Ae. albopictus*) and malaria (*An. albitarsis*) vectors was greater in human-dominated landscapes. By integrating local landscape-level mosquito abundance records across 632 sites, I was able to detect substantial taxonomic differences in biodiversity responses to land use, demonstrating important proof of concept for this methodology. Further, with the addition of more data these methods could be applied on a broader global and regional scale to investigate how mosquito vectors respond in environments subject to anthropogenic pressures.

Land-use change is expected to lead to an overall decline in biodiversity, primarily due to habitat loss. However, disturbance can favour opportunistic species that are able to adapt to anthropogenic environments (McKinney, 2002; Multini *et al.*, 2019; Wilke *et al.*, 2021). The strong decrease in *Aedes* (26%) and *Anopheles* (37%) mosquito species richness in urban areas in this study is in agreement with previous studies that demonstrate decreased mosquito biodiversity in urban and fragmented landscapes (Ferraguti *et al.*, 2016; Hernández-Valencia *et al.*, 2020). In some instances, biodiversity can provide a protective effect for disease emergence by regulating the abundance of vectors through intra- and interspecies competition, as well as through predation (Laporta *et al.*, 2013). Disruption of this protective effect can however facilitate increased abundance of certain species able to adapt to novel environments. For example, decreased mosquito biodiversity in agricultural frontiers in the Amazon favours higher abundances of *An. darlingi* and drives subsequent malaria risk (Chaves *et al.*, 2021). Similarly in a malaria endemic region of Colombia, communities of *Anopheles* mosquitoes were less diverse in highly fragmented landscapes in comparison to more intact landscapes (Hernández-Valencia *et al.*, 2020). In this study, the lower mosquito species richness found in urban environments, combined with the elevated abundance of select mosquito vectors (*Ae. aegypti, Ae. albopictus* and *An. albitarsis*) in human-dominated landscapes suggests reduced biodiversity may also facilitate increased disease risk.

In general, urbanisation decreases the available habitat for mosquitoes as forested areas provide a diverse range of habitats and environmental niches for mosquito species, especially for resting adult mosquitoes (Shannon, 1931; Shochat *et al.*, 2006; Rejmánková *et al.*, 2013; Wilke *et al.*, 2021). Here, *Anopheles* mosquito abundance was lower in urban landscapes compared to primary vegetation sites and was elevated at managed sites. Agricultural landscapes provide diverse breeding habitats for *Anopheles* species, including footpath depressions found in plantations and rice fields (Thongsripong *et al.*, 2013; Prescott *et al.*, 2015; Hawkes *et al.*, 2019). The reduced abundance of *Anopheles* mosquitoes in urban areas, compared to primary vegetation sites is likely due to the preference of resting adults for forested habitat (Hiwat and Bretas, 2011). Greater abundances of anopheline mosquitoes have been found in forest habitat compared to human settlements in Malaysia (Hawkes *et al.*, 2019). Likewise, in Ecuador human habitations were found to provide unsuitable habitat for anopheline larvae due to low amounts of available standing water and vegetation coverage (Pinault and Hunter, 2011). In the Brazilian Amazon, anopheline mosquitoes were captured almost exclusively in preserved forest environments (Guimaraes *et al.*, 2003), which provide suitable habitats such as streams, dense forest cover and flooded forest environments (Jiménez *et al.*, 2014). However, increased mosquito vector abundance in forested areas may not necessarily lead to lower disease transmission. Vector-human contact rates in forested areas can remain high due to anthropogenic development and activity. Although the main vector of human and simian malaria in the Atlantic Forest, *An. cruzii* (Duarte *et al.*, 2013) prefers habitats with high forest coverage, growth of forest edges due to human activity triggers greater ground-level of activity of this mosquito, and subsequently increases human exposure (Medeiros-Sousa *et al.*, 2019).

In addition to genus-specific responses to land-use change, I additionally found pronounced species-specific abundance responses. The differential response of mosquito species to land-use change is likely to be driven by the unique life-history characteristics and habitat preferences of each species (Becker *et al.*, 2010; Tucker Lima *et al.*, 2017). As expected, I found increased abundance of opportunistic species in disturbed landscapes, including *Ae. aegypti* and *Ae. albopictus* mosquitoes. Several *Aedes* mosquitoes such as *Ae. aegypti* and *Ae. albopictus* are highly adapted to human-dominated landscapes, which provide a range of artificial breeding sites such as crops, water storage containers, tyres and drains (Paploski *et al.*, 2016). These novel habitats facilitate increased abundance, densities, development and survival of *Aedes* mosquitoes in urban and agricultural areas (Thongsripong *et al.*, 2013; Li *et al.*, 2014). The adaptation of *Aedes* mosquito vectors to anthropogenic landscapes represents a threat to human health due to a greater number of opportunities for vector-human contact in areas with high population densities (Wilke *et al.*, 2021). However, here I was unable to detect a significant positive effect of *Ae. aegypti* abundance in urban areas. This could be due to the diversity of sites classified as urban in the study, which range from rural and peri-urban sites, to densely populated and developed cities. Peri-urban sites with minimal use intensity in this study likely have a reduced number of aquatic breeding habitats in comparison to urban centres. Accounting for finer-scale variation across urban landscapes, as well as use intensity may enable the response of *Ae. aegypti* in urban landscapes to be teased out. For example, gradients of urban development could be accounted for by using estimates of human population density at 1 km resolution from WorldPop (https://www.worldpop.org), enabling the detection of finer-scale responses of mosquito species to urbanisation.

Habitat disturbance can increase the number of transitional environments across a landscape and facilitate opportunistic species well-suited to disturbance. In the southern Amazon, landscape disturbance was linked to increased biodiversity (richness and abundance) of arbovirus vectors, specifically in small forest remnants with high edge densities (da Silva Pessoa Vieira *et al.*, 2021). In contrast to *Ae. aegypti*, I found that *Ae. albopictus* abundance was greater in disturbed primary vegetation and in secondary vegetation sites. *Ae. albopictus* is commonly found in rural domestic environments in close proximity to humans, and is capable of dispersing into densely urbanised areas (Tsuda *et al.*, 2006; Ayllón *et al.*, 2018). Human population densities and therefore vector-human contact rates are expected to be higher in these disturbed sites compared to areas with more pristine primary vegetation. *Ae. aegypti* abundance was highest in managed sites and there was evidence of a similar positive trend for *Ae. albopictus*. These findings have important consequences for the emergence of arboviruses transmitted by *Ae. aegypti* and *Ae. albopictus*, such as dengue, yellow fever and chikungunya, as disease transmission could be facilitated in anthropogenic environments without the implementation of adequate control measures. The strong response of these mosquitoes to anthropogenic disturbance combined with rapid development in the Amazon, expansion of arboviruses into urbanised forest (Lowe *et al.*, 2020) and rising climate suitability (Romanello *et al.*, 2021), poses a substantial threat of mosquito-borne disease in Latin America.

In contrast to *Ae. aegypti* and *Ae. albopictus*, several *Aedes* mosquitoes displayed a negative response to land-use change. For example, *Ae. serratus,* a vector of yellow fever (Cardoso *et al.*, 2010) and *Ae. scapularis*, exhibited reduced abundance at managed sites and primary vegetation sites with substantial use intensity. *Ae. serratus* is likely not adapted to anthropogenic environments and the ecological conditions associated with reduced primary vegetation, which include the loss of forest habitat structures and natural water bodies, as well as higher temperatures. Indeed, *Ae. serratus* is highly sensitive to human activity, demonstrating strong declines in abundance with higher levels of disturbance in the Atlantic Forest (Orlandin *et al.*, 2020).

Whereas several *Aedes* mosquito species showed strong responses to land use, I detected a minimal response of *Anopheles* species. However, *An. albitarsis* an emerging secondary malaria vector in the Amazon (Povoa *et al.*, 2006; Abou Orm *et al.*, 2017) and the Atlantic Forest (da Silva *et al.*, 2013), exhibited higher abundances at managed sites. Furthermore, higher *An. albitarsis* abundance was associated with increasing deforestation. This mosquito has become adapted to non-forest environments, where it exhibits highly anthropophilic behaviour (Tadei and Dutary Thatcher, 2000; Foley *et al.*, 2014). These results provide important evidence that habitat alterations favouring secondary malaria vectors pose a substantial risk of disease emergence. In addition, the divergent abundance responses detected amongst *Aedes* and *Anopheles* mosquitoes highlights the importance of considering species-specific responses to land-use change when developing both predictive disease models and targeted control programs.

An. darlingi is a highly efficient anthropophilic malaria vector that predominates in the Amazon region (Natal *et al.*, 2007; Sinka *et al.*, 2010). It has been well-documented that *An. darlingi* exhibits a preference for disturbed deforested landscapes, especially in locations close to human settlements in agricultural frontier regions (Vittor *et al.*, 2009; Barros *et al.*, 2011). Here, *An. darlingi* exhibited the strongest response to deforestation and a trend towards increased abundance in secondary vegetation. Secondary growth, particularly at forest fringes, offers a range of suitable environmental conditions for *An. darlingi*, including increased sunlight, refugia and ground pools (Barros *et al.*, 2011; Rejmánková *et al.*, 2013; Sanchez-Ribas *et al.*, 2017). There was however substantial uncertainty in the abundance response of *An. darlingi* detected at secondary vegetation sites.

Owing to the lack of representative sampling of secondary vegetation sites in the study (n=57), I was unable to capture fine-scale ecological processes that likely drive mosquito-borne disease risk. For example, there is a strong temporal component in the relationship between malaria and deforestation (Laporta *et al.*, 2021). Greater availability of forest edge habitat and lower forest cover, which occurs at intermediate levels of deforestation (Chaves *et al.*, 2021), is favoured by *An. darlingi*. Based on this evidence, it is highly likely that *An. darlingi* exhibits a positive abundance response at younger secondary vegetation sites with greater amounts of forest fringe habitat. However, as the age of secondary vegetation renewal was not accounted for in this study, there was a high level of uncertainty and divergence in the response. By combining remotely sensed estimates of recent deforestation (in the last five years) with the mosquito dataset, I was able to detect an increase in *An. darlingi* abundance with deforestation. This association likely captures the effect of increased abundance at intermediate levels of forest loss and is supported by previous findings of elevated *An. darlingi* abundance in deforested sites (Vittor *et al.*, 2009). Moreover, these findings support studies that have demonstrated higher malaria risk with deforestation, in areas where *An. darlingi* is a vector (Chapter 3).

Despite providing important evidence of species- and genus-specific responses to land-use change, this study has several limitations. First, owing to the high levels of mosquito biodiversity in the Amazon and Atlantic forests captured in this study, the dataset is geographically biased towards these regions and rainforest biomes. Indeed, 68% of sites included in the study were in the Amazon basin. However, the findings of this study were broadly robust to both random and species-level subsampling. Second, studies included in the dataset are likely to underestimate the true abundance of mosquito species as the methods employed in each study were biased towards anthropophilic mosquitoes and species that are easier to find and capture. Nonetheless, several studies included in the dataset sampled mosquitoes using multiple sampling methods. For example, mosquito sampling was performed in many studies using human-landing catch, which primarily captures anthropophilic mosquitoes, although can be used to capture both endophilic (indoor-resting) and exophilic (outdoor) mosquitoes (Lima *et al.*, 2014). Other studies used baited traps and ovitraps left overnight to capture nocturnal mosquitoes and those at different life stages, such as larvae and pupae.

In addition, the random effects structure of the model accounted for differing sampling methodologies that may explain a proportion of the variation in mosquito abundance observed. The mosquito species included in the dataset are likely to be biased towards dominant and incriminated vector species, such as *An. darlingi* and *Ae. aegypti*. Future assessments could consider species bias by taking into account publication effort (Gibb *et al.*, 2020) to ensure under-represented species that may well be efficient vectors of human diseases are included. Additionally, abundance records in the dataset included a high number of zero observations, resulting from sampling of species at sites where occurrence was low. Incorporating species occurrence probability into the modelling framework may be a method to address the zero-inflation of abundance data (Gibb *et al.*, 2020).

Mosquitoes are ectothermic and are therefore highly sensitive to climate conditions, such as seasonal temperature fluctuations (Huber *et al.*, 2018). The responses of mosquitoes to land-use change detected in this study therefore could be confounded by climate conditions. However, the inclusion of ecoregion as a model random effect will likely account for variation due to climate. Other potential confounders in this study include mosquito vector control, which would underestimate and potentially mask the effect of land use, especially in areas with high population exposure such as urban landscapes. Finally, the mosquito biodiversity dataset lacked a large number of representative samples from several land-use types and use intensities. These included agricultural sites, plantations, and pasture. For example, the dataset only included 93 managed sites and only 48 secondary vegetation sites. Additionally, in the abundance and species richness models, land-use intensity only varied at primary vegetation sites, which represented 47% of total sites in the dataset.

Global studies assessing biodiversity responses to land-use change have enabled the detection of fine-scale responses at varying levels of use-intensity and at more specific land-use types. For instance, variations in terrestrial biodiversity have been detected in cropland, and young- and mature-secondary vegetation sites (Newbold *et al.*, 2015). Moreover, vertebrate biodiversity responses to land use have also been linked to species' climatic tolerances, enabling an enhanced understanding of the interacting effects of climate and land-use on biodiversity (Williams and Newbold, 2021). A larger dataset with a greater number of representative samples, across more diverse sites with differing levels of use-intensity could help disentangle more complex responses to anthropogenic land-use change. Despite shortfalls in representative data sampling, this study demonstrates the utility of a comparative approach to detect considerable genus- and species-specific mosquito responses to land-use change.

Ecological changes caused by anthropogenic land-use change have a wide range of cascading effects on mosquito-borne disease risk. By affecting habitat availability and the abundance and distribution of mosquito vectors, patterns of emerging and re-emerging diseases can be dramatically altered. A comprehensive grasp of how mosquito species are affected by anthropogenic disturbance will facilitate the development of highly effective disease control measures. A greater understanding could additionally equip vector control efforts with species-specific information to support targeted elimination efforts for mosquito-borne diseases such as dengue, yellow fever, malaria and chikungunya. Here, I present a comparative dataset of 10,004 *Aedes* and *Anopheles* mosquito records in Latin America and the Caribbean, which is a valuable resource for investigating the effect of land-use change on mosquito-borne disease risk that is epidemiologically relevant at the regional scale. I demonstrate considerable species-specific responses, which represent the diverging impacts of land-use change on mosquito fauna. These findings add certainty to future assessments of how opportunistic species contribute to elevated mosquito-borne disease risk in anthropogenic environments.

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SECTION A – Student Details

Student	Isabel Fletcher
Principal Supervisor	Rachel Lowe
Thesis Title	Assessing the impact of global environmental change on mosquito-borne disease: A Planetary Health approach

<u>If the Research Paper has previously been published please complete Section B, if not please move to Section C</u>

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	**Chapter 6.4** of this thesis is being prepared for submission to The Lancet Planetary Health, in the form of a Personal View (Appendix V)
Please list the paper's authors in the intended authorship order:	**Isabel K. Fletcher**, Katja Frieler & Rachel Lowe
Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I lead this discussion piece and wrote the manuscript.

Student Signature: [redacted] **Date:** 25.09.2022

Supervisor Signature: [redacted] **Date:** 25.09.2022

Chapter 6 - Discussion and synthesis

Mobilisation of the health sector and the recent 'code red' warning for human health in a warmer world (Romanello *et al.*, 2021) has drawn a spotlight on the health argument for climate action. Fundamental to achieving global emissions targets is a greater understanding of how global environmental change is affecting human health. Addressing this problem through a Planetary Health lens, with an enhanced appreciation of how human and environmental health are interconnected, in the response to the climate change crisis will help accelerate understanding and provide key evidence for policymakers. In this final chapter, I synthesise research from this thesis to show how knowledge from multiple disciplines (climate science, public health and ecology) can be integrated to provide an understanding of how mosquito-borne disease risk is influenced by climate variation, socioeconomic factors, including elimination efforts, and land-use change. I also highlight policy implications of this research, discuss the remaining challenges and possible routes forward.

6.1. Summary of key findings and implications

A key challenge for understanding mosquito-borne diseases is identifying, accounting for and attributing variation in disease risk to multiple interacting components in a complex system. Disease risk is determined by a combination of hazard, exposure and vulnerability (Figure 1.2), which includes environmental and socioeconomic factors including climate variation, land use and elimination efforts. Understanding the relative importance of each of these risk components can help focus disease elimination efforts. In Chapter 2, I developed a statistical modelling framework that integrates multiple environmental and socioeconomic data sources to explore how malaria risk is influenced by the combination of the three risk components. Then, using the modelling framework I tested how the combined impact of climate variation and elimination efforts influences the spatiotemporal incidence of malaria, using a timely case study of malaria elimination in a high-risk border region of Ecuador. Whilst mechanistic studies have greatly improved our understanding of mosquito-borne disease transmission dynamics, such as the thermal optima for parasite development (Mordecai *et al.*, 2013), it is important not only to understand these processes empirically, but in context. This thesis has demonstrated how environmental factors, such as climate variation, influence mosquito-borne disease risk alongside socioeconomic factors such as healthcare accessibility and vector control measures. The detection of a strong climate response in Chapter 2, despite successful elimination efforts and low levels of transmission, draws attention to the ongoing risk of malaria resurgence in southern Ecuador with changing environmental conditions. Anthropogenic warming is increasing the environmental suitability of mosquito-borne diseases, including malaria, and risk remains high especially in developing countries (Romanello *et al.*, 2021). This is an important finding that needs to be communicated to policymakers, who must be aware that despite local elimination of malaria in regions vulnerable to climate change and experiencing ongoing migration, disease surveillance needs to be maintained and incorporated into funding for disease control.

In Chapter 2, I revealed that *P. falciparum* malaria is more climate-sensitive than *P. vivax* malaria, a key finding which has previously not been well-explored. Specifically, a 1°C increase in minimum temperatures was associated with a 146% increase in *P. falciparum* incidence, but a smaller 77% increase in *P. vivax*. The differential sensitivity is likely due to the relapsing nature of *P. vivax* infections, which are problematic to predict and infections can remain dormant for multiple months (White, 2011). In addition, minimum temperature was an important driver of malaria risk in southern Ecuador and explained nearly all the seasonal variation in *P. falciparum* malaria incidence, but not *P. vivax*. These findings have important implications for future climate warming in the region, which is likely to have a greater impact on *P. falciparum* malaria. Since different antimalarials are used to target the different parasites (WHO, 2021a), and effectiveness of vector control also varies between the two parasites (Chapter 2), health authorities will need to target interventions during periods of sustained warmer temperatures to optimise control efforts. This has consequences for climate change adaptation as it is clear that current control efforts, such as treatment, will need to be adjusted in the future to target a potential increase in *P. falciparum* malaria, in comparison to *P. vivax.*

Evaluating the effectiveness of disease control measures against the backdrop of environmental influences has previously proven difficult, owing to the lack of accurate data available. By accounting for vector control measures alongside climate variation, I found in Chapter 2 that the measures implemented differentially affected *P. falciparum* and *P. vivax* malaria in southern Ecuador. There was also additional spatial heterogeneity in the effectiveness of the control measures. Space spraying contributed the largest reduction in *P. vivax* incidence (19% with every household sprayed), whilst for *P. falciparum* IRS caused the largest reduction, although it was a modest 8%. A demonstration of the effectiveness of disease control measures in relation to other driving factors can be used as a basis for targeting future local disease control measures in southern Ecuador. Local policymakers can use this information to decide on optimal strategies for vector control in the area, including which methods such as space spraying, should be deployed. This is now becoming ever more important as malaria cases are increasing across the country and recent elimination targets have not been met (WHO, 2020).

The differential impact of vector control measures on *P. falciparum* and *P. vivax* malaria identified, is also important to consider given the shifting epidemiological patterns of malaria in southern Ecuador. During the elimination phase of the study (2001-2018), *P. falciparum* was reduced more than *P. vivax*, and more so in rural compared to urban areas. As urban development continues to grow in Ecuador, it is therefore likely that *P. vivax* malaria, a complex disease governed less by environmental conditions, will become more dominant. Traditionally, malaria transmission is higher in rural areas (Hay *et al.*, 2005), but findings from Chapter 2 suggest that once vector control is implemented, urban malaria could become more problematic and difficult to eliminate. This has implications for policymakers when developing elimination programs targeted in urban areas, which may require a different suite of vector control approaches, such as the targeting of urban aquatic mosquito habitats. Since 2003, malaria transmission in sub-Saharan African cities has been increasing and mosquito vectors have adapted to the diversity of aquatic habitats provided in urban landscapes (Doumbe-Belisse *et al.*, 2021). In addition, high population mobility in urban and suburban areas can facilitate the expansion of malaria transmission, posing further challenges for malaria control in urban areas (Johansen *et al.*, 2020; Salla *et al.*, 2020). Shifting urban and rural patterns of malaria transmission highlight the need for dynamic vector control programmes that keep pace with and adapt alongside changing disease epidemiology.

In Chapter 2, I assessed the relative importance of climate variation against the backdrop of socioeconomic influences such as elimination efforts, which determine disease exposure. However, land use and environmental degradation also modify mosquito-disease exposure. In Chapter 3, I used a timely case study of malaria-re-emergence in Venezuela to demonstrate that mining was an influential factor driving the spatial patterns of malaria incidence in Bolívar, an important malaria foci in the country. Previous research had hypothesised that mining activity was facilitating the rapid resurgence of malaria across Venezuela (Grillet *et al.*, 2021), but this had not been quantified. Evidence has also linked mining activity to rising malaria cases in other Latin American countries, although the majority of this evidence was based on using proxies for mining activity, such as gold prices (De Salazar *et al.*, 2021). Building on this evidence, I explicitly quantify the malaria variation that is explained by mining activity, which is an important step forward. Using remotely sensed locations of mining sites, I showed that mining accounted for up to 51% of the spatial variation in *P. falciparum* incidence in the San Isidro parish hotspot. In contrast, less (40%) spatial variation in *P. vivax* incidence could be explained by mining. The overall picture was similar across Bolívar. Including mining activity in the model reduced the unexplained spatial variation in *P. falciparum* malaria in nearly half of parishes in Bolívar, and for *P. vivax* in 43% of parishes. These results support the findings of Chapter 2, where I demonstrated a stronger sensitivity of *P. falciparum* malaria to environmental conditions, specifically minimum temperatures. Under conditions of land-use change, environmental degradation such as gold mining, creates suitable habitats for the proliferation of malaria vectors (Moreno *et al.*, 2007; Vittor *et al.*, 2009). In addition, warmer temperatures facilitate increased mosquito and parasite development and enhance malaria transmission (Bayoh and Lindsay, 2003; Ohm *et al.*, 2018). Further support for the differential environmental sensitivity of *P. falciparum* and *P. vivax* highlights the need to design suitable targeted control efforts and incorporate this sensitivity into future predictions of how climatic change may influence malaria distribution both regionally and globally.

P. vivax malaria incidence was positively associated with deforestation in southern Venezuela, whilst no association was found for *P. falciparum* malaria (Chapter 3). The differential impact of deforestation on malaria risk is important to consider in light of findings from Chapter 2, where the effect of control measures on *P. falciparum* and *P. vivax* malaria varied substantially. For instance, if deforestation is unlikely to increase *P. falciparum* malaria in some areas (e.g. in Bolívar state, Chapter 3) then policymakers should preferentially target interventions at *P. vivax*, conserving precious public health resources. The relationship between deforestation and malaria has proved contentious in previous research and can be highly context-dependent (Tucker Lima *et al.*, 2017; Burkett-Cadena and Vittor, 2018). As detailed in Chapter 1, initial stages of deforestation in agricultural frontiers result in rapid ecological changes that favour proliferation of anopheline vectors such as *An. darlingi,* a vector of both *P. falciparum* and *P. vivax* malaria parasites (Laporta *et al.*, 2021). However, as time progresses deforestation frontiers become more developed and malaria risk is greatly reduced. Bolívar state, in which the study in Chapter 3 was conducted is not a typical agricultural frontier region. Instead, the majority of deforestation is driven by small-scale artisanal mining and so the socioeconomic development that typifies frontier regions does not occur. The detection of an association between deforestation and increased *P. vivax* malaria in Bolívar could be explained by inadequate access to treatment, and high population mobility and exposure, which allows for sustained circulation of *P. vivax* malaria parasites.

An increasing number of studies are beginning to account for the spatiotemporal complexities in the deforestation-malaria relationship. For example, a recent study in Laos demonstrated a positive association between malaria and deforestation, which was only evident in the early years of deforestation (1-3 years) and in deforested areas that were further away from villages (Rerolle *et al.*, 2021). In Chapter 5, I was able to detect a positive association between *An. darlingi* abundance and recent deforestation (in the last five years) adding further evidence to support the dynamics of malaria risk in deforested landscapes. This suggests that increases in *P. vivax* malaria with deforestation in southern Venezuela (Chapter 3) may be facilitated by rises in *An. darlingi* abundance. Despite this recent evidence, accounting for complex socioecological processes in the deforestation-malaria relationship remains problematic and can be a hindrance to developing effective disease control efforts at deforestation frontiers.

Understanding how components of global environmental change interact with each other to determine overall mosquito-borne disease risk and identifying those most vulnerable to global environmental change are other challenges addressed in this thesis. Interacting effects are important to consider as more regions of the world are compounded by the combined impacts of climatic change and land-use alterations. By combining Earth observations of climate variables and land-use change, I provided evidence that environmental degradation can modify the climate-malaria relationship (Chapter 3). This is an important new insight in climate-disease research, which had previously received little attention. In high mining areas of southern Venezuela, the influence of temperature on malaria incidence was exacerbated, with warmer temperatures (up to 26.5°C for *P. falciparum* and 28.1°C for *P. vivax*) associated with elevated malaria incidence. This contrasted with the minimal effect of temperature on malaria in low mining areas. Based on these results, mining communities remain highly vulnerable to the compounding health effects of environmental degradation and warming temperatures. Therefore, health authorities should target malaria intervention efforts preferentially in these areas, as they are more at risk of climate-induced malaria surges. These findings also add support to arguments for conserving the environment to protect human health. Further, these results have implications for understanding the complexities of global environmental change, principally how components can interact to determine overall disease risk and how such complexities can be accounted for in predictive models.

The malaria situation in Venezuela shows little sign of abating and is a major threat to elimination in the Latin American region (Daniels, 2018; WHO, 2020). Findings of Chapter 3, principally how malaria can rapidly re-emerge in a country that had previously achieved elimination throughout much of its territory (Gabaldon, 1983), highlight the vulnerability of regions with high levels of political instability. Even if local elimination is achieved and transmission rates remain low, a combination of environmental threats such as gold mining and climate variation can work together to provoke a surge in mosquito-borne diseases. Serious lessons can be learned here, as other countries in Latin America approach malaria elimination. The synergistic effects of climate warming and anthropogenic environmental degradation pose a substantial threat for mosquito borne disease risk in the Latin American region.

A major obstacle when accounting for multiple components of the disease risk framework to investigate global environmental change and mosquito-borne disease (Chapters 2-3), is the integration of relevant data. The climate data products used to inform the underlying hazard risk component in Chapters 2-3 were selected based on their fine-scale spatial resolutions and temporal coverage, which matched the malaria case data. However, it was not clear whether choice of product would affect the estimated climate-disease association. In Chapter 4, I discussed the issue of data product choice with reference to climate services for health. I provided an assessment of the challenges associated with integrating climate data products into health applications, such as climate-sensitive disease models. These challenges include issues of matching health and climate data across differing spatial scales and selecting the most appropriate data product despite such wide availability and accessibility. In addition, ensuring remotely sensed climate observations are matched carefully to ground truth data such as that obtained from local meteorological stations before their use, is also important.

By comparing the climate data products used in Chapters 2-3 alongside three other products, I revealed important differences in temperature and precipitation trends of the global products, compared to local meteorological station observations (Chapter 4). For instance, temperatures from the CRU and ERA5-Land global datasets were up to 5°C cooler than the local meteorological station observations. In addition, up to 40 mm more rainfall per day was observed in the ERA5-Land dataset, compared to the meteorological station observations. These findings highlight that in some instances, global climate data products may not be able to adequately capture local climate conditions on the ground and therefore may not be the most appropriate data source to use in climate-sensitive disease models.

In Chapter 4, I also demonstrated that five different climate data products applied to the same disease models (dengue and malaria) resulted in measurable differences in the climate-disease association. Previous studies using global sources of climate data in health impact models have not considered the impact of data product choice, despite the wide range of products that are available. In temporal models of dengue and malaria in southern Ecuador using different climate data as inputs, model parameter estimates varied substantially from each other and from local station data, translating into substantial differences in disease risk. In the dengue model informed by local meteorological station observations, a 68% increase in dengue was linked to 1°C rise in temperature. In contrast, the model informed by CRU climate data showed only a 40% increase in dengue cases. In the malaria models, the parameter estimates diverged even further, with some climate-informed models demonstrating increased malaria risk with temperature (ERA5-Land dataset and local station observations), whilst others showed no relationship (TerraClimate, CRU and CHELSA datasets). The rainfall estimates for the malaria models also diverged, with the CRU model showing a positive relationship, whilst the local meteorological observations, CHELSA and ERA5-land models showed that increased rainfall would lead to a reduction in malaria cases. The results of this chapter highlight the challenges associated with incorporating knowledge across disparate disciplines in Planetary Health, such as climate and public health. These findings also have considerable implications for how data products are used in climate-sensitive disease modelling, including an appreciation of how health outcomes can be influenced by underlying data. As described in the recommendations in Chapter 4, future climate-sensitive disease models that are developed should firstly probe model sensitivity with different data products to ensure downstream health outcomes are not heavily influenced by product choice. Data challenges however can be overcome through improved communication and co-development of the climate service, and ensuring transparency is maintained with policymakers.

The findings of Chapter 4, principally the variation in model results due to different data products highlights a wider challenge in epidemiological research; translating and communicating model output to policy. Communicating model results is important given that the way in which model results are communicated to policymakers can influence how resulting control measures are designed and implemented in practice (Leach and Scoones, 2013). In Chapter 4 for example, the relationship between malaria risk and rainfall diverged depending on the choice of model, which would also influence how and when interventions would be deployed in rainy conditions. If the diverging results of all models were presented to policymakers this would however give a confusing message to policymakers, who may lose trust in these models as tools to provide evidence for policymaking. Here, it is important that when translating models into policy, the narrative of how the model output will be used, such as for identifying environmental predictors of disease risk, should be clear. In addition, modelling tools should be shaped alongside policymakers from their early development, to ensure they have not only impact but are truly useful for decision making.

In Chapters 2-3, I used climate variation to account for the underlying hazard component of the risk framework (the mosquito vector). However, the mosquito vectors are not only influenced by climate variation but also by land-use change. To address this gap, I drew on ecological knowledge in Chapter 5 to understand how mosquito vectors of diseases investigated in Chapters 2-4 are affected by anthropogenic land-use change. By compiling an extensive dataset of mosquito abundance records in Latin America and the Caribbean, I demonstrated that both *Aedes* and *Anopheles* species richness is substantially reduced in anthropogenic environments. In this study, I combined records across 605 sites whilst accounting for between-study differences and sampling methods. I demonstrated consistent regional responses of mosquito biodiversity to land-use change and taxonomic differences in the responses. Despite the reduction in overall biodiversity with anthropogenic disturbance, key malaria and arboviral vectors responded positively, including the mosquito vectors *Ae. aegypti*, *Ae. albopictus* and *An. albitarsis*. These results suggest that human disturbance, whilst facilitating an overall reduction in biodiversity, can favour the emergence of opportunistic and synanthropic disease vectors, highlighting the vulnerability of populations living in heavily modified environments. This knowledge complements findings from previous chapters, providing evidence on how mosquito vectors of dengue and malaria are influenced by anthropogenic land-use changes such as deforestation, in addition to climate variation (Chapters 2-4).

I also showed how a hazard-based approach could further be used to address important questions in mosquito ecology, including how deforestation differentially impacts *Aedes* and *Anopheles* mosquitoes. In Chapter 3, I demonstrated elevated *P. vivax* malaria risk with deforestation, supporting small-scale local studies that have previously demonstrated sensitivities of select mosquito vectors to land-use change, such as *An. darlingi* and deforestation (Barros and Honório, 2015). I also found a positive response of *An. darlingi* to deforestation in Chapter 5, which was in comparison to the minimal response of *Aedes* vectors. Identification of species-specific mosquito responses to anthropogenic land use that are consistent across geographical regions has implications for designing vector control programs in areas undergoing rapid land-use change. Since different mosquito species have different control methods, policymakers can use this information when designing vector control programs by optimising them for species-specific disease threats. High-risk areas include agricultural frontier regions in the Amazon, vulnerable mining communities in Venezuela (Chapter 3) as well as encroached parts of the Atlantic Forest due to expanding human activity. In the remainder of this chapter, I discuss the wider implications and contributions of this thesis to Planetary Health research, key methodological developments and remaining challenges in the field.

6.2. Contributions to malaria research

Since 2000, global malaria incidence rates have declined by 37% and mortality by 60%, primarily due to the scaling up of insecticide-treated nets and indoor residual spraying campaigns (Cibulskis *et al.*, 2016). Since beginning the work for this thesis, substantial advances in malaria control have been achieved, including the recommendation of the ground-breaking RTS,S vaccine for *P. falciparum* malaria in children (WHO, 2021b). Despite great leaps in progress, malaria still remains a significant challenge to public health, exemplified by the fact that half of the world is still at risk (WHO, 2020). The complex nature of *P. vivax* malaria, including the characteristic relapsing infections, concerns of insecticide and antimalarial drug resistance, emergence of peri-urban malaria, as well as weakening of control programmes, still poses a formidable challenge for malaria control (Recht *et al.*, 2017).

The success of malaria control and elimination efforts is underpinned by a thorough understanding of the factors driving transmission. The comparative differences in the climate responses of the two most prevalent malaria parasites, *P. falciparum* and *P. vivax* remains to be fully understood and is only recently being considered in mechanistic models of malaria and climate (Villena *et al.*, 2020). In addition, the two parasites are frequently combined in spatiotemporal models, which does not allow for the detection of comparative climate responses (Hurtado *et al.*, 2018; Rodó *et al.*, 2021). I addressed this gap in Chapter 2, where I showed that modelling *P. falciparum* and *P. vivax* separately, enables the detection of a differential sensitivity to climate conditions. This is an important development in the understanding of malaria that has been previously little explored and will be useful to inform future predictive models of disease risk, as well as vector control measures. By identifying key differences in the climatic responses of *P. falciparum* and *P. vivax* malaria I hope to enhance understanding and facilitate incorporation of these differences into targeted disease control programmes.

In Chapter 5, I also provide a meaningful contribution to malaria research, by identifying differing taxonomic responses of malaria vectors to anthropogenic land-use change, specifically mosquito abundance and species richness. Prior to this thesis, much of the work on malaria-environment relationships had focused on identifying climatic responses. For example, global predictive models of how malaria risk is likely to change under future climate change scenarios have identified that highland areas are prone to increases in outbreak frequency (Caminade *et al.*, 2014). Other studies have demonstrated the added value of climate information in explaining the spatiotemporal patterns of malaria, for example in Malawi (Lowe *et al.*, 2013). However, land cover and land use patterns significantly influence the distribution of malaria vectors, which is especially important to consider given the synergistic effects of land use on climate-malaria relationships (Chapter 3).

To enhance understanding of how factors other than climate influence disease risk, I provided an investigative framework in Chapter 5 to address this. I demonstrated that the most important malaria vector in the Amazon region, *An. darlingi* (Sinka *et al.*, 2010), shows a consistent increase in abundance with deforestation across Latin America. This supports the findings of Chapter 3, where I showed that deforestation was associated with increased *P. vivax* malaria in a region where *An. darlingi* is dominant, providing support to local-scale studies that have demonstrated increased abundance with deforestation (Vittor *et al.*, 2006, 2009). I also showed in Chapter 5 that other secondary malaria vectors, such as *An. albitarsis* increased in abundance in managed landscapes, which has implications for designing sustainable land management practices in malaria-endemic areas where this vector is present. These results provide an important way forward, signalling the relative importance of land use in determining current and future risk of malaria.

6.3. Methodological developments

Hierarchical mixed effects models, estimated in a Bayesian framework, enable underlying sources of uncertainty to be accounted for (Lowe *et al.*, 2012, 2014). For example, parameter uncertainty can be accounted for by assigning prior distributions to the parameters (Blangiardo *et al.*, 2013; Lawson, 2021). These models also allow additional unknown sources of variation, such as changing population immunity, to be accounted for in spatiotemporal disease models (Lowe *et al.*, 2018). In Chapters 2 and 3, I developed statistical modelling frameworks to integrate multiple sources of data (climate, land use and vector control measures) to examine the spatiotemporal variation in malaria incidence in Ecuador and Venezuela. By comparing the seasonal random effects of a model with and without minimum temperature, I found that temperature was influential in driving the seasonality of *P. falciparum* malaria incidence in Ecuador (Chapter 2). This approach improves upon quantifying directional associations between climate and malaria, allowing for the explicit attribution of temperature to seasonal malaria variation. By using the model random effects structure further, I was able to explore other sources of unexplained heterogeneity not accounted for in the model of malaria incidence in Ecuador. This proved useful for identifying possible disease risk determinants, including when strong El Niño events may have elevated malaria risk. Exploring additional sources of variability in this way will also prove useful when developing risk estimates with stakeholders and public health experts. Local on-the-ground knowledge can be combined with peaks in disease variability uncovered from model random effects and used as a tool to identify additional sources of variation in disease risk.

The use of the random effects model structure was further developed in Chapter 3. I performed a sensitivity analysis of the model random effects to assess the impact of mining on the spatial variation in malaria incidence. This enabled the identification of specific areas in southern Venezuela where the impact of mining on malaria was most influential, such as disease hotspots, in addition to areas where malaria incidence was likely not driven by factors in the model. A similar approach could be applied in other instances, where the relative influence of an environmental factor on disease risk is unknown. Probing the random effects of spatiotemporal models in this way, to identify sources of variation will be a useful tool for assessing future impacts of environmental change on mosquito-borne disease.

Earth observations, such as the remotely sensed mining sites used to inform models of malaria re-emergence in Chapter 3, represent important resources for accelerating research in Planetary Health. In this thesis, I showed how multiple sources of Earth observations could be integrated to gather a more coherent picture of the environmental, socioeconomic and ecological processes that determine disease risk. Remotely sensed observations provide a direct advantage over using proxy variables, such as gold prices (De Salazar *et al.*, 2021), as the risk component can be directly accounted for. Climate observations have been employed on a number of occasions to investigate climate-driven disease patterns (Ebhuoma and Gebreslasie, 2016) and land use (Rubio-Palis *et al.*, 2013), although are rarely used together. Remotely sensed climate data are also used to inform disease early warning systems. For example, temperature, rainfall and humidity observations were recently used to inform seasonal probabilistic dengue forecasts for Vietnam (Colón-González, Soares Bastos, *et al.*, 2021). Disease forecasts that rely on this climate data must be well-matched to local climate conditions in order to provide reliable and timely information for public health decision-making.

Whilst Earth observations of climate variables are widely available, integrating data products into climate-disease models is not straightforward (Chapter 4). From the outset of this thesis, it was challenging to select the most appropriate climate data product for analyses (Chapters 2-3), with no assessment of whether choosing a certain product would have an impact on the overall health outcome. By addressing this important methodological gap in Chapter 4, I provide an enhanced understanding of how and why health outcomes might differ when using different data products. By doing so I hope to guide future climate-disease research, ensuring data products are not selected solely on their availability. Finally, in Chapter 5 I developed an approach to identify consistent mosquito responses to anthropogenic land-use change, demonstrating important proof-of-concept that can be applied to other regions, diseases and vectors. This approach has already proved useful for identifying global responses of terrestrial biodiversity to land use (Newbold *et al.*, 2015; Millard *et al.*, 2021), although has not yet been applied to understand disease risk in changing landscapes. Applying this approach to mosquito vectors can help solidify findings from local-scale studies and identify generalised vector responses relevant in multiple disease control settings.

6.4. Deciphering climate change and vector-borne disease research for policymakers

Attributing the effects of climate variation and change on vector-borne disease is vital for informing impact assessments. However, while reviewing the literature for this research, it became clear that the way in which variation in vector-borne diseases is attributed to climate variation and change varies greatly. For example, in Chapter 1.5 I described how the impact of climate variation on vector-borne disease risk can be quantified by attributing the variation explained by a climate variable, or by linking an increase in disease risk with a unit increase in a climate variable. In this discussion piece, I show that a major limitation in understanding the effects of climate variation and change on vector-borne disease risk, is how these effects are quantified. I draw attention to this issue and identify best-practice approaches for quantifying the impact of climate variation and change on vector-borne diseases for policy-relevant impact assessments. This will enable climate-disease associations, such as those reported in Chapters 2-4 to be more effectively incorporated in policy-relevant material. This discussion piece is extended to encompass other vector-borne diseases as well as mosquito-borne diseases, which is in line with policy-relevant impact assessments including the work of the Intergovernmental Panel on Climate Change (IPCC) Working Group II (WGII).

Quantifying the impacts of historical climate change on vector-borne disease is vital for assessing the health implications of a warmer world. A unified approach, whereby other influencing and interacting factors, such as land-use change and socioeconomic pressures are considered, is needed to effectively communicate the impacts of climate variation and change on vector-borne diseases to policymakers. This will ensure a diverse range of research informs evidence-based policies to build resilience to climate change. In particular, there is also an increasing need to consider individual contexts, whereby influencing factors such as environmental degradation will have a specific localised effect. This will require tailoring climate services to ensure their maximal value in decision making processes. The IPCC Working Group I (WGI) recently warned that unless immediate action is taken to reduce global greenhouse gas emissions, more than 1.5°C warming of the global climate will be inevitable (IPCC, 2021). Already the effects of climate change are rapidly intensifying and they will have widespread and overwhelming consequences for human health and wellbeing (Myers, 2017). Of particular concern is the threat of emerging and re-emerging vector-borne diseases due to global heating and more frequent extreme weather events. Indeed, there is already profound evidence that climate change is altering vector-borne disease transmission, with impacts likely to worsen if current trends in greenhouse gas emissions continue to rise (Romanello *et al.*, 2021).

The WGI recent report has exemplified the importance of effectively communicating the evidence for climate change, including the impacts on human health (IPCC, 2021). Now more than ever, accurate and coherent quantification of both the impacts of short-term weather variations (weather sensitivity) and long-term climate change (attribution of observed changes to climate change) is needed for evidence-based policies to protect human health and wellbeing. Currently, the lack of consistency in quantifying the weather sensitivity of vector-borne diseases or the contribution of long-term climate change to observed changes in disease occurrence presents an obstacle to effectively integrating climate and vector-borne disease research into policy. Despite ample evidence for the impacts of climate variation and long-term change on vector-borne diseases, making global assessments for the IPCC is challenging, and limited to selected studies with consistent reporting methodologies. Here, I call for improved reporting of the health impacts of climate change to ensure valuable climate change research is not excluded from decision-making. To generate critical understanding of the contribution of climate variation and change to observed changes in vector-borne diseases, robust detection and impact attribution assessments are urgently required.

6.4.1. Communicating uncertainty in impact assessments

The IPCC WGII aims to assess the global consequences and vulnerability of socioeconomic and natural systems to climate change, as well as the historical impacts. This assessment includes quantifying a wide range of observed changes in natural systems due to climate change such as coral bleaching, water availability and crop yields (IPCC, 2014). Impacts on society are often derived from empirical models quantifying observed responses to weather fluctuations. These include impacts on heat-related mortality, malnutrition, social conflict and migration. Empirical models provide an opportunity to attribute observed changes in human systems to climate change, or other socioeconomic drivers such as population fluctuations, economic development and disease control measures. It is important to adequately distinguish the attribution of observed changes in vector-borne diseases to long-term climate change from the detection of responses to short-term (e.g. monthly or annual) weather fluctuations. For example, evidence demonstrating that variations in weather conditions induce interannual variation in vector-borne disease incidence does not imply the attribution of observed changes or fluctuations to long-term climate change.

The IPCC Fifth Assessment Report (AR5) defines impact attribution as addressing the magnitude of the contribution of long-term climate change to an observed change in a system (Cramer *et al.*, 2014), in this case vector-borne diseases. In addition, “detection of impacts” of climate change is defined as addressing the question of whether a natural or human system is changing beyond a specified baseline that characterises its behaviour in the absence of climate change (Stone *et al.*, 2013). The ‘no climate change’ baseline can be stationary or vary according to changes in the drivers of vector-borne diseases other than climate. In this way, the IPCC has developed a framework to enable the production of a comprehensive assessment of the impacts of climate change, with consistent messaging. However, in practice the detection of impacts and impact attribution can be challenging given the difficulty in isolating the impacts of climate change amongst from confounding factors, including disease control measures and socioeconomic development.

The IPCC framework enables global comparisons to be made and increases the effectiveness of the assessment for policymakers to use as the basis for sound decision-making. Communicating uncertainty in the findings by reporting quantitative estimates, reviewing and evaluating the evidence and considering all plausible sources of uncertainty, is a key component. To do this, calibrated language is used to synthesise judgements about the confidence of a finding as a measure of the evidence, i.e., quality of individual studies and the level of agreement across the literature. For example, if multiple high-quality studies provide evidence of an increasing trend in malaria cases with warming temperatures, the assessment would be made with robust evidence and agreement across different studies i.e., high confidence. In contrast, if only a single study provided evidence attributing observed increases in malaria cases to warming trends, the confidence level would be very low. This consistent messaging allows for evidence to be summarised and communicated effectively to policymakers. However, supporting evidence may fail to conform with this consistent messaging. Climate and vector-borne disease research may provide a valuable impact attribution, but in a format incompatible with IPCC assessments. Consequently, pertinent scientific research risks being excluded, resulting in low confidence assessments.

6.4.2. Quantifying observed impacts of climate variation and change on vector-borne diseases

The climate-vector-borne disease literature is vast and constantly expanding. Despite advances in our understanding of climate and disease relationships at the local level, the diversity with which climate-disease relationships are reported has created a barrier to integrating empirical research into policy-informative material, such as IPCC assessment reports. The IPCC framework for impact attribution requires quantitative evidence on the links between long-term climate change and observed trends or strength of disturbances of a vector-borne disease. The framework also relies on evidence quantifying the variation in vector-borne diseases that can be explained by weather fluctuations ('weather sensitivity') as a first step to actual impact attribution. Here, I summarise approaches used to quantify the impact of short-term climate variation and long-term change on vector-borne diseases (Table 6.1). The myriad ways that researchers quantify the impact of climate on disease risk and communicate their findings makes it challenging to synthesise research into global impact assessments.

To compare how the impacts of climate on disease risk are quantified, representative case studies of climate-disease relationships were selected based on how the impacts were quantified, for example by quantifying variation explained or change in the distribution of a disease vector (Table 6.1). Examples of other common vector-borne diseases, such as Lyme disease and West Nile, were also selected to represent the diversity in the approaches that are used in impact assessments, such as that for the IPCC. All studies in Table 6.1 would qualify for inclusion as evidence for climate-impacts on disease risk in the IPCC WGII assessment report.

Several studies combine multiple data sources, such as Earth observations from satellites and case data into spatiotemporal modelling frameworks to identify the sensitivity in vector-borne disease burden to climate conditions (Lowe *et al.*, 2021). Other studies use indirect measures, such as vector infestation and oviposition (da Cruz Ferreira *et al.*, 2017; German *et al.*, 2018). Evidence directly attributing changes in vector-borne disease risk to long-term trends in climate is more challenging and difficult to quantify, since this relies on long-term observations. As a result, there is limited evidence explicitly linking long-term warming trends or climate variability associated with climate change, to changes in vector-borne disease risk. However, some studies have been able to explicitly link warming trends to disease risk (Table 6.1). For example, resurgent malaria epidemics from the 1970s to the 1990s, in the east African highlands have been linked to warming temperature trends (e.g. Pascual *et al.*, 2006; Chaves *et al.*, 2012). Other studies have quantified the impact of climate change on vector-borne disease risk by linking warming trends to alterations in vector abundance, distribution and range. For example, increasing climate suitability is linked to the northward range expansion of the Lyme disease vector *Ixodes scapularis* in Canada (Clow *et al.*, 2017). Other studies have assessed climate suitability for other vector-borne diseases, such as dengue. For example, between 1950-2020 the global climate suitability for dengue transmission has increased by 13% (Romanello *et al.*, 2021).

Table 6.1. Summary of attributions of long-term climate trends and weather sensitivity to vector-borne disease risk. Selected studies providing evidence of observed changes in vector-borne diseases due to climate change, attributing long-term trends in vector-borne disease risk and sensitivity to climate change.

Attribution	**Method**	**Vector-borne disease**	**Study area**	**Quantification**	**Reference**
Long-term climate trends	Time-series analysis	Malaria	African highlands	Warming trends between 1950-2002 were associated with increased incidence	Pascual *et al.*, 2006
	Generalised additive model	Dengue	South and Southeast Asia	Outbreak risk peaks at the highest monthly temperatures of 33.5°C and due to climate change, these high monthly temperatures now occur in previously colder areas	Servadio *et al.*, 2018
	Mixed multivariable logistic regression model	Lyme disease	Canada	The *Ixodes* tick vector has expanded its range northward	Clow *et al.*, 2017
	Spatial analysis	Malaria	Global	Between 2010-2019 transmission suitability in highland areas was 39% higher compared to the 1950s baseline	Romanello *et al.*, 2021
Weather sensitivity	Spatiotemporal model	Dengue	Thailand	8% of interannual variation in relative risk was be explained by temperature and precipitation	Lowe *et al.*, 2016
	Spatiotemporal model	Malaria	Ecuador	1°C increase in minimum temperature was associated with a 146% rise in *P. falciparum* malaria incidence	Fletcher *et al.*, 2020 (Chapter 2)
	Case-crossover study	West Nile	USA	5°C increase in maximum weekly temperatures was associated with 32-50% higher incidence	Soverow *et al.*, 2009

Attributing variation in vector-borne diseases to short-term weather fluctuations (e.g. daily, monthly or annual variation) is more common, although highly varied (Table 6.1). I identified several studies providing evidence attributing observed variation in vector-borne diseases to weather variations in an intuitive way for policymakers. For example, the variation explained by particular climate variables can be quantified (e.g. Lowe *et al.*, 2016) or the percentage change in disease incidence can be linked to a unit change in a climate variable (e.g. Chapter 2). Moreover, I identified studies quantifying the effect of climate variation on other vector-borne disease parameters, such as mosquito oviposition and infestation (da Cruz Ferreira *et al.*, 2017; German *et al.*, 2018). I recommend communicating the impact of climate variation on vector-borne disease by quantifying the variation explained by a given climate variable, using robust modelling techniques that account for unexplained sources of variation and confounding factors. Alternatively, observed changes in disease risk can be quantified with respect to changes in key climatic variables, such as temperature and rainfall (Table 6.1). Producing quantifications in this way will allow for robust quantitative assessment of the sensitivity of vector-borne disease to weather variations, providing higher confidence impact assessments.

The increased momentum in the engagement of health professionals in climate change has generated valuable research and insights into quantifying the effects of historical climate change on vector-borne diseases. Despite this and given the substantial global variation in the response of vector-borne diseases to climate variation and long-term change, it has been challenging to synthesise, compare and attribute the effects of climate change on vector-borne diseases at the global and regional scale. Inconsistent reporting practices obstruct the inclusion of valuable policy-relevant research into important global assessments. I hope that by identifying these inconsistencies and highlighting the types of research that are included in the assessments of observed impacts, will raise awareness in the health and climate science community of how to make research relevant and useful for policymakers.

6.5. Remaining challenges and future research directions

Achieving a greater understanding of the impacts of global environmental change on mosquito-borne diseases that will be useful for policymakers, requires a careful considered approach to leveraging data, knowledge and disciplines. This presents several challenges. In particular, there is a need to account for socioeconomic dynamics such as population mobility and connectivity, which influence spatiotemporal disease risk but are difficult to quantify (Prothero, 1977; Stoddard *et al.*, 2009; Lee *et al.*, 2021). In Chapter 2, due to the study location along a migratory route in southern Ecuador, it was highly likely that malaria cases were driven by human mobility, in addition to the other socioeconomic and environmental factors included in the model. However, no detailed data were available to capture the effect of population mobility on malaria incidence during the study period. In Chapter 3, I accounted for the environmental disturbance effect of mining activity, which is expected to affect malaria risk through habitat-mediated alterations to mosquito vector abundance (Moreno *et al.*, 2007; Jorge E. Moreno *et al.*, 2009). Nonetheless, another important component is the altered human behaviour and dynamic population fluxes that are typically associated with small-scale mining communities. Accounting for human mobility patterns is important because they determine the exposure to mosquito vectors. In addition, understanding how underlying population mobility and connectivity impacts disease risk is important for improving surveillance programs and the strategic planning of elimination strategies (Pindolia *et al.*, 2012).

Mining populations such as those in Chapter 3, are incredibly mobile and are often vulnerable populations with limited access to healthcare (Ache *et al.*, 2002; Douine *et al.*, 2020). It is therefore likely that this human movement has a considerable impact on resulting malaria transmission patterns, although is poorly understood. Accounting for changing socioeconomic dynamics, including population mobility is a particular challenge in Planetary Health research. The rising availability of human mobility data provides a valuable resource for evaluating how human population movements influence disease risk (Tizzoni *et al.*, 2014). Moreover, recent applications of novel data streams, such as Google mobility data (Cot *et al.*, 2021), alongside the incorporation of mobile phone data to improve dengue forecasts (Kiang *et al.*, 2021) and to identify malaria source-sink dynamics (Wesolowski *et al.*, 2012) is contributing solutions to address this challenge. However, integration and application of these data into disease risk analysis is limited and improvements in estimating population mobility remain to be made.

Since many epidemiological and ecological processes, such as deforestation and climate-land use interactions, operate dynamically over multiple spatiotemporal scales, it is also challenging to accurately and reliably account for these processes. Applications of new technologies such as drones can help address this data gap and gather fine-scale information to better understand these processes. In particular, the amount of forest cover remaining is an important determinant of the deforestation-malaria relationship (Laporta *et al.*, 2021), which I was unable to account for in Chapter 3, owing to the lack of fine-scale data. Leveraging fine-scale point data in combination with new technologies may allow for the further teasing out of the mechanistic relationships between climate variation, land use and malaria incidence.

In Chapter 5, I found a high level of uncertainty in the response of the main Amazonian malaria vector *An. darlingi* to secondary vegetation. This is likely due to the habitat preferences of *An. darlingi* that were not captured in the aggregated land use categories in the study. Another important step forward is to identify specific mosquito bionomic traits, such as feeding and resting behaviours, which facilitate mosquito vector responses to land-use change. Answering this question could be tackled by combining mosquito abundance data across land-use types with other regional databases of mosquito bionomic information (e.g. Massey *et al.*, 2016). Doing so would enable a more comprehensive, mechanistic understanding of how mosquito vectors are favoured in human-altered environments, and further inform land use management strategies.

An understanding of how mosquito-borne disease risk varies across fine-scale urban gradients also remains to be disentangled. In the models of land use and mosquito biodiversity in Chapter 5, a broad urban category was defined, which included sites ranging from urban parks, dense cities and informal settlements. Urban environments are extremely heterogeneous and include highly developed areas as well as urban fringes and peri-urban settlements with limited infrastructure, such as piped water and sewage systems. Therefore, these areas often have higher rates of mosquito-borne diseases due to lack of water supply, sanitation and adequate housing (Delmelle *et al.*, 2016; Espinosa *et al.*, 2016). The urban category in Chapter 5 likely does not allow for variation across the urban landscape. In Chapter 5, I demonstrated overall decreased mosquito richness, with some synanthropic mosquitoes such as *Ae. aegypti* and *Ae. albopictus* increasing in abundance. However, it is probable that mosquito abundance and richness varies across gradients of urbanisation. Indeed, *Ae. albopictus* has been found to be more common in rural areas (Tsuda *et al.*, 2006), which have distinctive ecological habitats compared to dense urban conglomerates. Combining the mosquito biodiversity dataset with high resolution urban footprint data (e.g. Liu *et al.*, 2020) may enable the teasing out of finer scale graded responses. Identifying species that are tolerant to higher or lower levels of urbanisation would be more useful at a policy-relevant scale, i.e., within cities and between neighbourhoods. The high level of uncertainty and lack of data representation for some land use categories in Chapter 5 also highlights the need for greater data coverage and sampling in these landscapes, such as plantations, managed forests, and pasture.

Predictions on how mosquito distribution and disease risk are likely to change under future warming conditions is central to informing adaptation capacities and mitigation policies. Typically, predictions are based on climate- and population-driven models of risk. For example, recent projections for how malaria and dengue suitability will change, estimate an additional 4.7 billion people will be at risk of these two diseases by 2070 if no concerted action is taken to limit carbon emissions (Colón-González, Sewe, *et al.*, 2021). In Chapter 3, I showed that warmer temperatures were associated with increased malaria risk but only in areas that were environmentally degraded by mining activity. This finding has important implications for informing prediction models and identifying areas that face compounding disease risk from climate variation and land-use change. The interaction between climate variation and land use on mosquito-borne disease could be considered in a model which combines predictions of future land use under a combination of Shared Socioeconomic Pathways (SSPs) and Representative Concentration Pathways (RCP) (Chen *et al.*, 2020) to understand not only the impact of climate change but also future land use.

6.6. Concluding remarks

Concrete change to combat the negative impacts of global environmental change relies on a fundamental understanding of how our activities are affecting our health. Enhanced understanding requires the harnessing of novel data sources and technologies, as well as enriched communication and knowledge exchange across multiple environmental and health disciplines. Whilst the research presented in this thesis represents a snapshot of the vast Planetary Health literature, it contributes crucial knowledge that accelerates understanding of how global environmental change impacts mosquito-borne diseases. In addition, these findings also provide important insight into how disease control programmes should be adapted with ongoing climate change, for example by considering an increase of *P. falciparum* with warming temperatures. By incorporating concepts from climate, health and ecological disciplines into distinctive case studies of mosquito-borne diseases in Latin America and the Caribbean, I enhance understanding of the impacts of environmental change, by considering multiple factors including climate variation, land-use change and socioeconomics. This thesis contributes not only a greater understanding of how multiple environmental and social processes interact to determine mosquito-borne disease risk in changing landscapes (Chapters 2-3), but also identifies practical considerations in Planetary Health research (Chapter 4) and integrates knowledge from multiple disciplines (Chapter 5). I show how climate variation jointly influences disease risk relative to the impact of elimination efforts (Chapter 2) and how the impact of climate on disease risk is amplified in environmentally degraded areas (Chapter 3). I additionally show that data product choice used to inform climate-disease models influences the associations between climate hazards and disease risk (Chapter 4). Finally, to address the lack of ecological information in epidemiology and health research I demonstrate diverging species-specific responses of mosquito vectors to land-use change (Chapter 5). I also highlight how climate-disease research should be communicated intuitively for integration into policy-relevant impact assessments. This thesis contributes to the Planetary Health and infectious disease knowledge base, providing sound evidence to help policymakers design effective interventions to build climate and environmental resilience to mosquito-borne disease threats.

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Appendices

Appendix I – Understanding the combined impact of climate variation and elimination efforts on malaria incidence in a high-risk border region of Ecuador

This appendix provides supplementary figures, tables and text for Chapter 2.

Text S2.1. Zero-inflated negative binomial models
Text S2.2. Prior distribution specifications
Text S2.3. Malaria vector control measures in El Oro 2001-2015.

Figure S2.1. Model posterior distributions with and without intervention information for *P. falciparum* and *P. vivax* malaria in El Oro 2001-2015.
Figure S2.2. Urbanised areas in El Oro province, 1990-2018.
Figure S2.3. Annual parasite incidence (API) in El Oro 1990-2015.
Figure S2.4. Rural and urban malaria in El Oro 1990-2018.
Figure S2.5. Seasonality of malaria incidence in El Oro.
Figure S2.6. Model improvement for climate variables in El Oro 1990-2018.
Figure S2.7. Minimum temperature trends in El Oro 1990-2018.

Table S2.1. Summary of model data sources.
Table S2.2. Parameter estimates and model adequacy for lagged vector control measures in intervention models of malaria incidence in El Oro 2001-2015.
Table S2.3. Parameter estimates and model adequacy for lagged climate variables in linear models of malaria incidence in El Oro 1990-2018.
Table S2.4. Model adequacy for lagged climate variables in non-linear models of malaria incidence in El Oro 1990-2018.
Table S2.5. Parameter estimates for explanatory covariates in full and intervention models of malaria incidence in El Oro 1990-2018.

Table S2.1. Summary of model data sources. Data sources for variables included in spatiotemporal models of malaria incidence in El Oro 1990-2016 and intervention models 2001-2015.

Data	**Inclusion in model**	**Description**	**Temporal resolution**	**Spatial resolution**	**Time period**	**Rationale**	**Source**
Malaria cases	Response	Number of *P. falciparum* and *P. vivax* cases recorded	Monthly	Canton (district)	January 1990-December 2018	-	Ministry of Health
Population	Offset	Population values from national census	Annual	Canton (district)	1990-2018 (2011-2018 were provided as projections. Annual estimates between census years were obtained using linear interpolation)	Controlling for the effects of human population on malaria incidence	Instituto Nacional de Estadística y Censos (INEC)
Poverty	Covariate	Proportion of the population with unmet basic needs	NA	Canton (district)	2010	Level of poverty influences housing quality and sanitation infrastructure and therefore *Anopheles* vector exposure	Instituto Nacional de Estadística y Censos (INEC)
Minimum temperature	Covariate	Average values derived from gridded remotely sensed observations	Monthly	Canton (district)	January 1990-December 2018	Temperature influences the environmental suitability for *Anopheles* vectors, and parasite development	TerraClimate
Precipitation	Covariate	Average values derived from gridded remotely sensed observations	Monthly	Canton (district)	December 2018	Precipitation provides important breeding habitat for *Anopheles* vectors	TerraClimate
Level of urbanisation	Covariate	Proportion (%) of urban land cover, derived from gridded remotely sensed observations	Annual	Canton (district)	1990-2018	Level of urbanisation impacts availability of *Anopheles* vector habitat, which is generally lower in urban areas, and healthcare accessibility (vulnerability)	European Space Agency (ESA) Climate Change Initiative (CCI)
Indoor residual spraying (IRS)	Covariate (intervention model only)	Number of households treated using IRS with insecticides (deltamethrin 5% concentrated suspension, deltamethrin 2.5%, malathion 50%, alphacypermethrin 10% concentrated suspension and betacipermethrin 2.5%)	Monthly	Canton (district)	January 2001-September 2013	Interventions decrease exposure to *Anopheles* vectors	Ministry of Health
Ultra-low-volume (ULV) fumigation	Covariate (intervention model only)	Number of neighbourhoods treated with 96% malathion via fumigation	Monthly	Canton (district)	January 2004-May 2015	Interventions decrease exposure to *Anopheles* vectors	Ministry of Health
Space spraying	Covariate (intervention model only)	Number of households sprayed with 2.5% deltamethrin	Monthly	Canton (district)	January 2004-May 2015	Interventions decrease exposure to *Anopheles* vectors	Ministry of Health

Text S2.1. Zero-inflated negative binomial models

Zero-inflated models have been developed to account for the high occurrence of zeros observed in overdispersed count data. A standard negative binomial model for the malaria case data in El Oro 1990-2018, would assume monthly malaria cases, y_{st} in each canton (s = 1,…14) for each timestep (t = 1,…,348) follow a negative binomial distribution $y_{st} \sim \mathrm{NegBin}(\mu_{st}, \kappa)$, where μ_{st} is the mean number of monthly cases of malaria in each canton, with parameter κ accounting for overdispersion, frequently observed with count data. The zero-inflated negative binomial model assumes that each zero j, has a probability π, to arise from the negative binomial distribution and a probability, 1 - π to arise as a result of a non-zero being undetected (excess zero). The zeros in the data are therefore modelled as a mixture of the negative binomial distribution and the logit distribution (Rue *et al.*, 2009). The distribution of y_{st} can then be written as:

$$Pr\left(y_{st} = j\right) = \begin{Bmatrix} \pi_{\mathrm{i}} + (1 - \pi_{\mathrm{i}})\ \mathrm{NegBin}\left(y_{\mathrm{i}} = 0\right) & \text{when } j = 0 \\ (1 - \pi_{\mathrm{i}})\ \mathrm{NegBin}\ \left(y_{\mathrm{i}}\right) & \text{when } j > 0 \end{Bmatrix}$$

Text S2.2. Prior distribution specifications

Model parameters were estimated in a Bayesian framework using Integrated Nested Laplace Approximation (INLA) and implemented in R-INLA (http://www.r-inla.org/) using R version 3.6.0. Unstructured random effects were included in the model framework to account for unknown and unobserved confounding factors influencing malaria in El Oro, such as healthcare access and population movements. These random effects introduce an extra source of variability into the model that can assist in modelling overdispersion (Lowe *et al.*, 2016). The annual cycle of malaria was accounted for by assigning autocorrelated random effects for each month, m_{t}. The monthly effect was assigned a random walk prior, in which the effect in one month is derived from the effect in the previous month, $m_{\mathrm{t}} - m_{\mathrm{t-1}} \sim \mathrm{N}(0, \sigma^2_{\beta})$, where β is the parameter estimate for each month January-December. Random effects for each year of the study, y_{t} (1990-2018) were assigned exchangeable priors, $y_{\mathrm{t}} \sim \mathrm{N}\ (0, \sigma^2_{y})$. Hyperparameters for the random effects were assigned the default gamma prior on the precisions, the inverse of the variance $\tau = 1/\sigma^2$ (Lowe *et al.*, 2018). The fixed effects in the models were assigned the default prior in R-INLA, $\beta \sim \mathrm{N}(0,1000)$. Non-linear relationships for the climate variables (minimum temperature, precipitation) were introduced using a random walk prior of order 1.

Text S2.3. Malaria vector control measures in El Oro 2001-2015.

Detailed monthly and district-level data of vector control interventions that were implemented across El Oro were provided by the Ecuadorian Ministry of Health for the period 2001-2015. Monthly estimates per canton for three control measures were available. The first measure was for the number of households that were sprayed using indoor residual spraying (IRS) with different insecticides; deltamethrin 5% concentrated suspension, deltamethrin 2.5%, malathion 50%, alphacypermethrin 10% concentrated suspension and betacipermethrin 2.5%. The number of households that were fogged, using a backpack fogger that creates a fog of insecticide to treat both inside and outside the home, for which 2.5% deltamethrin concentrated emulsion was used. Finally, data were available for ultra-low-volume (ULV) fumigation, which is performed by spraying entire neighbourhoods, or blocks using 96% malathion. These interventions were all carried out at different times with varying intensity, up until 2015. It is highly likely that other malaria interventions, such as smaller scale vector control programs, environmental management, insecticide treated net (ITN) distribution were implemented in El Oro during the whole study period (1990-2016), but no detailed data were available. Incorporating unstructured spatiotemporal random effects into the models allows for any additional variation due to unmeasured interventions (Lowe *et al.*, 2018).

As the detailed vector control measure data were only available between 2001-2015, I wanted to determine how influential the inclusion of these data were in the fitted models, i.e. whether they impacted the parameter estimates for the other covariates and model posterior distributions. To do this, I constructed two Bayesian hierarchical mixed effects models, for each malaria parasite, one to take advantage of the whole time series of case data for the period 1990-2018, with the assumption that interannual random effects can be used to account for variation caused by the vector control measures and other unknown and unmeasured factors, such as changes to malaria treatments and diagnostics. This model is referred to as the main model. Another model was formulated for the time period 2001-2015 and included the available data on the vector control measures implemented. This model is referred to as the intervention model. All other explanatory variables and random effects remained the same. I compared the posterior distributions for *P. falciparum* and *P. vivax* malaria incidence between 2001-2015 from the full models for the whole study period, without the vector control information to distributions from the intervention models. There was a greater amount of uncertainty in the model posterior distributions of the intervention models, especially between 2010-2015 and the posterior distributions from the full models were closer to the actual observed incidence (Figure S2.1). To test the inclusion of the limited vector control data further, I also tested if any of the variation in malaria incidence due to the vector control measures could be captured in the random effects structure of the full model. Here, I aimed to assess the extent to which the random effects could account for these variations in the absence of detailed intervention data for a longer time period, or another location without such data.

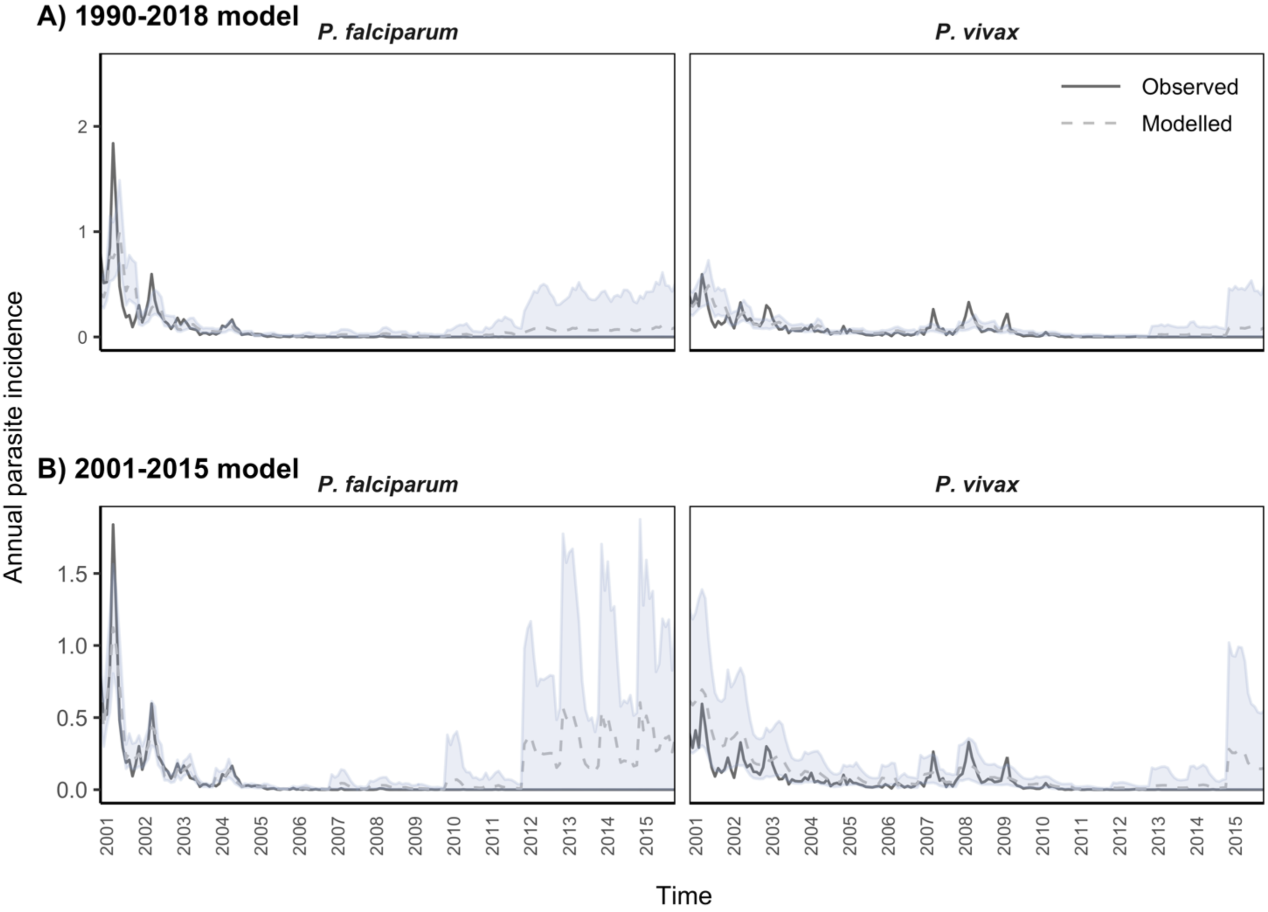


Figure S2.1. Model posterior distributions with and without intervention information for *P. falciparum* and *P. vivax* malaria in El Oro 2001-2015. Observed (grey solid line), posterior mean (blue dashed line) and 95% credible intervals (blue shading) for annual parasite incidence (API) for A) the full model for the whole time period (1990-2018) without intervention data and B) the intervention model for the period 2001-2015 including intervention data.

Table S2.2. Parameter estimates and model adequacy for lagged vector control measures in intervention models of malaria incidence in El Oro 2001-2015. Posterior mean estimates, lower (2.5%) and upper (97.5%) credible intervals (CI), deviance information criterion (DIC) and Watanabe-Akaike information criterion (WAIC) for intervention models of *P. falciparum* and *P. vivax* malaria in El Oro 2001-2015 that include the control measures, indoor residual spraying, ULV fumigation and space spraying, at time lags from 0-3 months. Time lags highlighted in grey are those selected to be used in the final model.

Control measure	Parasite	Lag	Estimate	LCI	UCI	DIC	WAIC
Indoor residual spraying	*P. falciparum*	0	-0.12	-0.33	0.08	3755.73	3760.48
		1	-0.12	-0.32	0.09	3757.23	3761.49
		2	-0.12	-0.33	0.08	3757.61	3761.96
		3	-0.12	-0.32	0.08	3749.58	3754.29
	P. vivax	0	0.03	-43.88	43.89	6013.69	6021.87
		1	0.01	-0.05	0.08	6015.51	6023.68
		2	0.02	-0.04	0.08	6015.30	6023.71
		3	-0.04	-0.10	0.02	6013.86	6021.52
ULV fumigation	*P. falciparum*	0	-0.12	-0.33	0.09	3757.63	3762.34
		1	-0.16	-0.38	0.06	3756.92	3761.56
		2	-0.14	-0.35	0.07	3757.28	3762.78
		3	-0.11	-0.32	0.10	3756.02	3761.52
	P. vivax	0	0.06	-0.09	0.23	6015.16	6024.08
		1	-0.01	-0.19	0.16	6015.83	6024.96
		2	-0.09	-0.23	0.05	6013.72	6022.63
		3	-0.20	-0.38	-0.01	6011.34	6019.63
Space spraying	*P. falciparum*	0	0.03	-0.61	0.66	3757.70	3762.37
		1	-0.06	-0.72	0.57	3756.38	3758.43
		2	-0.10	-0.76	0.54	3756.07	3757.18
		3	-0.01	-0.66	0.62	3758.32	3760.46
	P. vivax	0	-0.09	-0.17	0.00	6015.43	6024.24
		1	-0.15	-0.25	-0.05	6012.22	6020.17
		2	-0.11	-0.19	-0.02	6014.39	6022.65
		3	-0.17	-0.28	-0.06	6010.41	6018.35

Table S2.3. Parameter estimates and model adequacy for lagged climate variables in linear models of malaria incidence in El Oro 1990-2018. Posterior mean estimates, lower (2.5%) and upper (97.5%) credible intervals (CI), deviance information criterion (DIC) and Watanabe-Akaike information criterion (WAIC) for full models of *P. falciparum* and *P. vivax* malaria in El Oro 1990-2018 that include minimum temperature, maximum temperature and precipitation as linear terms at time lags from 0-3 months.

Variable	**Parasite**	**Lag**	**Estimate**	**LCI**	**UCI**	**DIC**	**WAIC**
Minimum temperature	*P. falciparum*	0	11938.92	11960.72	-0.28	-0.66	0.09
		1	11948.20	11963.51	0.22	-0.14	0.57
		2	11961.86	11980.42	0.84	0.62	1.05
		3	11927.02	11940.85	1.01	0.79	1.23
	P. vivax	0	17824.32	17833.30	0.08	-0.17	0.33
		1	17820.73	17829.48	0.42	0.17	0.66
		2	17815.34	17823.67	0.55	0.34	0.73
		3	17804.16	17812.64	0.58	0.37	0.79
Maximum temperature	*P. falciparum*	0	11941.31	11970.30	-0.04	-0.32	0.23
		1	11948.45	11962.52	0.33	0.10	0.57
		2	11937.95	11954.81	0.59	0.45	0.74
		3	11937.51	11950.74	0.61	0.47	0.75
	P. vivax	0	17820.63	17829.29	0.18	0.02	0.34
		1	17813.42	17821.37	0.4	0.25	0.54
		2	17806.51	17814.84	0.44	0.32	0.55
		3	17810.93	17819.62	0.34	0.20	0.48
Precipitation	*P. falciparum*	0	11944.85	11961.75	-0.03	-0.18	0.13
		1	11944.55	11960.66	0.00	-0.14	0.14
		2	11943.98	11961.78	-0.03	-0.20	0.13
		3	11938.59	11963.29	0.24	0.09	0.38
	P. vivax	0	17824.24	17833.24	-0.06	-0.15	0.02
		1	17822.93	17831.12	-0.07	-0.17	0.02
		2	17828.16	17837.31	0.01	-0.08	0.11
		3	17828.61	17837.34	0.10	0.01	0.18

Table S2.4. Model adequacy for lagged climate variables in non-linear models of malaria incidence in El Oro 1990-2018. Deviance information criterion (DIC) and Watanabe-Akaike information criterion (WAIC) for full models of *P. falciparum* and *P. vivax* malaria in El Oro 1990-2018 that include minimum temperature, maximum temperature and precipitation as non-linear function at time lags from 0-3 months. Time lags highlighted in grey are those selected to be used in the final model.

Variable	**Parasite**	**Lag**	**DIC**	**WAIC**
Minimum temperature	*P. falciparum*	0	11948.55	11964.97
		1	11944.32	11960.74
		2	11936.44	11953.48
		3	11921.09	11934.96
	P. vivax	0	17830.35	17836.07
		1	17814.22	17822.74
		2	17800.4	17810.46
		3	17792.98	17801.97
Maximum temperature	*P. falciparum*	0	11924.61	11940.9
		1	11935.75	11952.17
		2	11944.67	11956.47
		3	11934.27	11946.95
	P. vivax	0	17812.66	17831.57
		1	17809.03	17822.45
		2	17802.44	17817.49
		3	17778.01	17806.46
Precipitation	*P. falciparum*	0	11943.34	11961.06
		1	11953.66	11985.54
		2	11949.65	11964.34
		3	11941.54	11961.58
	P. vivax	0	17820.31	17832.98
		1	17820.92	17832.56
		2	17821.94	17830.92
		3	17823.07	17831.76

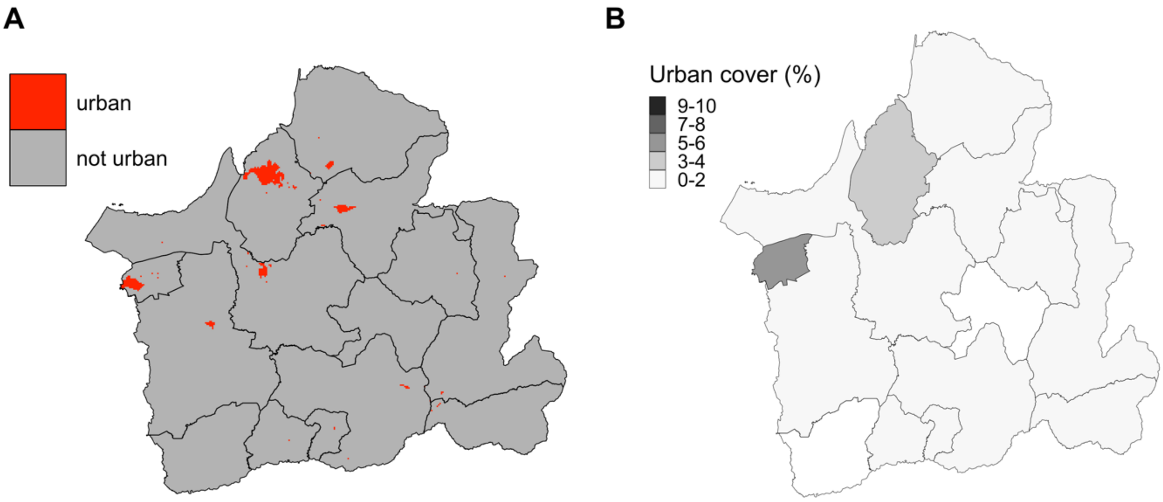
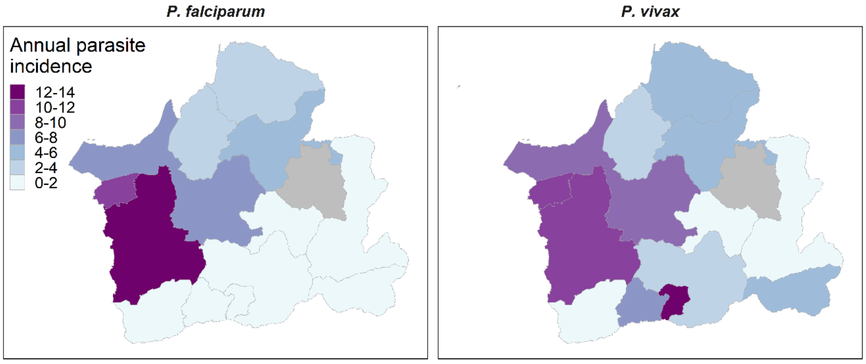


Figure S2.2. Urbanised areas in El Oro province, 1990-2018. A) Gridded land cover map of urban areas in El Oro, 2018. Sourced from the ESA CCI. B) Mean percentage of urban cover in each canton 1990-2018. Percent cover was defined as the proportion of the number of grid cells categorised as urban, according to the United Nations Land Cover Classification System (LCCS).

A) 1990-2000



B) 2001-2015

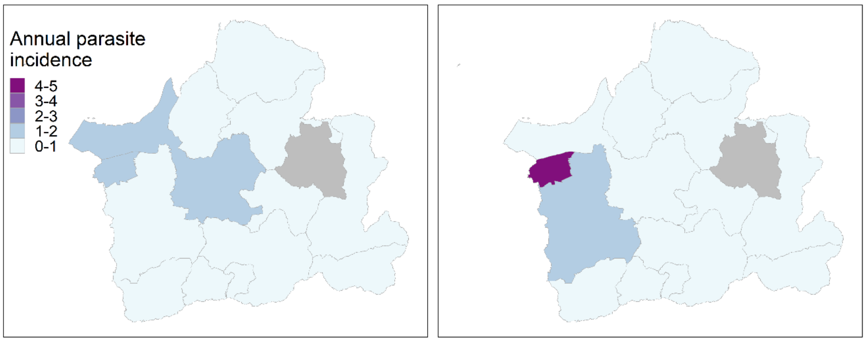


Figure S2.3. Annual parasite incidence (API) in El Oro 1990-2015. Mean API (per 1,000) for *P. falciparum* and *P. vivax* malaria for each canton in El Oro a) between 1990-2000 before the period for which intervention data was available and b) 2001-2015 during the intervention period. Grey areas show missing data.

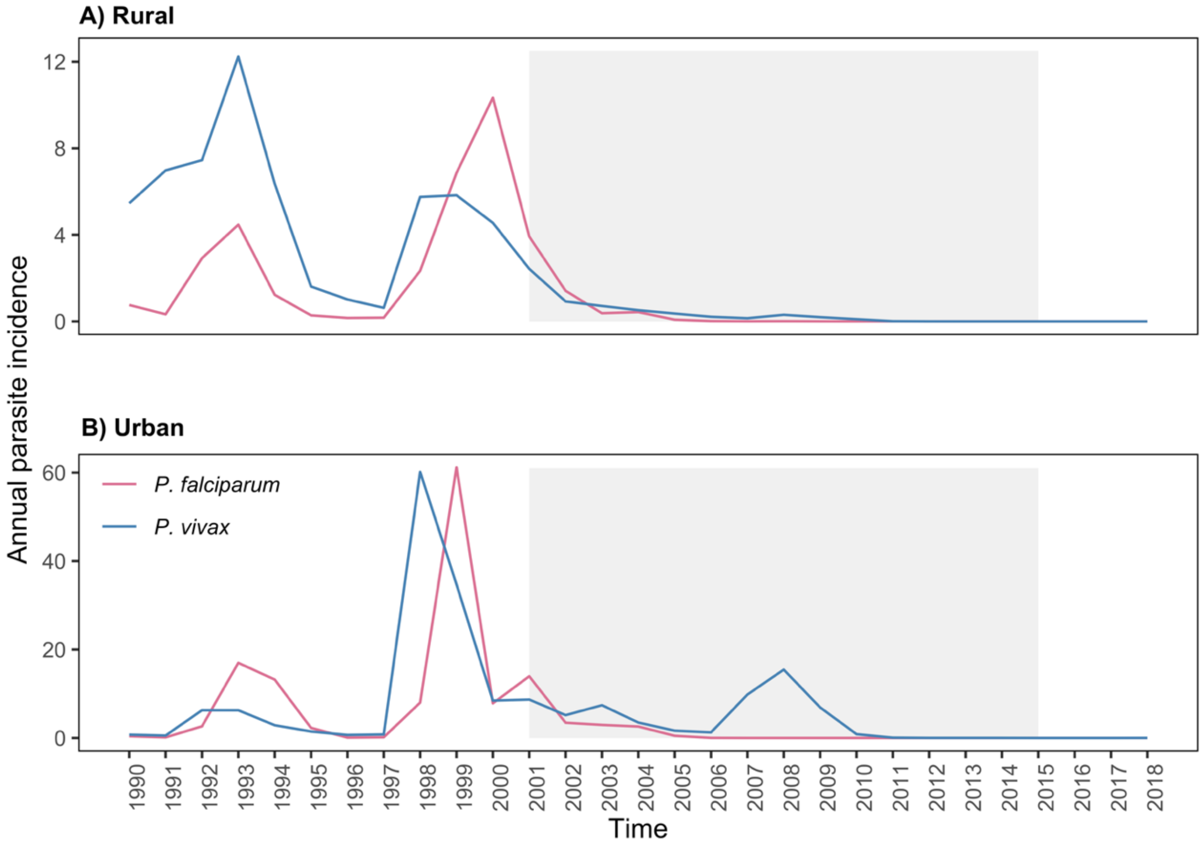


Figure S2.4. Rural and urban malaria in El Oro 1990-2018. Annual parasite incidence (API), per 1,000, of *P. falciparum* (pink) and *P. vivax* incidence (blue) in A) rural and B) urbanised areas. Grey shading represents the period of intensive vector control in El Oro, 2001-2015. Urban areas were defined as cantons that had urban cover above or equal to 5% of total land cover.

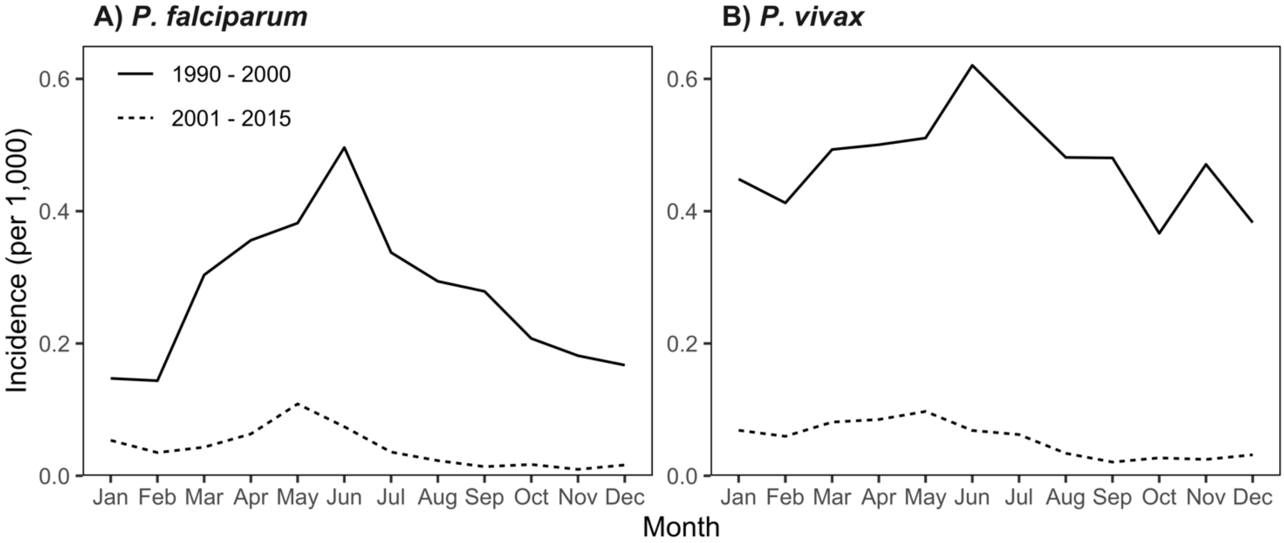


Figure S2.5. Seasonality of malaria incidence in El Oro. Monthly incidence (per 1,000) of A) *P. falciparum* and B) *P. vivax* malaria in El Oro before the vector control measures were implemented 1990-2000 (solid curve) and during the elimination period 2001-2015 (dashed curve).

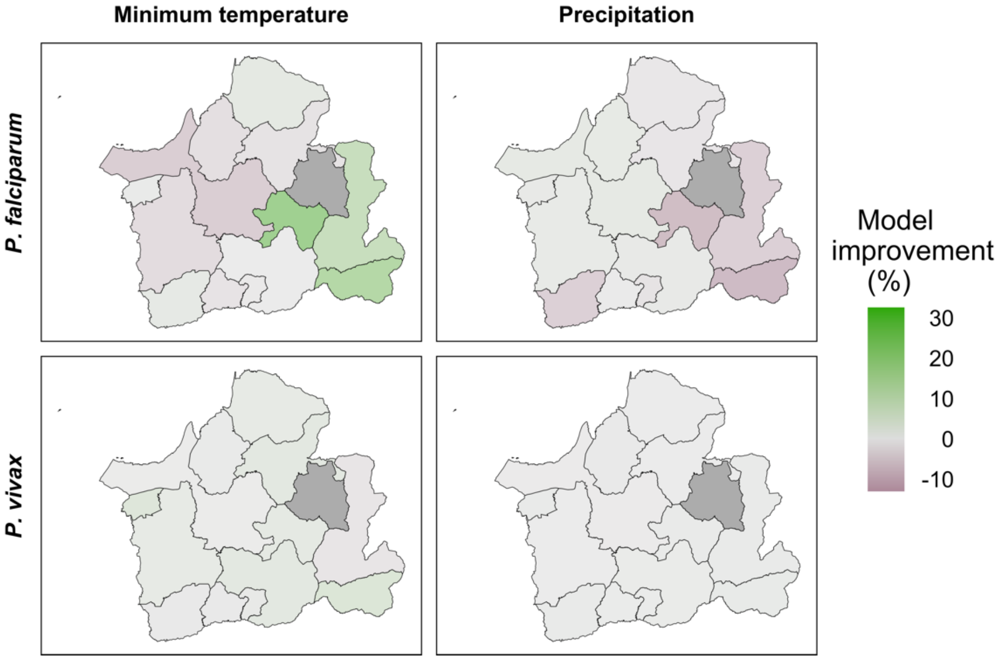


Figure S2.6. Model improvement for climate variables in El Oro 1990-2018. Model improvement, calculated as percentage change in root mean square error (RMSE) between spatiotemporal models of *P. falciparum* and *P. vivax* malaria excluding each climate variable, minimum temperature and precipitation, and models including each variable. Minimum temperature, lagged by three months was included as a linear term for *P. falciparum* models and as a non-linear function for *P. vivax* models. Precipitation, lagged by three months for *P. falciparum* was included as a linear term and for *P. vivax* was lagged one month and included as a non-linear function.

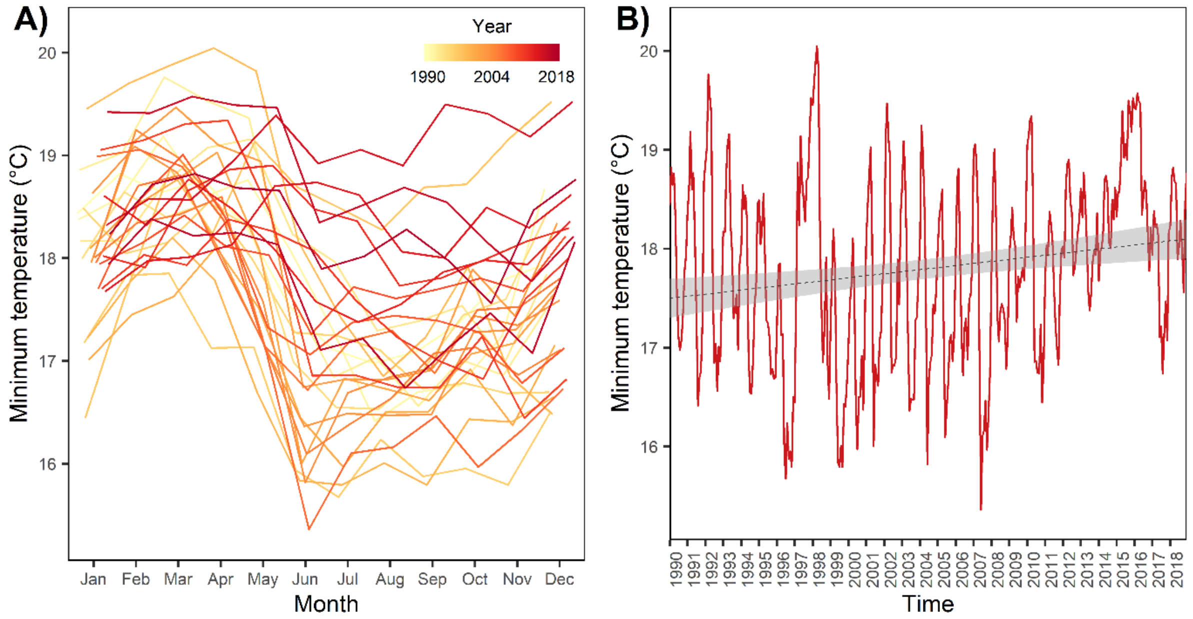


Figure S2.7. Minimum temperature trends in El Oro 1990-2018. A) Mean monthly minimum temperatures for each year 1990-2018 and B) mean minimum temperature 1990-2018 (red curve), logistic regression line (dashed curve) and 95% confidence intervals (grey shading).

Table S2.5. Parameter estimates for explanatory covariates in full and intervention models of malaria incidence in El Oro 1990-2018. Posterior mean estimates, lower (2.5%) and upper (97.5%) credible intervals (CI) for explanatory variables for main models of *P. falciparum* and *P. vivax* malaria in El Oro between 1990-2018 (without intervention data) and for intervention models between 2001-2015 (including intervention data).

Variable	**Parasite**	**Model**	**Estimate**	**LCI**	**UCI**
Minimum temperature	*P. falciparum*	1990-2018	0.90	0.60	1.20
		2001-2015	1.31	0.84	1.79
	P. vivax	1990-2018	0.57	0.35	0.79
		2001-2015	0.75	0.36	1.12
Precipitation	*P. falciparum*	1990-2018	0.08	-0.05	0.21
		2001-2015	-0.12	-0.32	0.09
	P. vivax	1990-2018	-0.05	-0.14	0.04
		2001-2015	0.03	-0.14	0.20
Level of urbanisation	*P. falciparum*	1990-2018	0.23	0.06	0.40
		2001-2015	0.00	-0.16	0.16
	P. vivax	1990-2018	0.02	-0.10	0.14
		2001-2015	0.04	-0.12	0.20
Poverty	*P. falciparum*	1990-2018	0.56	-0.43	1.60
		2001-2015	0.15	-0.45	0.76
	P. vivax	1990-2018	-0.03	-0.71	0.63
		2001-2015	0.82	0.12	1.46

Appendix II – Synergies between environmental degradation and climate variation on malaria re-emergence in southern Venezuela

This appendix provides supplementary figures and tables for Chapter 3.

Figure S3.1. Influence of El Niño on malaria incidence at varying monthly lags.
Figure S3.2. Land-use change in Bolívar, southern Venezuela.
Figure S3.3. Bivariate relationship between deforestation, mining, and urbanisation in Bolívar.
Figure S3.4. Associations between El Niño and climate conditions in Bolívar.
Figure S3.5. Variation in malaria incidence explained by mining activity.
Figure S3.6. Environmental and socioeconomic drivers in linear models of malaria in Bolívar state.

Table S3.1. Summary of model data sources.
Table S3.2. Land cover classifications summarised from the original ESA CCI land cover classes.
Table S3.3. Model adequacy of linear and non-linear models of malaria incidence in Bolívar.

Table S3.1. Summary of model data sources. Data sources for variables included in spatiotemporal models of malaria incidence in Bolívar 1996-2016.

Data	**Inclusion in model**	**Description**	**Temporal resolution**	**Spatial resolution**	**Time period**	**Rationale**	**Source**
Malaria cases	Response	Number of *P. falciparum* and *P. vivax* cases recorded	Monthly	Parroquia (parish)	January 1996-December 2016	-	Ministry of Health
Population	Offset	Population values	Annual	Parroquia (parish)	1996-2016	Controlling for the effects of human population on malaria incidence	Ministry of Health
Mean temperature	Covariate	Average values derived from gridded remotely sensed observations	Monthly	Parroquia (parish)	January 1996-December 2016	Temperature influences the environmental suitability for *Anopheles* vectors, and parasite development	European Centre for Medium-Range Weather Forecasts (ECMWF) ERA5-Land
Precipitation	Covariate	Average values derived from gridded remotely sensed observations	Monthly	Parroquia (parish)	January 1996-December 2016	Precipitation provides important breeding habitat for *Anopheles* vectors	European Centre for Medium-Range Weather Forecasts (ECMWF) ERA5-Land
Niño 3.4	Covariate	Sea-surface temperature anomalies for the Niño 3.4 region	Monthly	NA	January 1996-December 2016	The El Niño Southern Oscillation (ENSO) influences interannual variability in malaria incidence, through climatic changes	National Oceanic and Atmospheric Administration (NOAA)
Mining	Covariate	Number of suspected mining sites (mainly for gold) identified from satellite imagery 2009-2018	NA	Parroquia (parish)	NA	Environmental alteration caused by land clearance for mining is thought to increase the breeding habitat of *Anopheles* vectors	Rede Amazónica de Información Socioambiental Georeferenciada
Healthcare inaccessibility	Covariate	Mean travel time to nearest health site	NA	Parroquia (parish)	NA	Access to healthcare affects malaria diagnosis and treatment	Malaria Atlas Project and Humanitarian Data Exchange
Deforestation	Covariate	Cumulative decrease in forest cover (km^2)	Annual	Parroquia (parish)	1996-2016	Deforestation provides favourable habitat for *Anopheles* vectors, most notably *An. darlingi*	European Space Agency (ESA) Climate Change Initiative (CCI)
Urbanisation	Covariate	Cumulative increase in urban cover (km^2)	Annual	Parroquia (parish)	1996-2016	Level of urbanisation impacts availability of *Anopheles* vector habitat, which is generally lower in urban areas, and healthcare accessibility	European Space Agency (ESA) Climate Change Initiative (CCI)

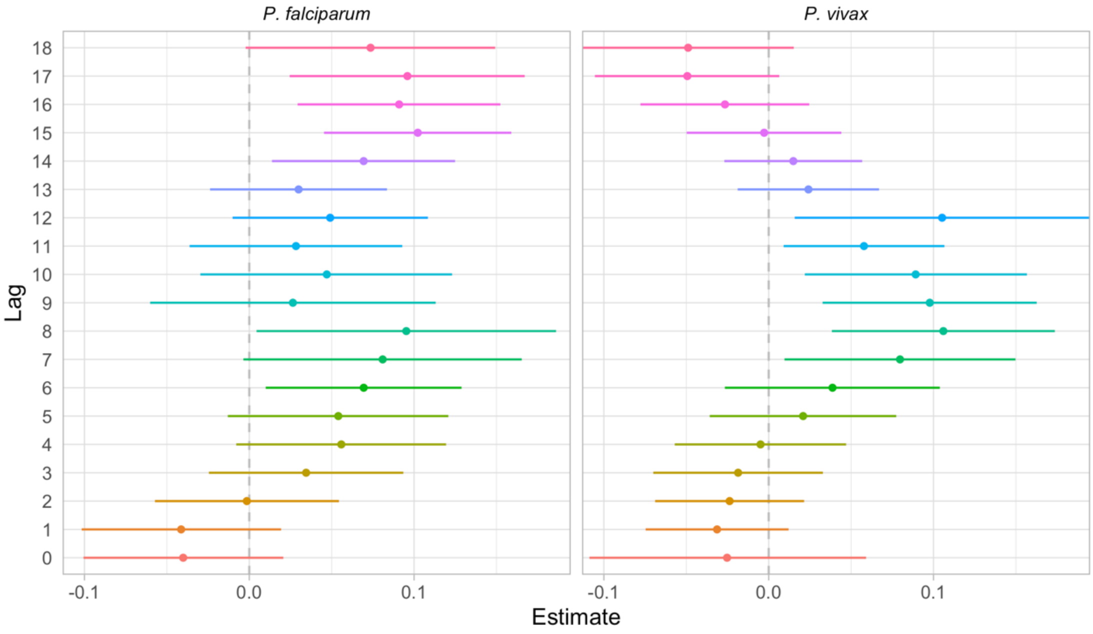


Figure S3.1. Influence of El Niño on malaria incidence at varying monthly lags. Posterior mean estimates and 95% credible intervals for spatiotemporal models of *P. falciparum* (left panel) and *P. vivax* (right panel) malaria in Bolívar state. The model included the Niño 3.4 index lagged from zero to 18 months, and also included an interaction term between high and low levels of mining and nonlinear functions of temperature and rainfall. The model also included the impact of deforestation, urbanisation, healthcare accessibility and random effects, to account for seasonality, interannual variability and spatial dependency structures. The monthly time lag selected to be used in the final models was eight months.

Table S3.2. Land cover classifications summarised from the original ESA CCI land cover classes. Seven classes were aggregated to forest/tree cover and a single class defined as urban. The change in these land cover classes over time were then used to extract variables of deforestation and urbanization.

Value	**Label**	**Revalued class**
50	Tree cover, broadleaved, evergreen, closed to open (>15%)	Forest/tree cover
60	Tree cover, broadleaved, deciduous, closed to open (>15%)	
70	Tree cover, needleleaved, evergreen, closed to open (>15%)	
80	Tree cover, needleleaved, deciduous, closed to open (>15%)	
90	Tree cover, mixed leaf type (broadleaved and needleleaved)	
100	Mosaic tree and shrub (>50%) / herbaceous cover (<50%)	
110	Mosaic herbaceous cover (>50%) / tree and shrub (<50%)	
190	Urban areas	Urban

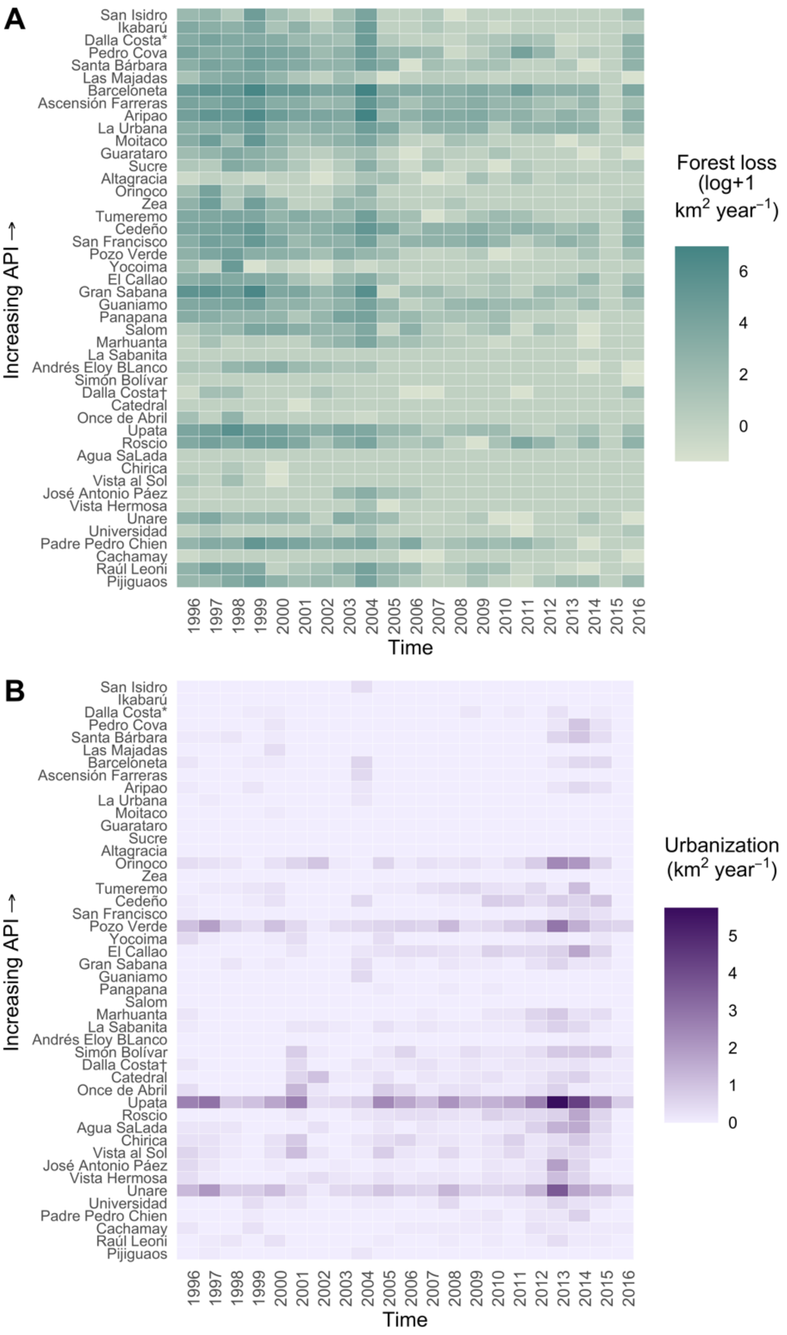


Figure S3.2. Land-use change in Bolívar, southern Venezuela. A) Annual decrease (log +1 km^2) 1996-2016 in forest cover identified from satellite land cover maps for the 46 parishes of Bolívar state. Parishes are ordered by annual parasite incidence (API, per 1,000), with those at the top representing areas with the highest malaria incidence and those at the bottom with the lowest recorded malaria incidence. B) Annual increase (km^2) 1996-2016 in urban cover identified from satellite land cover maps for the 46 parishes of Bolívar state. Parishes are ordered by annual parasite incidence (API), with those at the top representing areas with the highest malaria incidence and those at the bottom with the lowest recorded malaria incidence. *Dalla Costa parish, Sifontes municipality. †Dalla Costa parish, Caroní municipality.

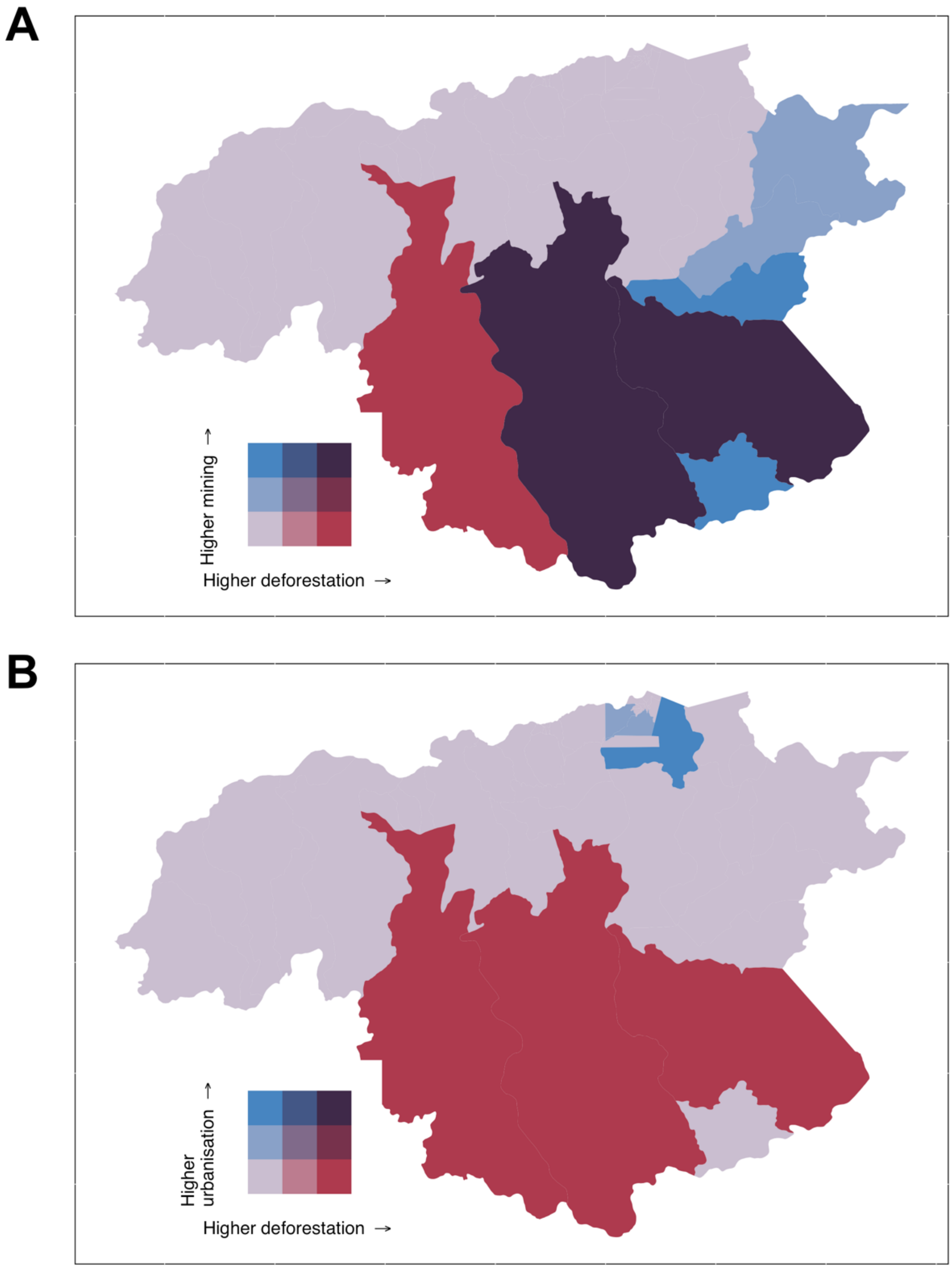


Figure S3.3. Bivariate relationship between deforestation, mining, and urbanisation in Bolívar. A) Relationship between mining activity and forest loss between 1996-2016 across Bolívar. Dark purple colours represent parishes with both high levels of mining and high levels of deforestation, whilst pale colours represent areas with minimal mining activity and low deforestation. B) Relationship between urbanisation and forest loss between 1996-2016 across Bolívar. Dark purple colours represent parishes with both high levels of urbanisation and high levels of deforestation, whilst pale colours represent areas with low urbanisation and low deforestation. Data shown is aggregated to the parish level.

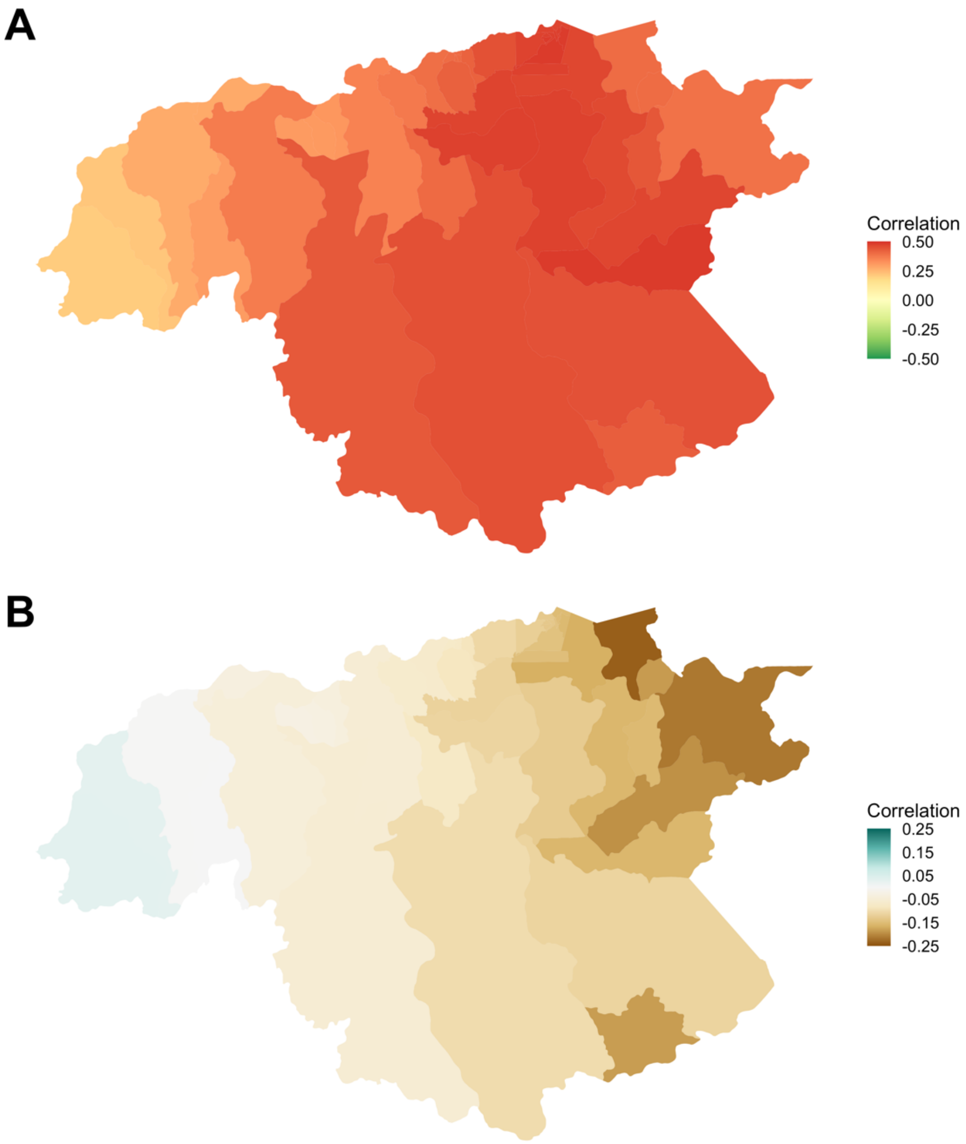


Figure S3.4. Associations between El Niño and climate conditions in Bolívar. Pearson correlation coefficients between the Niño 3.4 index and A) mean temperatures (°C) and B) mean precipitation (mm/day) between 1996-2016 in Bolívar, southern Venezuela. Climate data are aggregated to the parish level.

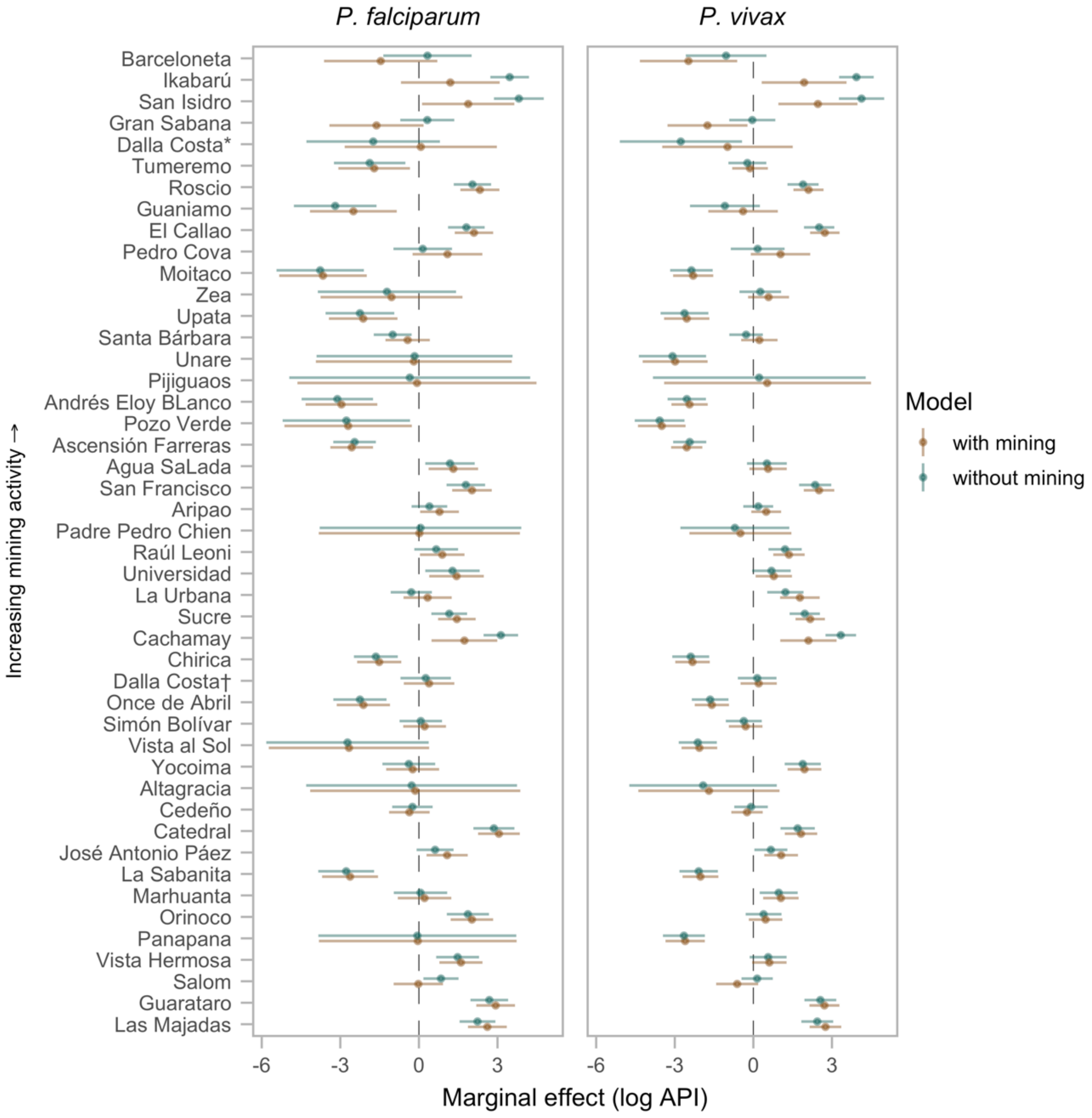


Figure S3.5. Variation in malaria incidence explained by mining activity. Marginal effect (mean and 95% credible intervals of the spatial random effect) of log annual parasite incidence (API), of spatiotemporal models for *P. falciparum* (left panel) and *P. vivax* (right panel) malaria that exclude (light blue) and include (dark blue) mining activity across Bolívar as a covariate. A reduction in mean estimate towards zero indicates where mining activity explains the spatial variation in malaria incidence. The model also included the impact of deforestation, urbanisation, El Niño, healthcare accessibility, and an interaction term between level of mining and nonlinear functions of temperature and rainfall, and random effects, to account for seasonality, interannual variability and spatial dependency structures. *Dalla Costa parish, Sifontes municipality. †Dalla Costa parish, Caroní municipality.

Table S3.3. Model adequacy of linear and non-linear models of malaria incidence in Bolívar. Deviance information criterion (DIC) and Watanabe-Akaike information criterion (WAIC) for spatiotemporal models of monthly *P. falciparum* and *P. vivax* malaria incidence in Bolívar 1996-2016 that included the linear effect of climate and the non-linear effect of climate and its interaction with mining. Models also included the impact of deforestation, urbanisation, El Niño, healthcare accessibility and random effects, to account for seasonality, interannual variability and spatial dependency structures.

Model formula	**Parasite**	**DIC**	**WAIC**
Linear climate model	*P. falciparum*	41241.52	41242.97
$\log(\rho_{st}) = \upsilon_s + v_s + m_t + y_t + \Sigma\beta x_i$	*P. vivax*	61721.31	61762.47
Non-linear climate model, including an interaction between climate and level of mining	*P. falciparum*	40704.95	40741.82
$\log(\rho_{st}) = \upsilon_s + v_s + m_t + y_t + \Sigma\beta x_i + f(x1_m) + f(x2_m)$	*P. vivax*	61601.23	61653.46

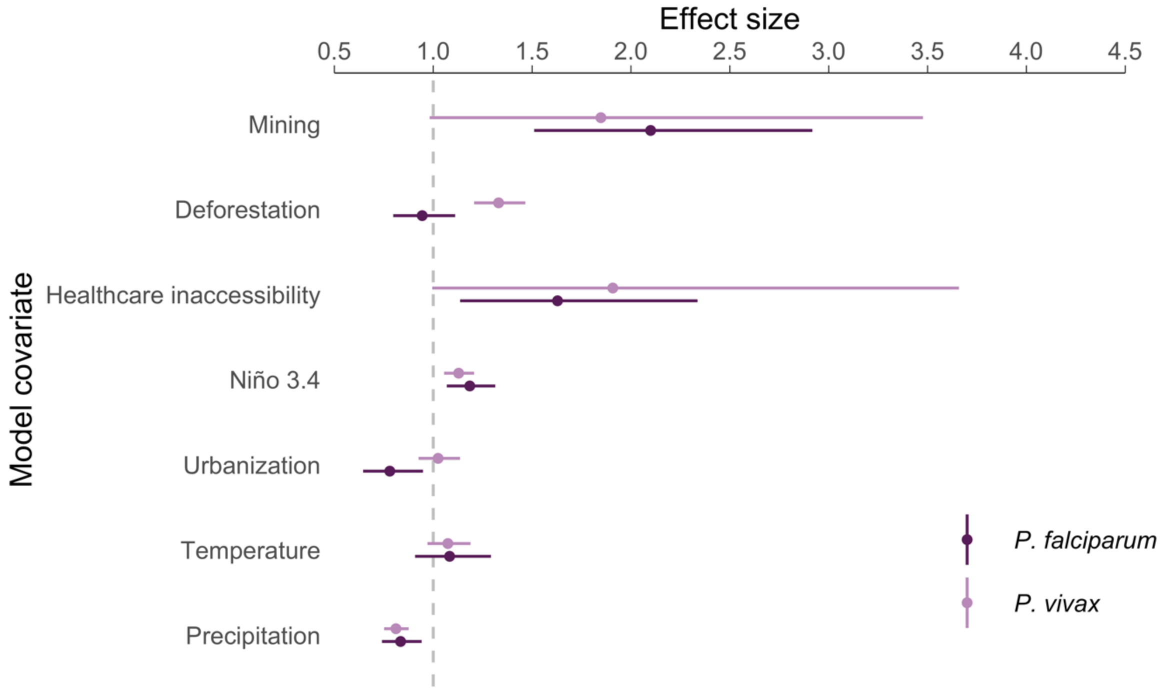


Figure S3.6. Environmental and socioeconomic drivers in linear models of malaria in Bolívar state. Effect size and 95% credible intervals for environmental and socioeconomic covariates in spatiotemporal models of *P. falciparum* (purple bars) and *P. vivax* (pink bars) malaria incidence. Models accounted for the linear effect of climate (temperature and precipitation), and included random effects, to account for seasonality, interannual variability and spatial dependency structures.

Appendix III – Climate services for health: from global observations to local interventions

This appendix provides supplementary figures and tables for Chapter 4:

Figure S4.1. Seasonality of malaria and dengue cases, and climate.

Table S4.1. Influence of climate on dengue risk in models using different global climate products.

Table S4.2. Influence of climate on malaria risk in models using different global climate products.

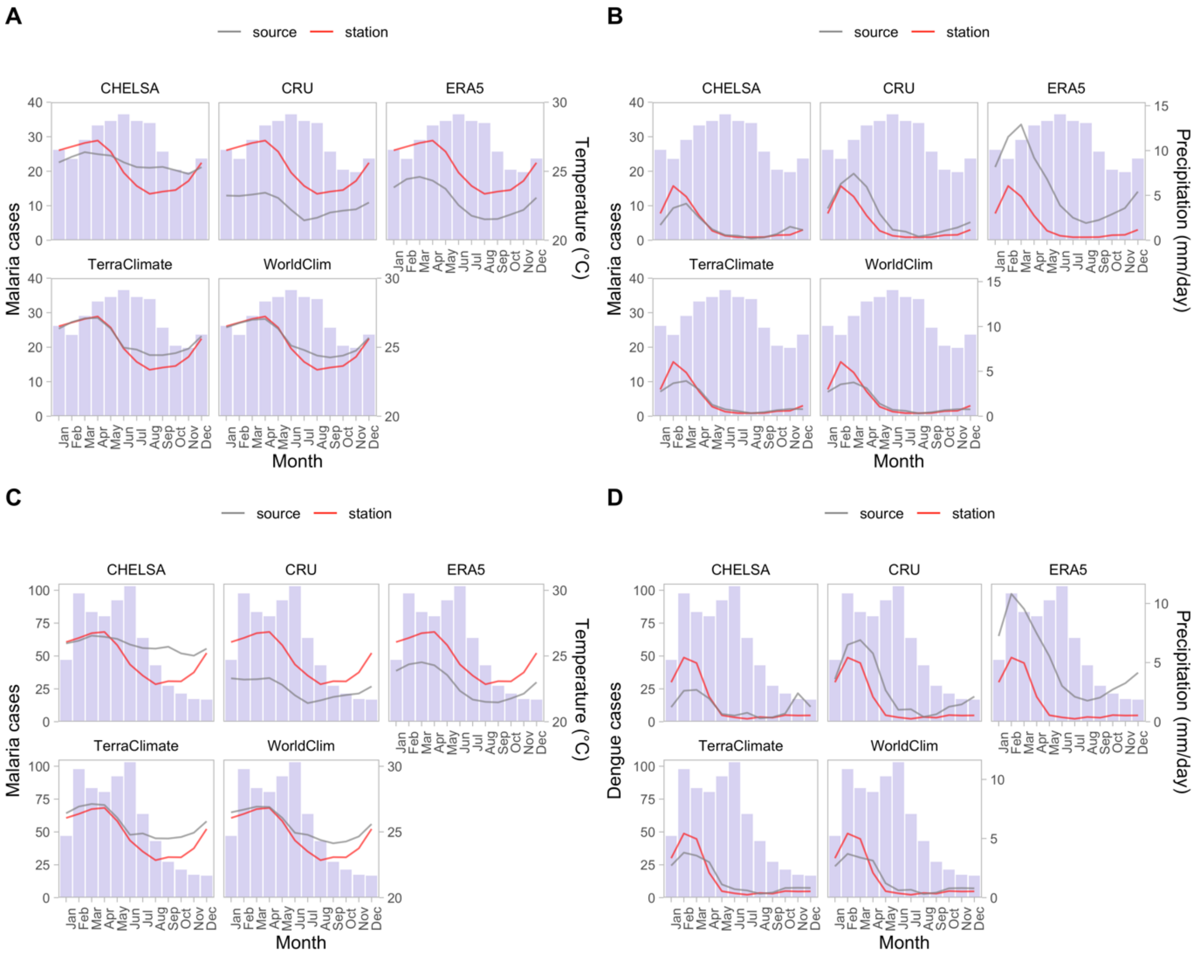


Figure S4.1. Seasonality of malaria and dengue cases, and climate. A-B) Annual cycle of cases of *P. vivax* malaria 1990-2015 and C-D) dengue 2002-2014 with A-C) mean temperature and B-D) precipitation, in Machala, Ecuador. Red curves represent data from local meteorological station observations and grey curves represent data from the CHELSA, CRU, ERA5, TerraClimate and WorldClim global datasets.

Table S4.1. Influence of climate on dengue risk in models using different global climate products. Posterior mean estimates, lower and upper 95% credible intervals (CI) for climate models of dengue 1990-2015 in Machala, Ecuador, using climate data from local meteorological observations, the CHELSA, CRU TS, ERA5-Land, TerracClimate and WorldClim datasets.

Variable	Climate source	Mean	LCI	UCI
Mean temperature	Station	0.52	0.32	0.73
	CHELSA	0.50	0.26	0.73
	CRU	0.33	0.09	0.57
	ERA5	0.39	0.08	0.70
	TerraClimate	0.49	0.22	0.77
	WorldClim	0.49	0.24	0.74
Precipitation	Station	0.17	-0.04	0.39
	CHELSA	0.04	-0.16	0.25
	CRU	0.21	-0.06	0.48
	ERA5	0.24	-0.08	0.58
	TerraClimate	0.10	-0.17	0.37
	WorldClim	0.16	-0.09	0.42

Table S4.2. Influence of climate on malaria risk in models using different global climate products. Posterior mean estimates, lower and upper 95% credible intervals (CI) for climate models of malaria 1990-2015 in Machala, Ecuador, using climate data from local meteorological observations, the CHELSA, CRU TS, ERA5-Land, TerracClimate and WorldClim datasets.

Variable	Climate source	Mean	LCI	UCI
Mean temperature	Station	0.32	0.22	0.43
	CHELSA	-0.04	-0.22	0.13
	CRU	0.05	-0.08	0.18
	ERA5	0.41	0.30	0.51
	TerraClimate	0.12	-0.02	0.26
	WorldClim	0.15	0.02	0.29
Precipitation	Station	-0.20	-0.30	-0.09
	CHELSA	-0.15	-0.28	-0.02
	CRU	0.13	0.01	0.25
	ERA5	-0.31	-0.41	-0.21
	TerraClimate	0.06	-0.07	0.20
	WorldClim	0.04	-0.10	0.17

Appendix IV – Differing genus- and species-specific responses of mosquito vectors to anthropogenic land-use change in Latin America

This appendix provides supplementary figures and tables for Chapter 5.

Table S5.11. Parameter estimates for land-use types in mosquito species richness models.

Table S5.12. Parameter estimates for land-use types in mosquito abundance models.

Table S5.13. Parameter estimates for land-use types in species-level mosquito abundance models.

Table S5.1. Search terms used for systematic data search. Mosquito, geographical and land use specific terms used to systematically search three databases (Medline, Scopus and Web of Science) for *Aedes* and *Anopheles* mosquito abundance records across multiple land-use types in Latin America and the Caribbean. * denotes wildcard terms.

Mosquito search terms
mosquito* OR anophel* or aedes
Geographical search terms
(south* AND america*) OR amazon* OR brazil* OR bolivia* OR colombia* OR surinam* OR guiana* OR venezuela* OR ecuador* OR peru* OR guyana* OR chile* OR argentin* OR uruguay* OR paraguay* OR america* OR (central AND america*) OR (latin AND america*) OR caribbean OR anguilla* OR antigua* OR barbuda OR (antigua* AND barbuda*) OR aruba* OR bahama* OR baham* OR barbados* OR barbadian* OR belize* OR bermud* OR (british AND virgin AND island*) OR cayman OR (cayman AND island*) OR (costa AND rica*) OR cuba* OR curacao* OR dominica* OR (dominica* AND republic) OR (el AND salvador*) OR grenad* OR guadeloup* OR guatemala* OR haiti* OR hondura* OR jamaica* OR martiniqu* OR mexic* OR montserrat* OR antill* OR nicaragua* OR panama* OR (puerto AND ric*) OR (saint AND kitts AND nevis) OR (saint AND kitts) OR (saint AND lucia*) OR (saint AND vincent) OR (saint AND vincent AND grenadine*) OR (saint AND martin) OR (sint AND maarten) OR trinidad* OR (trinidad AND tobago) OR tobago* OR (turks AND caicos))
Land use search terms
land* OR urban* OR deforest* OR logg* OR intensification OR manag* OR unmanage* OR felling OR plantation OR habitat* OR forest* OR mining OR mine* OR clear* OR degrad* OR develop* OR agricultur* OR landscape* OR crop* OR farm* OR canal* OR dams OR dam OR pond*

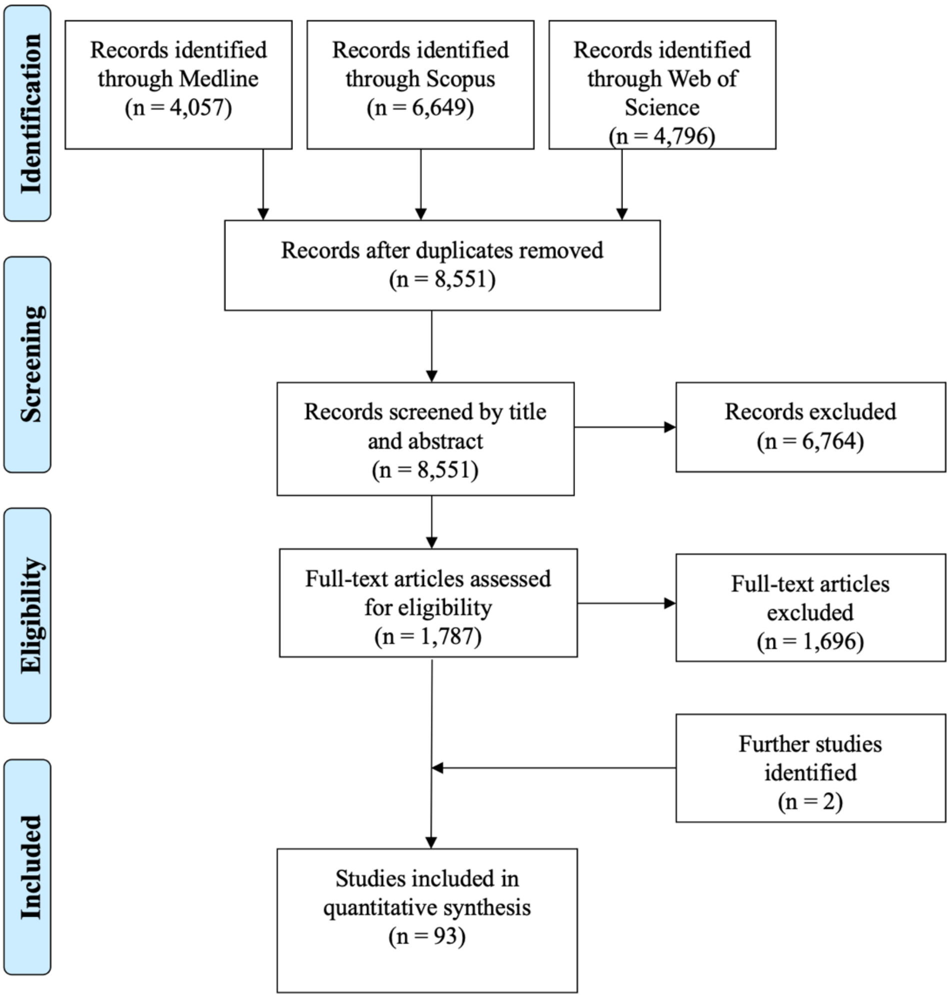


Figure S5.1. PRISMA flow of the systematic data search process. PRISMA flow diagram of the systematic data collection process for mosquito biodiversity data in Latin America and the Caribbean. Three databases were searched (Medline, Scopus and Web of Science) and results combined before studies were screened by title and abstract (n = 8,554). A total of 1,790 studies were screened by full text, leading to inclusion of 85 studies that had suitable data.

Table S5.2. Summary of site-level information extracted from included studies. Site-level information extracted from each included study to formulate a dataset of mosquito vector biodiversity over different land-use types. The nested structure of the dataset (study number, site number, study block and study sample) followed that of the PREDICTS database (Hudson *et al.*, 2014).

Name	Description
Collection	Sample collection indoor or outdoor
Country	Country sample was performed
Development stage	Sampled mosquito development stage (pupae, larvae, immature, adult)
Ecoregion	Assigned ecoregion according to the 14 WWF global terrestrial ecoregions (WWF, 2021)
Genus	Mosquito genus
Site description	Detailed description of sampled site, according to study
Land use	Predominant land-use type (primary vegetation, secondary vegetation, managed or urban)
Land-use intensity	Predominant intensity of land use (minimal or substantial)
Lat	Latitude
Lon	Longitude
Measurement	Value of species-level abundance measurement
Metric	Metric of abundance measurement (e.g. number of individuals or larval density)
Reference	Study reference
Sample daytime	Time of day when sample was taken
Sample start	Start date of sample
Sample end	End date of sample
Sample month	Month of sampling
Sample season	Climatic season of sampling (wet or dry)
Sampling effort	Value of sampling effort
Sampling effort unit	Unit of sampling effort (e.g. trap days or man hours)
Sampling method	Method of sampling (e.g. light trap, oviposition trap or human landing catch)
Site number	Assigned site number within study
Species study name	Species name according to study
Study block	Spatial arrangement of site within a study
Study number	Assigned study number
Study sample	Sample within a study with consistent sampling methodology

Table S5.3. Land-use intensity categories used in *Aedes* and *Anopheles* abundance and species richness models. Site-level distribution and number of abundance records per land-use category. Use intensity for managed and urban land-use types were aggregated due to low data representation.

Land-use intensity		**Number of sites**	**Number of records**
Primary vegetation			
	Minimal	224	2,388
	Substantial	68	1,351
Secondary vegetation			
	Combined	57	1,325
Managed			
	Combined	98	1,420
Urban			
	Combined	195	3,520

Table S5.4. Summary of all main models included in the analysis. Genus-, j and species-level, i, abundance y_A and richness, y_R models, deforestation abundance and richness models included in the main analysis. Models included land-use type as a fixed covariate, x_1, and a combination of best-fitting random effects; study v, site υ, species γ, study sample ε and ecoregion σ. Models where deforestation was included as a fixed continuous covariate, x_2, are also shown.

Models	Response	Random effects	Equation
Genus-level models			
Aedes richness *Anopheles* richness Total (*Aedes* and Anopheles) richness	Species richness	study, site, study sample, ecoregion	$y_{Rj} = \beta_0 + \beta_1 x_{1j} + v_j + \upsilon_j + \varepsilon_j + \sigma_j$
Aedes abundance *Anopheles* abundance Total abundance	log(adjusted abundance)+1	study, site, species, study sample, ecoregion	$y_{Aj} = \beta_0 + \beta_1 x_{1j} + v_j + \upsilon_j + \gamma_j + \varepsilon_j + \sigma_j$
Species-level abundance models			
Ae. aegypti *Ae. albopictus* *Ae. scapularis* *Ae. serratus* *An. albimanus* *An. albitarsis* *An. darlingi* *An. nuneztovari*	log(adjusted abundance)+1	study, site, study sample, ecoregion	$y_{Ai} = \beta_0 + \beta_1 x_{1i} + v_i + \upsilon_i + \varepsilon_i + \sigma_i$
Deforestation models			
Aedes richness *Anopheles* richness	Species richness	Study, site, study sample, ecoregion	$y_{Rj} = \beta_0 + \beta_2 x_{2j} + v_j + \upsilon_j + \varepsilon_j + \sigma_j$
Aedes abundance *Anopheles* abundance	log(adjusted abundance)+1	study, site, species, study sample, ecoregion	$y_{Aj} = \beta_0 + \beta_2 x_{2j} + v_j + \upsilon_j + \gamma_j + \varepsilon_j + \sigma_j$
Ae. aegypti abundance *Ae. albopictus* abundance *Ae. serratus* abundance *Ae. scapularis* abundance *An. albitarsis* abundance *An. darlingi* abundance *An. mattogrossensis* abundance *An. nuneztovari* abundance		study, site, study sample, ecoregion	$y_{Ai} = \beta_0 + \beta_2 x_{2i} + v_i + \upsilon_i + \varepsilon_i + \sigma_i$

Table S5.5. Summary of land-use intensity models. Summary of components of total, *Aedes* and *Anopheles* abundance and species richness models. The number of sites and site-level records in each model is shown.

Model	Response	Random effects	Number of sites	Number of site-level records
Total abundance	Total log(adjusted abundance)+1	study, site, species, study sample, ecoregion	632	4,582
Aedes abundance	log(adjusted abundance)+1	study, site, species, study sample, ecoregion	379	2,118
Anopheles abundance	log(adjusted abundance)+1	study, site, species, study sample, ecoregion	495	2,464
Total species richness	Total (*Aedes* and *Anopheles*) species richness	study, site, study sample, ecoregion	434	656
Aedes species richness	*Aedes* species richness	study, site, study sample, ecoregion	238	330
Anopheles species richness	*Anopheles* species richness	study, site, study sample, ecoregion	291	433

Table S5.6. *Anopheles* and *Aedes* mosquito species included in species-specific abundance models of land-use intensity. Site-level distribution and number of site-level abundance records per *Aedes* and *Anopheles* species with greatest representation in the dataset.

Species	Number of sites	Number of site-level records	Disease(s)
Aedes aegypti	233	422	Dengue, zika, chikungunya, Mayaro virus, yellow fever
Primary vegetation - minimal	58	104	
Primary vegetation - substantial	18	33	
Secondary vegetation	22	27	
Managed	10	19	
Urban	125	239	
Aedes albopictus	248	519	Dengue, zika, chikungunya, yellow fever
Primary vegetation - minimal	73	153	
Primary vegetation - substantial	22	50	
Secondary vegetation	29	40	
Managed	6	9	
Urban	128	267	
Aedes scapularis	230	395	Chikungunya, yellow fever

Primary vegetation - minimal	74	146	
Primary vegetation - substantial	23	29	
Secondary vegetation	24	30	
Managed	19	24	
Urban	90	166	
Aedes serratus	206	363	Yellow fever, chikungunya
Primary vegetation - minimal	71	140	
Primary vegetation - substantial	15	20	
Secondary vegetation	18	23	
Managed	14	16	
Urban	88	164	
Anopheles albimanus	22	30	Malaria
Primary vegetation - minimal	2	4	
Primary vegetation - substantial	8	8	
Secondary vegetation	5	7	
Managed	4	8	
Urban	3	3	
Anopheles albitarsis	68	129	Malaria
Primary vegetation - minimal	22	39	
Primary vegetation - substantial	13	23	
Secondary vegetation	8	15	
Managed	17	39	
Urban	8	13	
Anopheles darlingi	170	354	Malaria
Primary vegetation - minimal	88	149	
Primary vegetation - substantial	17	28	
Secondary vegetation	10	24	
Managed	37	113	
Urban	18	40	
Anopheles nuneztovari	55	111	Malaria
Primary vegetation - minimal	15	18	
Primary vegetation - substantial	11	12	
Secondary vegetation	9	20	
Managed	11	34	
Urban	9	27	

Table S5.7. Iterative models for selecting the best-fitting random effects structure for models of land-use intensity and species richness. Deviance information criterion (DIC) and Watanabe-Akaike information criterion (WAIC) for models of total, *Aedes* and *Anopheles* species richness with the addition of random effects structures. Each random effect was added iteratively to assess model performance.

Species	**Random effects**	**DIC**	**WAIC**
Total	Study number + site number	2348.93	2336.89
	… + study block	2333.09	2312.23
	… + study sample	2329.84	2306.76
	… + ecoregion	2329.92	2304.82
Aedes	Study number + site number	975.97	960.29
	… + study block	975.78	960.11
	… + study sample	975.80	960.11
	… + ecoregion	975.90	960.10
Anopheles	Study number + site number	1639.04	1627.95
	… + study block	1621.46	1602.67
	… + study sample	1621.54	1602.76
	… + ecoregion	1642.26	1634.82

Table S5.8. Iterative models for selecting the best-fitting random effects structure for models of land-use intensity and abundance. Deviance information criterion (DIC) and Watanabe-Akaike information criterion (WAIC) for models of total, *Aedes* and *Anopheles* abundance with the addition of random effects structures. Each random effect was added iteratively to assess model performance.

Species	**Random effects**	**DIC**	**WAIC**
Total	Study number + site number	12322.72	12394.87
	… + study block	12317.85	12400.60
	… + study sample	12317.60	12399.18
	… + species	11861.55	11953.24
	… + ecoregion	11791.30	11887.80
Aedes	Study number + site number	6078.77	6135.98
	… + study block	6055.94	6134.66
	… + study sample	6056.86	6134.80
	… + species	5838.37	5922.44
	… + ecoregion	5790.53	5881.50
Anopheles	Study number + site number	5933.34	5950.19
	… + study block	5909.92	5941.45
	… + study sample	5850.84	5879.15
	… + species	5532.90	5576.95
	… + ecoregion	5533.65	5577.34

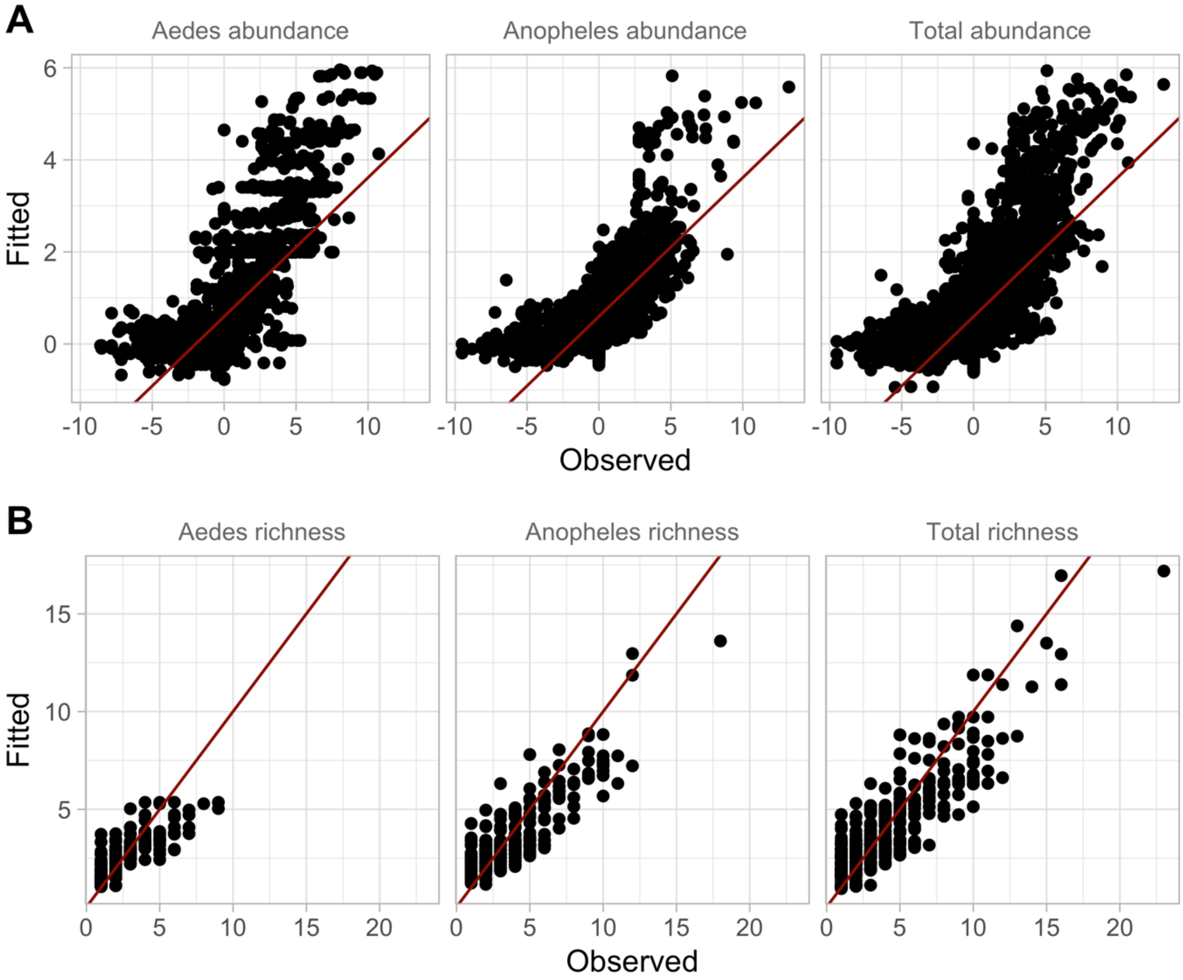


Figure S5.2. Observed and fitted observations for models of mosquito abundance and species richness. Observed and fitted model A) abundance (log +1) and B) species richness in models of total and *Aedes* and *Anopheles* mosquitoes. Red line represents the expectation if observed values equal fitted values.

Table S5.9. Summary of deforestation models. Summary of components of *Aedes* and *Anopheles* abundance and species richness models in response to recent deforestation. The number of sites and site-level records in each model is shown. Only records at primary and secondary vegetation sites were included.

Model	**Response**	**Random effects**	**Number of sites**	**Number of site-level records**
Aedes abundance	log(adjusted abundance)+1	study, site, species, study sample, ecoregion	81	572
Anopheles abundance	log(adjusted abundance)+1	study, site, species, study sample, ecoregion	167	526
Aedes species richness	*Aedes* species richness	study, site, study sample, ecoregion	36	50
Anopheles species richness	*Anopheles* species richness	study, site, study sample, ecoregion	89	101

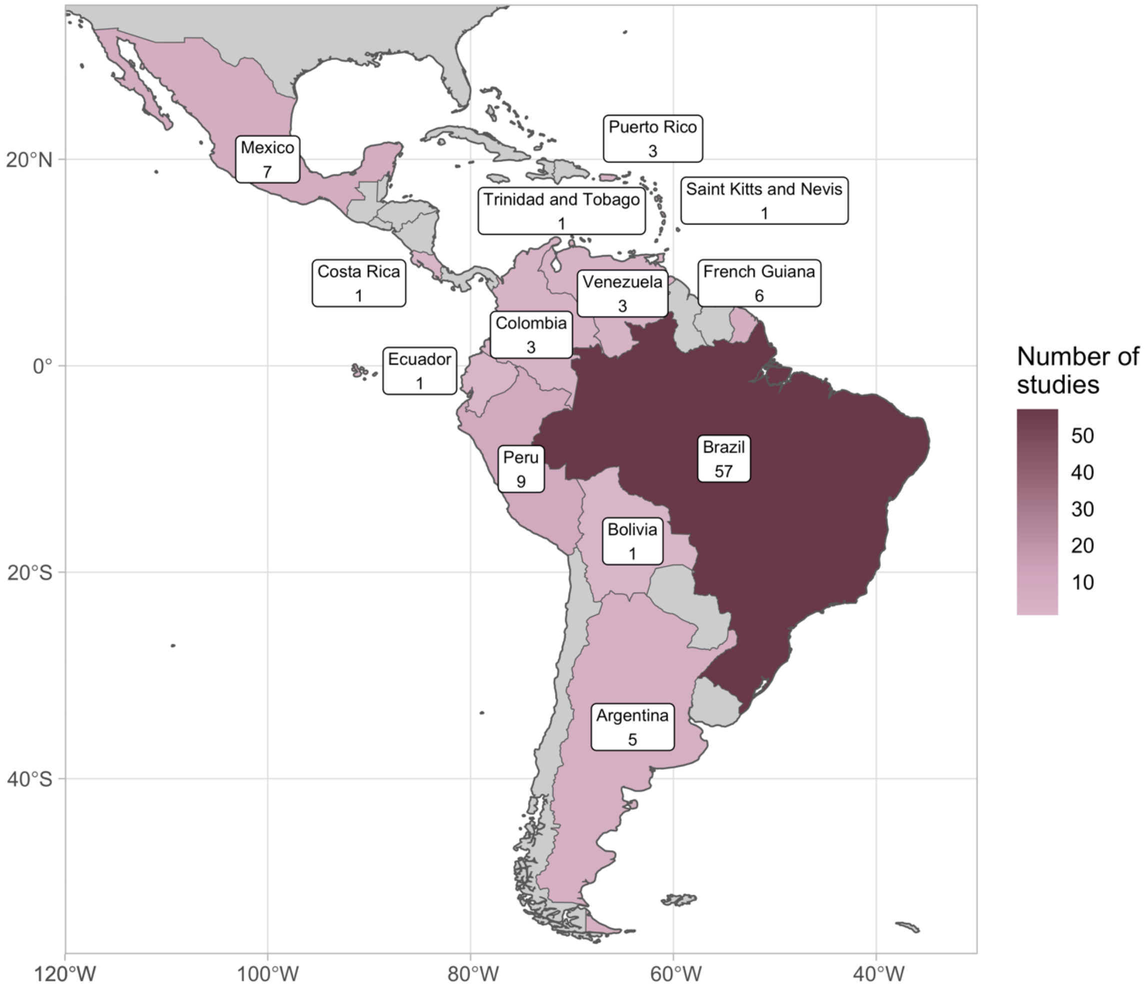


Figure S5.3. Distribution of studies included in the mosquito biodiversity dataset by country. Number of included studies by country in Latin America and the Caribbean. The total number of included studies was 93.

Table S5.10. List of *Aedes* and *Anopheles* mosquito species included in abundance and species richness models. List of *Aedes* and *Anopheles* mosquitoes (n=91) included in models and number of abundance records per species.

Genus	Species	Number of records
Aedes	aegypti	1819
Aedes	albifasciatus	50
Aedes	albopictus	1722
Aedes	angustivittatus	15
Aedes	argyrothorax	90
Aedes	busckii	20
Aedes	crinifer	62
Aedes	dupreei	5
Aedes	epactius	6
Aedes	fluviatilis	115
Aedes	fulvithorax	23
Aedes	fulvus	137
Aedes	guerrero	2
Aedes	hastatus	35
Aedes	hortator	27
Aedes	infirmatus	9
Aedes	mediovitattus	25
Aedes	mediovittatus	10
Aedes	nubilus	41
Aedes	oligopistus	34
Aedes	patersoni	8
Aedes	pennai	2
Aedes	phaenonotus	4
Aedes	podographicus	5
Aedes	quadrivittatus	32
Aedes	rhyacophilus	21
Aedes	scapularis	602
Aedes	serratus	548
Aedes	taeniorhynchus	79
Aedes	terrens	133
Aedes	tormentor	18
Aedes	tortilis	65
Aedes	trivittatus	4
Anopheles	albimanus	84
Anopheles	albitarsis	263
Anopheles	allopha	4
Anopheles	apicimacula	7
Anopheles	aquasalis	27
Anopheles	argyritarsis	129
Anopheles	arthuri	9
Anopheles	atropos	25
Anopheles	bellator	43
Anopheles	benarrochi	47
Anopheles	bradleyi	15
Anopheles	braziliensis	78
Anopheles	calderoni	4
Anopheles	costai	17

Anopheles	cruzii	132
Anopheles	darlingi	698
Anopheles	deaneorum	25
Anopheles	dunhami	44
Anopheles	eiseni	47
Anopheles	evansae	161
Anopheles	fluminensis	68
Anopheles	forattinii	17
Anopheles	galvaoi	85
Anopheles	gilesi	1
Anopheles	goeldii	41
Anopheles	grabhamii	25
Anopheles	ininii	12
Anopheles	intermedius	96
Anopheles	janconnae	21
Anopheles	kompi	15
Anopheles	konderi	9
Anopheles	lanei	20
Anopheles	lutzii	59
Anopheles	maculipes	9
Anopheles	malefactor	9
Anopheles	marajoara	51
Anopheles	mattogrossensis	226
Anopheles	mediopunctatus	136
Anopheles	minor	16
Anopheles	neivai	4
Anopheles	neomaculipalpus	9
Anopheles	nimbus	176
Anopheles	nuneztovari	171
Anopheles	oryzalimnetes	22
Anopheles	oswaldoi	183
Anopheles	parvus	25
Anopheles	peryassui	34
Anopheles	pseudopunctipennis	34
Anopheles	pseudotibiamaculatus	4
Anopheles	punctimacula	15
Anopheles	rangeli	86
Anopheles	rondoni	25
Anopheles	shannoni	27
Anopheles	squamifemur	9
Anopheles	strodei	187
Anopheles	tibiamaculatus	3
Anopheles	triannulatus	407
Anopheles	vestitipennis	40

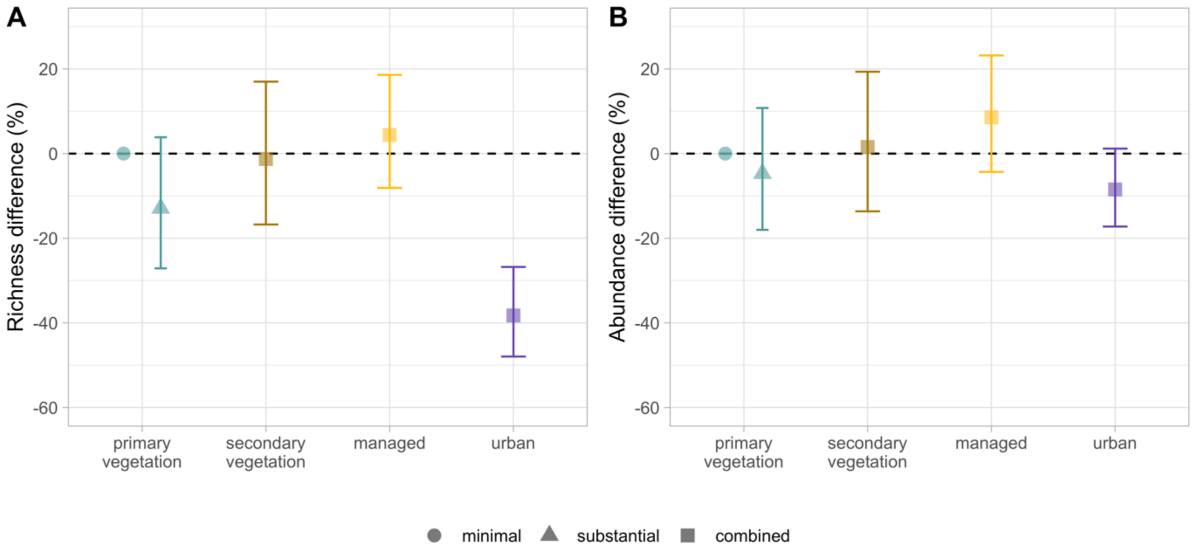


Figure S5.4. Responses of total *Aedes* and *Anopheles* mosquito richness and abundance to land-use type and intensity. Total (*Aedes* and *Anopheles*) mosquito richness (A) and abundance (B) responses to land-use types with minimal (circles), substantial (triangles) and combined (squares) use intensities. Effect sizes were adjusted to a percentage by expressing each mean fixed effect and 95% credible intervals as a percentage of the baseline (primary vegetation minimal use, shown as zero). Intensity levels for secondary vegetation, managed and urban land uses were aggregated due to a lack of data representation.

Table S5.11. Parameter estimates for land-use types in mosquito species richness models. Posterior mean estimates, lower (2.5%) and upper (97.5%) credible intervals (CI) for land-use types in species richness models of *Aedes* and *Anopheles* mosquitoes.

Model	Land-use type	Mean	LCI	UCI
Total species richness	Primary vegetation – minimal (intercept)	1.36	1.19	1.53
	Primary vegetation - substantial	-0.14	-0.32	0.04
	Secondary vegetation - combined	-0.01	-0.18	0.16
	Managed - combined	0.04	-0.08	0.17
	Urban - combined	-0.48	-0.65	-0.31
Aedes species richness	Primary vegetation – minimal (intercept)	0.95	0.74	1.16
	Primary vegetation - substantial	-0.12	-0.39	0.15
	Secondary vegetation - combined	0.01	-0.24	0.27
	Managed - combined	-0.11	-0.39	0.16
	Urban - combined	-0.31	-0.56	-0.05
Anopheles species richness	Primary vegetation – minimal (intercept)	0.95	0.74	1.16
	Primary vegetation - substantial	-0.12	-0.39	0.15
	Secondary vegetation - combined	0.01	-0.24	0.27
	Managed - combined	-0.11	-0.39	0.16
	Urban - combined	-0.31	-0.56	-0.05

Table S5.12. Parameter estimates for land-use types in mosquito abundance models. Posterior mean estimates, lower (2.5%) and upper (97.5%) credible intervals (CI) for land-use types in abundance models of *Aedes* and *Anopheles* mosquitoes.

Model	Land-use type	Mean	LCI	UCI
Total abundance	Primary vegetation – minimal (intercept)	0.59	-0.17	1.46
	Primary vegetation - substantial	-0.05	-0.20	0.10
	Secondary vegetation - combined	0.02	-0.15	0.18
	Managed - combined	0.08	-0.04	0.21
	Urban - combined	-0.09	-0.19	0.01
Aedes abundance	Primary vegetation – minimal (intercept)	0.70	-0.22	1.64
	Primary vegetation - substantial	-0.03	-0.21	0.16
	Secondary vegetation - combined	0.04	-0.16	0.24
	Managed - combined	-0.06	-0.28	0.15
	Urban - combined	-0.06	-0.16	0.04
Anopheles abundance	Primary vegetation – minimal (intercept)	0.59	0.33	0.84
	Primary vegetation - substantial	-0.12	-0.28	0.04
	Secondary vegetation - combined	-0.05	-0.20	0.11
	Managed - combined	0.11	0.00	0.21
	Urban - combined	-0.14	-0.25	-0.02

Table S5.13. Parameter estimates for land-use types in species-level mosquito abundance models. Posterior mean estimates, lower (2.5%) and upper (97.5%) credible intervals (CI) for land-use types in abundance models of four *Aedes* and four *Anopheles* mosquitoes.

Model	**Land-use type**	**Mean**	**LCI**	**UCI**
Aedes aegypti	Primary vegetation – minimal (intercept)	1.60	0.87	2.33
	Primary vegetation - substantial	-0.39	-0.86	0.07
	Secondary vegetation - combined	-0.81	-1.34	-0.28
	Managed - combined	1.12	0.56	1.68
	Urban - combined	0.16	-0.07	0.39
Aedes albopictus	Primary vegetation – minimal (intercept)	0.87	0.16	1.59
	Primary vegetation - substantial	0.66	0.23	1.09
	Secondary vegetation - combined	0.52	0.05	0.98
	Managed - combined	0.40	-0.48	1.28
	Urban - combined	0.10	-0.11	0.31
Aedes scapularis	Primary vegetation – minimal (intercept)	1.83	1.05	2.62
	Primary vegetation - substantial	-0.59	-0.86	-0.32
	Secondary vegetation - combined	0.08	-0.18	0.35
	Managed - combined	-0.07	-0.35	0.21
	Urban - combined	-0.02	-0.13	0.09
Aedes serratus	Primary vegetation – minimal (intercept)	1.86	1.03	2.69
	Primary vegetation - substantial	-0.93	-1.41	-0.46
	Secondary vegetation - combined	0.24	-0.25	0.73
	Managed - combined	-1.08	-1.58	-0.59
	Urban - combined	-0.11	-0.31	0.08
Anopheles albimanus	Primary vegetation – minimal (intercept)	0.41	-0.92	1.71
	Primary vegetation - substantial	0.86	-0.62	2.34
	Secondary vegetation - combined	0.02	-1.54	1.57
	Managed - combined	0.47	-1.09	2.02
	Urban - combined	0.46	-1.23	2.20
Anopheles albitarsis	Primary vegetation – minimal (intercept)	0.80	-0.01	1.62
	Primary vegetation - substantial	-0.05	-0.75	0.68
	Secondary vegetation - combined	0.38	-0.52	1.27
	Managed - combined	0.97	0.30	1.65
	Urban - combined	-0.02	-0.92	0.88
Anopheles darlingi	Primary vegetation – minimal (intercept)	1.40	0.81	1.98
	Primary vegetation - substantial	-0.21	-0.79	0.36
	Secondary vegetation - combined	0.37	-0.33	1.06
	Managed - combined	0.21	-0.12	0.54
	Urban - combined	-0.13	-0.80	0.54
Anopheles nuneztovari	Primary vegetation – minimal (intercept)	0.81	0.30	1.32
	Primary vegetation - substantial	-0.19	-0.79	0.41
	Secondary vegetation - combined	0.22	-0.47	0.89
	Managed - combined	-0.13	-0.71	0.44
	Urban - combined	-0.41	-1.05	0.21

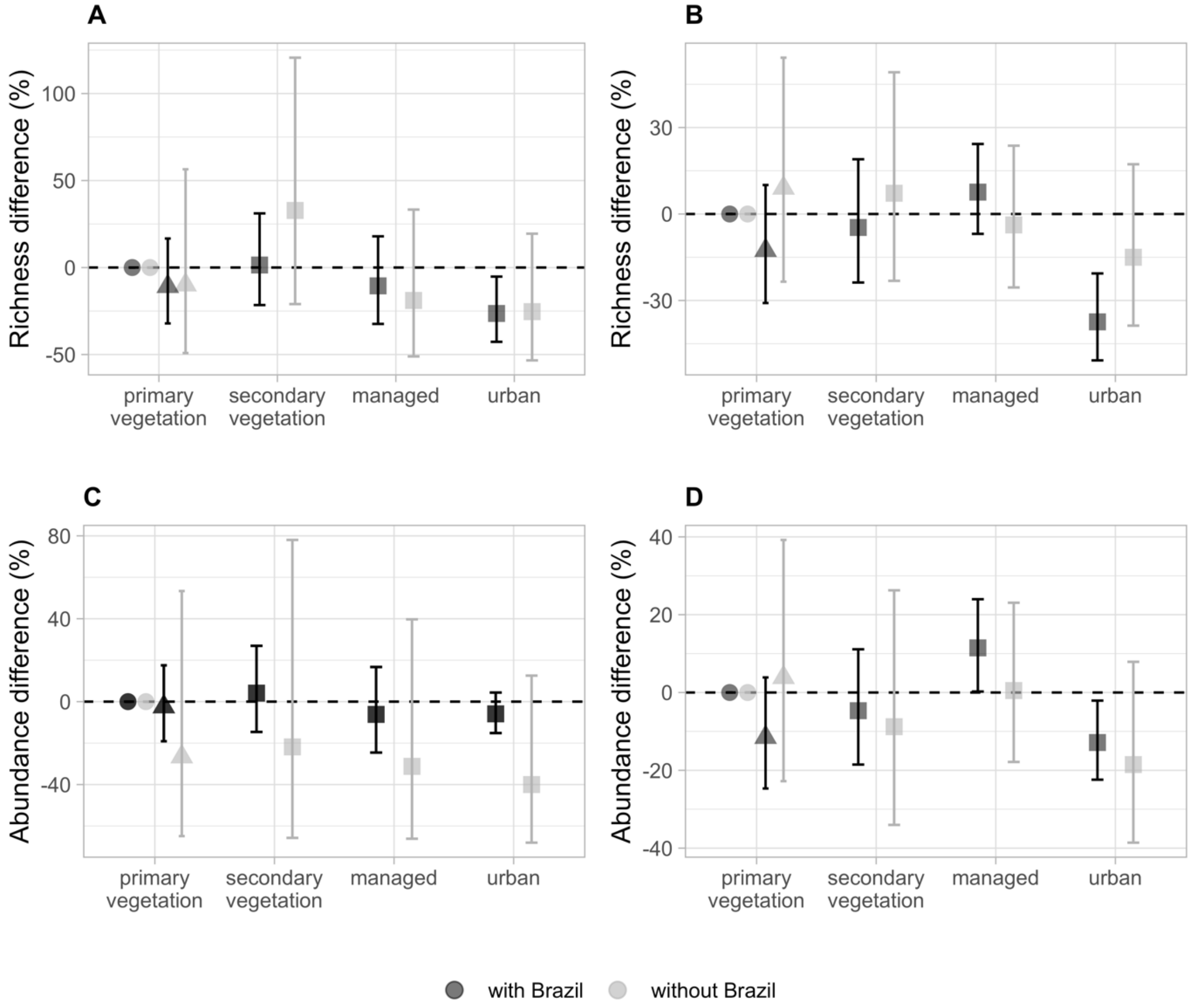


Figure S5.5. Geographical cross-validation of genus-level abundance and richness responses to land-use type and intensity. Response of *Aedes* (A, C) and *Anopheles* (B, D) mosquitoes to land-use type and intensity excluding sites from Brazil. Dark grey estimates show the genus-level richness (A-B) and abundance (C-D) models with all the data and the light grey estimates show modelled estimates excluding sites from Brazil. Effect sizes were adjusted to a percentage by expressing each mean fixed effect and 95% credible intervals as a percentage of the baseline (primary vegetation minimal use, shown as zero). Intensity levels for secondary vegetation, managed and urban land uses were aggregated due to a lack of data representation.

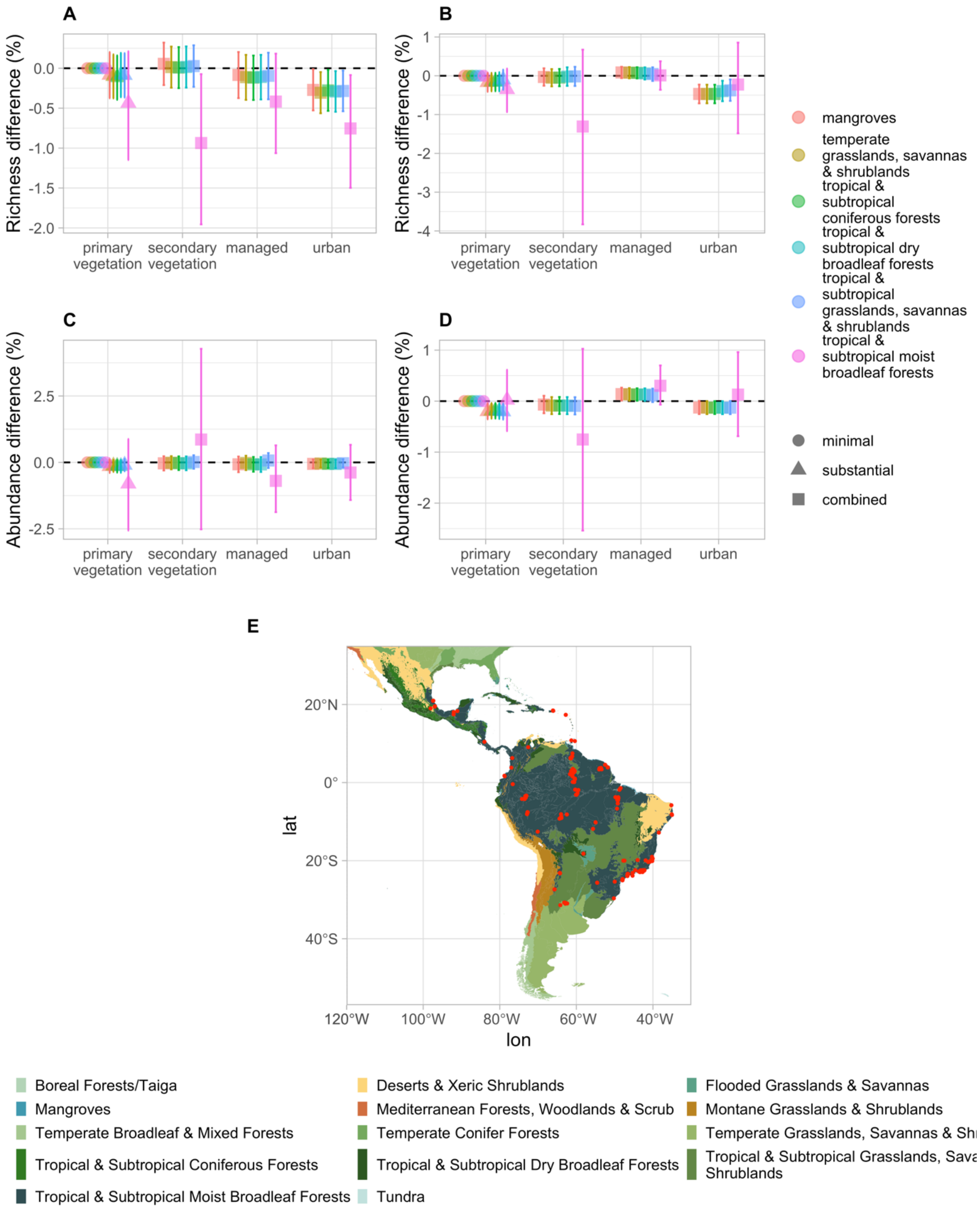


Figure S5.6. Ecoregion sensitivity analysis. Response of *Aedes* (A, C) and *Anopheles* (B, D) mosquito species richness (A-B) and abundance (C-D) to land-use type and intensity excluding each ecoregion in turn. Colours represent each ecoregion that was excluded. Effect sizes were adjusted to a percentage by expressing each mean fixed effect and 95% credible intervals as a percentage of the baseline (primary vegetation minimal use, shown as zero). Intensity levels for secondary vegetation, managed and urban land uses were aggregated due to a lack of data representation. Both abundance and species richness were highly sensitive to rainforest sites (pink - tropical and subtropical moist broadleaf forests), which is not surprising given the distribution of study sites (E; red points).

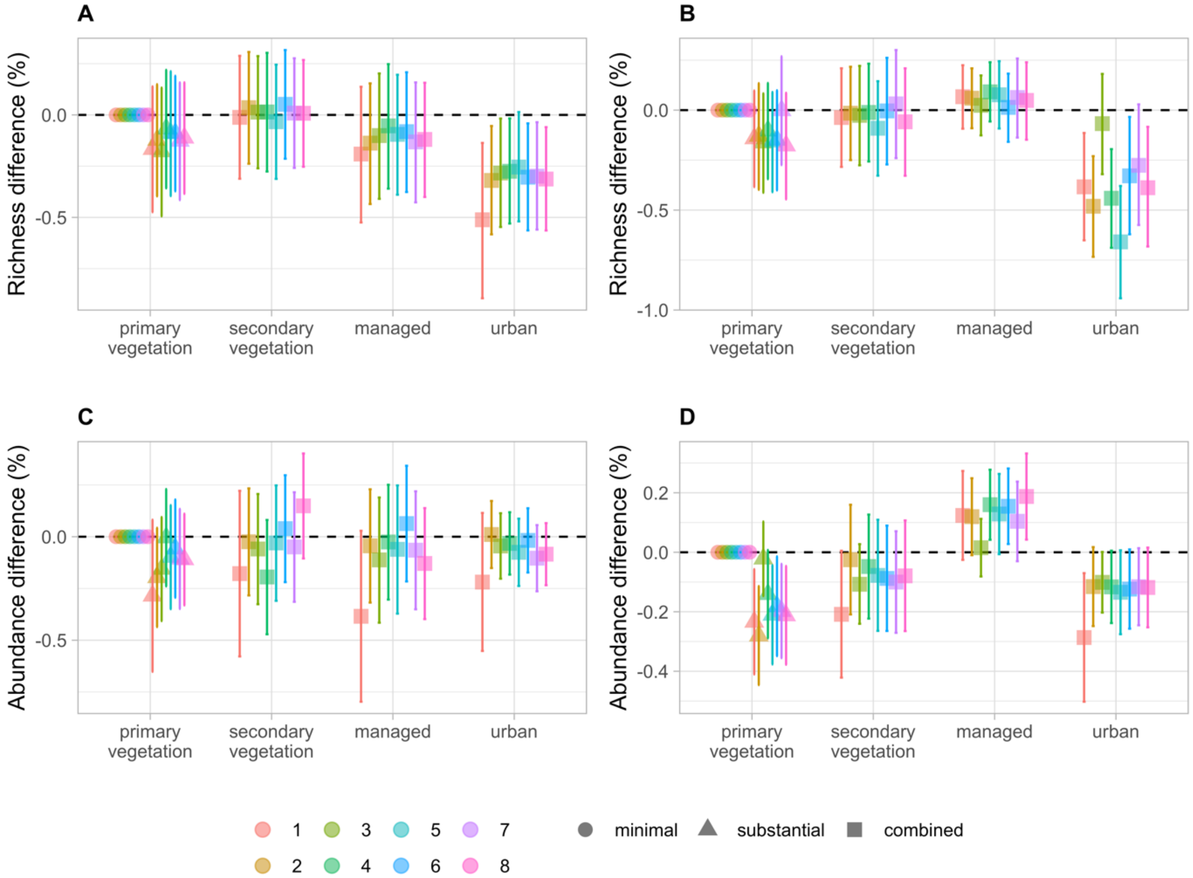


Figure S5.7. Random subsampling cross-validation analysis. Response of *Aedes* (A, C) and *Anopheles* (B, D) mosquito species richness (A-B) and abundance (C-D) to land-use type and intensity excluding 12.5% of the data at time. Colours represent each data group. Effect sizes were adjusted to a percentage by expressing each mean fixed effect and 95% credible intervals as a percentage of the baseline (primary vegetation minimal use, shown as zero). Intensity levels for secondary vegetation, managed and urban land uses were aggregated due to a lack of data representation.

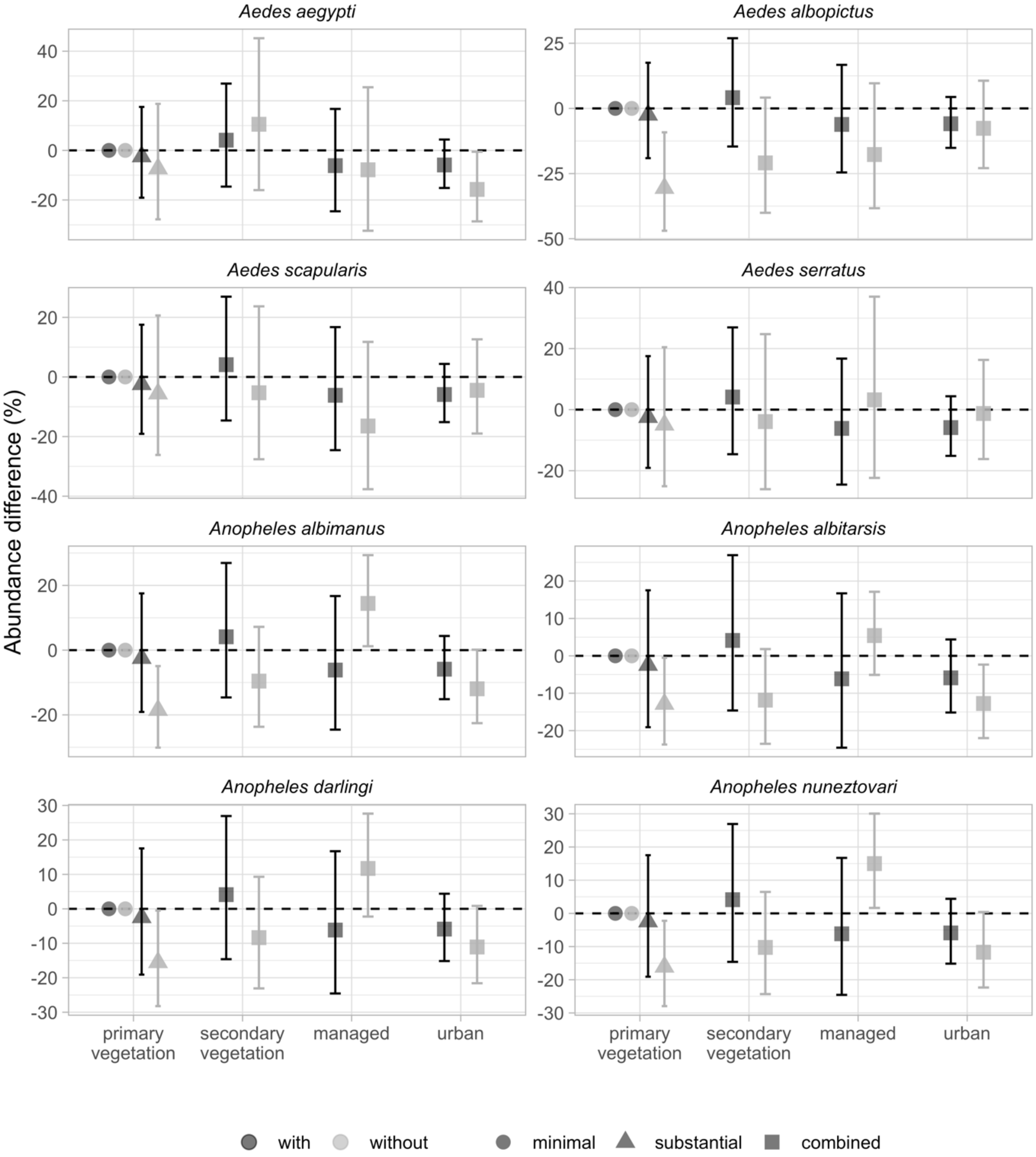


Figure S5.8. Species-level cross-validation of genus-level abundance responses to land-use type and intensity. Response of *Aedes* (A) and *Anopheles* (B) mosquito abundance to land-use type and intensity excluding influential species. Dark grey estimates show the genus-level abundance model with all the data and the light grey estimates show modelled estimates excluding data for each species. For each genus, the four most represented species in the dataset were selected. Effect sizes were adjusted to a percentage by expressing each mean fixed effect and 95% credible intervals as a percentage of the baseline (primary vegetation minimal use, shown as zero). Intensity levels for secondary vegetation, managed and urban land uses were aggregated due to a lack of data representation.

Appendix V – Publications, copyright and permissions

Chapter 2

The research presented in Chapter 2 was published on 27th August 2020 in *Frontiers in Environmental Science* (https://doi.org/10.3389/fenvs.2020.00135). This research article is open access and published with a Creative Commons license, and copyright is owned by the authors: Fletcher, Stewart-Ibarra, Sippy, Carrasco-Escobar, Silva, Beltran-Ayala, Ordoñez, Adrian, Sáenz, Drakeley, Jones and Lowe.

Chapter 3

The research presented in Chapter 3 was published on 1st September 2022 in the *Lancet Planetary Health* (https://doi.org/10.1016/S2542-5196(22)00192-9). This research article is open access and was published under a Creative Commons licenses and copyright is retained by the authors: Fletcher, Grillet, Moreno, Jones, Drakeley, Hernandez-Villena and Lowe. Preliminary results of this study were published in a special issue of the *Lancet Planetary Health* on 1st April 2021 (https://doi.org/10.1016/S2542-5196(21)00097-8).

Chapter 4

The review section and results presented in this chapter were published as a commentary on 9th April 2021 in *Med* (https:// doi.org/10.1016/j.medj.2021.03.010). Copyright for this commentary is owned by Elsevier Inc. and re-publication for use in a thesis is permitted (see https://www.elsevier.com/about/policies/copyright/permissions). For this thesis, the research was extended (section 4.2-4.4) and restructured into a chapter to include a more detailed description of the methods and allow for further exploration of model results. The review section (4.1) was also re-formatted to allow for a more cohesive chapter structure.

Chapter 5

The research presented in this chapter is being prepared for submission to *Proceedings of the Royal Society B: Biological Sciences*.

Chapter 6.4

This discussion piece is currently being prepared as a Personal View, for submission to *The Lancet Planetary Health.*