Spatial Risk Assessment of Mosquito-Borne Viral Diseases – Research at the Intersection of Ecology and Epidemiology.

Dissertation

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"Chikungunya is a specifically tropical disease. It is relatively uncommon and poorly documented" — Pialoux et al. (2007)

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Contents

Summary

Mosquito-borne viral diseases pose an increasing threat to human and animal health on a global level. Over the past few decades, competent vector species like the Asian tiger mosquito (*Aedes albopictus)* or the Asian bush mosquito (*Aedes japonicus*) have spread vigorously across the globe and far beyond their native distribution. During the same time, large outbreaks of diseases that are being transmitted by these and other mosquito species (such as chikungunya, Zika, West-Nile fever and Usutu) have been recorded. Diseases that were formerly considered purely tropical by many, such as dengue and chikungunya, showed repeated outbreaks along the coast of the Mediterranean Sea – far away from the tropics. Usutu virus (which was largely neglected in the past as long as it was spatially limited to Africa) emerged in Europe, causing mass extinction events among blackbird populations. Evidence suggests that increasing temperatures due to climate change will facilitate future spread. Clearly, there is an increasing need for spatial risk assessment of these diseases.

In this thesis, I use two established approaches, Ecological Niche Models and Epidemiological Models, to assess the spatial risk arising from different mosquito-borne viral diseases. Building models for chikungunya and Usutu viruses as well as the mosquito vector *Ae. albopictus*, I produce risk maps at global, continental, national and local scales. I explore the strengths and weaknesses of the different approaches and make suggestions for future improvements.

All models in this thesis suggest a potential for a continued increase in mosquito-borne viral disease occurrence in large parts of the respective study area. On a global scale, chikungunya is expected to increase its presence on all continents except for Antarctica as well as some areas in Australia and northern India (where climate change will lead to conditions that may prohibit vector survival). On a continental scale, two fundamentally different models for Usutu

suggest that large parts of Europe offer favorable environmental conditions for transmission of the disease. However, they differ considerably at the local scale. At the national scale, large parts of western Germany are projected to become climatically suitable for the establishment of *Ae. albopictus* in the near future due to climate change. Most of these areas (including those that are already highly suitable today) also showed elevated incidence rates of travel-related dengue and chikungunya infections, suggesting an elevated risk for virus transmission. Risk maps are an important tool that can be used by field entomologists and epidemiologists for more targeted surveillance and monitoring. And they can help to communicate essential information to politicians and decision makers in order to facilitate the establishment of the infrastructure that is necessary for these endeavors.

Both Epidemiological Models and Ecological Niche Models suffer from a lack of essential data. For Epidemiological Models, laboratory studies and field data about the underlying mechanisms of transmission are severely lacking for many diseases. This is demonstrated in this thesis using the extrinsic incubation period (EIP) of dengue as an example. It has long been known that the duration of the EIP inside the mosquito vector highly depends on ambient temperature. However, among the few experimental works that investigate that relationship, several are based on flawed methodology or otherwise outdated. For many less-studied diseases (such as Usutu) the gaps in knowledge are still much larger. The need for more fundamental research in this area is high.

For Ecological Niche Models, the availability of high-quality occurrence records of vectors and diseases is a major problem. International and interdisciplinary efforts towards a centralized, open data repository need to be intensified. The centralized climate data repository of the Earth System Grid Foundation (ESGF, https://esgf.llnl.gov) and the data base of species occurrence records at the Global Biodiversity Information Facility (GBIF, http://www.gbif.org) could serve as inspiration for this. Transferability of

model results across different climate zones is another issue that warrants further investigation.

Finally, different models have different pros and cons, and different questions require different approaches. Ecological Niche Models require only a limited amount of *a-priori* knowledge about the environmental parameters governing a species' spatial distribution. Even with relatively low numbers of occurrence records, they can be very useful for rapid, coarse scale risk assessment. Epidemiological Models are built upon a much more detailed theoretical background, and if they are parameterized thoroughly, they can add valuable information on fine spatio-temporal scales. While Ecological Niche Models have always been intended for spatial applications, the adaption of Epidemiological Models for the creation of spatial risk maps involves some unresolved hurdles that will be addressed in future works.

Zusammenfassung

Von Stechmücken übertragene Krankheiten stellen zunehmend eine Gefahr für die Gesundheit von Mensch und Tier dar. Im Laufe der letzten Jahrzehnte haben sich kompetente Vektoren wie die Asiatische Tigermücke (*Aedes albopictus)* und die Asiatische Buschmücke (*Aedes japonicus*) global energisch ausgebreitet. Es besteht Grund zu der Annahme, dass Klimawandel-bedingt zunehmende Temperaturen diesen Trend auch in Zukunft fördern werden. Gleichzeitig wurden weltweit große Ausbrüche von Krankheiten beobachtet, die von diesen und anderen Stechmückenarten übertragen werden (beispielsweise Zika, West-Nil-Fieber und Usutu). Entlang der Mittelmeerküste kam es wiederholt zu Ausbrüchen von Dengue und Chikungunya – Krankheiten die von vielen vormals als reine Tropenkrankheiten angesehen wurden. Auch das Usutu-Virus wurde, solange es nur sporadisch in Afrika gemeldet wurde, weitestgehend ignoriert. Das änderte sich erst, als es in Europas Vogelpopulationen zu großen Usutu-Ausbrüchen kam, die in Deutschland unter dem Namen „Amselsterben" Bekanntheit erlangten. Es besteht daher ein offenkundiger Bedarf für räumliche Abschätzungen des mit diesen Krankheiten verbundenen Risikos.

In dieser Dissertation verwende ich zwei etablierte Methoden (Ecological Niche Models und ein epidemiologisches Modell) zur räumlichen Risikobeurteilung einiger durch Stechmücken übertragener Viruserkrankungen. Ich erstelle Risikokarten für Chikungunya, Usutu, und die Vektorart *Ae. albopictus* auf unterschiedlichen räumlichen Skalen. Ich untersuche Stärken und Schwächen der unterschiedlichen Methoden und mache Vorschläge für zukünftige Verbesserungen.

Ausnahmslos alle Modelle in dieser Dissertation deuten darauf hin, dass das Auftreten von durch Stechmücken übertragenen Viruserkrankungen in weiten Teilen des jeweiligen Untersuchungsgebiets weiternehmen wird. Auf globaler

Ebene wird erwartet, dass sich die Präsenz von Chikungunya auf allen Kontinenten außer der Antarktis erhöht. Ausnahmen bilden einige Gebiete in Australien und Nordindien, in denen der Klimawandel zu Bedingungen führen wird, die das Überleben von Vektoren verhindern können. Auf kontinentaler Ebene deuten zwei grundlegend unterschiedliche Modelle für Usutu darauf hin, dass große Teile Europas günstige Umweltbedingungen für die Übertragung der Krankheit bieten. Allerdings unterscheiden sich die Ergebnisse der beiden Modelle auf lokaler Ebene teils erheblich. Auf nationaler Ebene werden Klimawandel-bedingt große Teile Westdeutschlands in naher Zukunft die klimatischen Anforderungen für eine Etablierung von *Ae. albopictus* erfüllen. Die meisten dieser Gebiete (einschließlich derjenigen, die bereits heute sehr gut geeignet sind) wiesen in der Vergangenheit auch erhöhte Inzidenzraten für reisebedingte Dengue- und Chikungunya-Infektionen auf, was auf ein erhöhtes Risiko für die Übertragung von Viren hinweist. Risikokarten sind ein wichtiges Instrument, das von Feldentomologen und Epidemiologen zur gezielteren Überwachung (sowohl *surveillance* als auch *monitoring*) verwendet werden kann. Und sie können dazu beitragen, Politikern und Entscheidungsträgern wichtige Informationen zu übermitteln, um den Aufbau der für diese Bemühungen erforderlichen Infrastruktur zu erleichtern.

Sowohl epidemiologische Modelle als auch Ecological Niche Models leiden unter einem Mangel an wesentlichen Daten. Für epidemiologische Modelle fehlen für viele Krankheiten Laborstudien und Felddaten zu den zugrundeliegenden Übertragungsmechanismen. Dies wird in dieser Arbeit am Beispiel der extrinsischen Inkubationsperiode (EIP) von Dengue demonstriert. Es ist seit langem bekannt, dass die Dauer der EIP innerhalb des Mückenvektors stark von der Umgebungstemperatur abhängt. Unter den wenigen experimentellen Arbeiten, die diese Beziehung untersuchen, basieren einige auf fehlerhaften Methoden oder sind anderweitig stark veraltet. Der Bedarf an Grundlagenforschung in diesem Bereich ist hoch, da bei vielen weniger untersuchten Krankheiten (wie z.B. Usutu) noch viel erheblichere Wissenslücken bestehen.

Ein Hauptproblem von Ecological Niche Models ist die Verfügbarkeit hochwertiger Aufzeichnungen über das Auftreten von Vektoren und Krankheiten. Die internationalen und interdisziplinären Bemühungen um ein zentrales, offenes Datenarchiv müssen intensiviert werden. Das zentralisierte Klimadatenarchiv der Earth System Grid Foundation (ESGF, https://esgf.llnl.gov) und die Datenbank für Vorkommensdaten von Arten in der Global Biodiversity Information Facility (GBIF, http://www.gbif.org) könnte als Inspiration dafür dienen. Die Übertragbarkeit von Modellergebnissen über verschiedene Klimazonen hinweg ist ein weiteres Problem, das weitere Untersuchungen erfordert.

Letztendlich bieten unterschiedliche Modelle unterschiedliche Vor- und Nachteile, und unterschiedliche Fragen erfordern unterschiedliche Lösungsansätze. Ecological Niche Models erfordern nur ein begrenztes *a-priori* Wissen über die Umweltparameter, die die räumliche Verbreitung einer Art bestimmen. Selbst mit einer relativ geringen Anzahl von Vorkommensdaten können insbesondere sie für eine schnelle, räumlich grob aufgelöste Risikobewertung sehr nützlich sein. Epidemiologische Modelle bauen auf einem viel stärker theoretisch geprägten Hintergrund auf. Eine adäquate Parametrisierung vorausgesetzt, können sie wertvolle Informationen auf feinen räumlich-zeitlichen Skalen beitragen. Während Ecological Niche Models von Grund auf für räumliche Anwendungen gedacht sind, birgt die Anpassung epidemiologischer Modelle für die Erstellung räumlicher Risikokarten einige ungelöste Hürden, die das Objekt zukünftiger Arbeiten sein werden.

Introduction

Author's note

This dissertation touches a broad spectrum of different disciplines: From ecology to epidemiology, from the very coarse scales of climatology down to the microscopic scales of virology, from human to animal health. This inevitably means that not every reader will be familiar with the terminology used in all of these fields. Some terms might even be counter-intuitive. For convenience, I have thus decided to include a Glossary of the most important terms in the Appendix.

Regarding italicization, capitalization and abbreviation of viral taxa and non-taxonomical names, this dissertation follows the recommendations of the International Committee on Taxonomy of Viruses (ICTV, 2019). In accordance with this, as well as common practice in the scientific and non-scientific English language literature, only elements of virus and disease names that refer to individual persons or geographic entities are capitalized (for example "Carrion's disease", which was named after Daniel Alcides Carrión, or "Marburg virus", which was named after the city of Marburg).

Mosquito-Borne Viral Diseases

Overview

The term "Mosquito-Borne Viral Diseases" (MBVD) describes a group of diseases that are caused by viral pathogens and transmitted among vertebrate hosts through the bites of blood-sucking mosquitoes (Diptera: *Culicidae*). As such, they are part of the larger group of vector-borne diseases – diseases where the transmission between humans or other vertebrate hosts requires (or strongly relies on) another species serving as a vector (Verwoerd, 2015). Many MBVD are also zoonotic diseases, commonly defined as diseases that can be transmitted between humans and other vertebrates (Porta, 2014).

The pathogens causing vector-borne diseases include prokaryotes (e.g. the *Borrelia* genus of bacteria causing Lyme disease), protozoa (e.g. the various *Plasmodium* species causing malaria) as well as multicellular organisms (e.g. the *Filarioidea* superfamily of nematodes causing various forms of filariasis). However, most human-relevant vector-borne pathogens are viruses, causing diseases such as yellow fever, dengue fever, Japanese encephalitis or the recently emerging Zika fever.

Mosquitoes (Culicidae, *Diptera*) represent the most important group of vector species, followed by other arthropods such as fleas (*Siphonaptera*), true bugs (*Hemiptera*), sucking lice (*Anoplura*), cockroaches (*Blattidae*), ticks (*Ixodidae*, *Argasidae*) and mites (*Dermanyssidae*, *Trombiculidae*) (Gubler, 2009).

It is thus justified to focus this study on Mosquito-Borne Viral Diseases. This important subset of vector-borne diseases includes viruses from at least three families of RNA viruses (Gubler, 2009; Clements, 2012, pp. 91–104): *Bunyaviridae* (e.g. Rift Valley virus), *Flaviviridae* (e.g. dengue virus) and *Togaviridae* (e.g. chikungunya virus). The relevant insect vector species belong to either of the two genera *Culex* and *Aedes*.

This thesis focuses on the effects climate has on mosquito-borne viral diseases and their implications on spatial risk assessment.

A short history of mosquito-borne diseases

Mosquito-borne diseases like malaria have occurred since at least the classical antiquity, though the mechanisms of transmission were unknown at the time (Cox, 2010). Proto-globalization during the Age of Discovery (ca. 15th–18th century) facilitated a first wave of worldwide spread of vector-borne diseases. Freshwater storage aboard the sail ships of the time provided the necessary breeding grounds for mosquitoes, so that transmission among crew and passengers could be upheld throughout the journey (compare e.g. Christophers, 1960, pp. 40–57 & 77; Smith & Gibson, 1986). Most notably, it is generally

assumed that the shipping of African slaves was the main driver for the introduction of *Aedes aegypti* (globally one of the most important mosquito vectors today) to the Americas (Reiter, 2008). Large outbreaks of yellow fever, dengue, malaria, and other vector-borne diseases followed. Gubler (1998) even claims that, from the 17th to early 20th century, vector-borne diseases alone were the primary reason for human disease and death.

The transmission pathway of these diseases remained unclear until 1877, when Patrick Manson discovered that *Wuchereria bancrofti*, the parasite causing lymphatic filariasis (better known as "elephantiasis"), is transmitted by mosquitoes (Chernin, 1983). This paved the road for further studies on other diseases, leading to the discovery of the malaria transmission pathway in the late 1890ies (Cox, 2010). Soon after that, several more vector-borne diseases were identified as such, including yellow fever, dengue and Chagas disease (Gubler, 1998). From the early 20th century on, efforts in disease control focused strongly on the vector species. For mosquitoes, physical measures such as the destruction of breeding sites and installation of shielded doors and windows were combined with the application of insecticides such as Paris Green, Pyrethrum and later DDT (Severo, 1955; Stapleton, 2004; Floore, 2006). Major mosquito control campaigns were conducted from the beginning of the 20th century until the end of the 1960s. By this time, mosquito-borne diseases were no longer seen as a substantial threat any more in the industrialized parts of the world (Gubler, 1998; Reiter, 2001; WHO, 2014a). Subsequently, funding was withdrawn from mosquito eradication campaigns after their apparent success and directed towards more pressing issues (Phillips, 2008).

However, these advances proved to be a short-term solution. For example, the Global Malaria Eradication Programme established by the WHO in 1955 failed, and was stopped in 1969 when it became clear that complete eradication was not possible in practice (Nájera et al., 2011). The use of DDT and other insecticides had to be reduced considerably after the targeted mosquitoes developed resistances (Hemingway & Ranson, 2000; Rivero et al., 2010).

Consequently, the 1970s were marked by an unexpected global resurgence of vector-borne diseases (Gubler, 1998) that continues until today. Notable recent examples include the return of dengue and introduction of chikungunya to Europe (Rezza, 2016), the 2013–2014 chikungunya epidemic in the Americas (Yactayo et al., 2016) or the unexpected appearance of the formerly disregarded Zika virus as a "Public Health Emergency of International Concern" (Heymann et al., 2016; Sikka et al., 2016). According to the World Health Organization (WHO), vector-borne diseases today "account for more than 17% of all infectious diseases, causing more than 700,000 deaths annually" (WHO, 2020).

Transmission cycle

The typical transmission pathway of a Mosquito-Borne Viral Disease can be classified as propagative biological transmission (Gubler, 2009). It is based on the mandatory feeding of female mosquitoes on vertebrates: These bloodmeals are needed for the development of eggs. The transmission cycle begins with an already infected host that is viremic, i.e. has viral particles in its bloodstream. If a female mosquito takes a bloodmeal from that host, the virus enters the insect's digestive system. There, it replicates and spreads out through the vector's body, possibly overcoming several barriers (Franz et al., 2015; Kramer & Ciota, 2015) and ultimately reaching the salivary glands. Mosquito saliva contains a series of enzymes, that support the bloodmeal. The mosquito spills saliva into the entry wound in order to widen blood vessels, prevent clogging and suppress pain (Clements, 2000; Ribeiro & Francischetti, 2003). When a mosquito with infected salivary glands takes a second bloodmeal from another host, viral particles are released into the host's bloodstream, completing the transmission cycle (Clements, 2012, pp. 116–117).

Although the process outlined above is generally thought to be the main mechanism for arboviral dispersal and maintenance, additional transmission pathways exist for some pathogens and vectors (Clements, 2012, pp. 5–8). Most importantly, vertical transmission among mosquitoes from mother to offspring has been demonstrated for several diseases. This pathway has long been

suspected to serve as a secondary mechanism for maintaining the virus in a mosquito population under conditions where the normal transmission cycle is difficult to complete. This hypothesis is supported by a recent meta-analysis by Lequime et al. (2016). Laboratory experiments have shown that vertically infected male mosquitoes can transmit viruses to uninfected females during copulation (e.g. Mavale et al., 2010; Pereira-Silva et al., 2018). To which degree this venereal transmission pathway plays a role in-situ is unknown, though, as it has not been documented in the field (Clements, 2012, pp. 119–124).

Among hosts, direct transmission of mosquito-borne diseases does not usually occur. A notable exception to this is the Rift Valley virus, where animal–animal and animal–human transmission through direct contact with infected tissues or bodily fluids is relatively common (Anyangu et al., 2010; Pepin et al., 2010). For some MBVD vertical transmission among humans can happen during pregnancy or at birth (e.g. Lenglet et al., 2006; Tan et al., 2008; Tabata et al., 2016). In rare cases, vertical transmission through breastfeeding has also been observed (Barthel et al., 2013; Colt et al., 2017). It is known that Zika can occasionally be transmitted sexually between humans (Counotte et al., 2018), and recently it has been suggested that this may be the case for dengue as well (Wilder-Smith, 2019; Grobusch et al., 2020).

Diseases covered in this dissertation

Dengue

Dengue, the "world's fastest growing vector-borne disease" (WHO, 2014b, p. 1), is caused by the dengue virus (DENV) and mainly transmitted by *Aedes aegypti* and *Ae. albopictus*. The symptoms of human dengue infections are diverse. Most patients experience the non-severe form of dengue that is characterized by a high fever (thus the name "dengue fever") in combination with headache, pain behind the eyes, joint and muscle pains, nausea, vomiting, swollen glands and/or rash (WHO, 2017). However, a small proportion of patients develop serious complications that are summarized under the term "severe dengue" (formerly "dengue haemorrhagic fever"). These symptoms are potentially life-threatening and include severe bleeding, severe organ impairment and/or plasma leakage that may be accompanied by respiratory distress and can result in fluid accumulation and shock (WHO, 2009).

DENV, a single-stranded RNA virus from the family of *Flaviviridae*, was first isolated in 1943 in Nagasaki, Japan by Kimura and Hotta (Hotta, 1952; Gubler, 2006; Kuno, 2007). DENV can be divided into four distinct serotypes, DENV-1 to 4, that differ both phylogenetically and antigenically (Messina et al., 2014). A fifth serotype (DENV-5) was recently proposed (Mustafa et al., 2015), but has not been formally acknowledged yet (Taylor-Robinson, 2016). Surviving an infection with one of these serotypes grants life-long immunity against this specific serotype. However, previous infection with one serotype increases the likelihood of developing severe dengue when infected with another serotype (WHO, 2017).

The dengue virus probably originated from Asia or possibly Africa, where it diverged from its ancestors approximately 1000 years ago (Holmes & Twiddy, 2003; Clements, 2012, pp. 197–198). Initially transmitted among non-human primates by forest-dwelling mosquitoes, the virus adapted to new hosts and vectors when it established in settlements. There, it was transmitted among the

human population by *Ae. albopictus* and other related mosquitoes (Gubler, 2006, p. 198; Clements, 2012). The global spread of the very competent African vector *Ae. aegypti* by sail ships was soon followed by outbreaks of dengue fever. Although dengue was already endemic across the tropics during the 18th century, major epidemics were rather rare and usually limited to the *Ae. aegypti*-infested port cities (Gubler, 2006).

The currently ongoing global pandemic started in the Asian and Pacific region during World War II. While campaigns to eradicate *Ae*. *aegypti* appeared to be successful in the Americas (Clements, 2012, pp. 200–201), here the effects of war and the following urbanization facilitated outbreaks of dengue and further global spread (Figure 1). With the termination of the *Ae. aegypti* eradication campaign in the 1970s, both the mosquito and virus returned to the Americas (Gubler, 2011; Messina et al., 2014). An "unprecedented increase in the number of cases" and Pan-American outbreaks followed in the 2000s (Dick et al., 2012). This trend continues through the 2010s in South and Central America, the Pacific and Asia (Roth et al., 2014; WHO, 2017). The situation in Africa is less clear, as the disease is under-recognized and thus under-reported there. However, outbreaks have occurred and autochthonous transmission has been reported from at least 20 African countries (Amarasinghe et al., 2011; Were, 2012).

Since World War II, regions outside the tropical zone have been largely spared from autochthonous transmission of dengue. Notable exceptions included northern Mexico (Machado-Machado, 2012) and the US state of Texas, where transmission sporadically occurred near the Mexican border (Rigau-Perez et al., 1994; Setlik et al., 2004; Ramos et al., 2008). In recent years, though, autochthonous transmission of dengue has increasingly occurred in sub-tropical and temperate climates, including Florida (US) (Trout et al., 2010), Croatia (Schmidt-Chanasit et al., 2010; Gjenero-Margan et al., 2011b), France (La Ruche et al., 2010b; Marchand et al., 2013b; Succo et al., 2016b), Madeira,

Portugal (Sousa et al., 2012), Japan (Arima et al., 2014) and China (Lai et al., 2015).

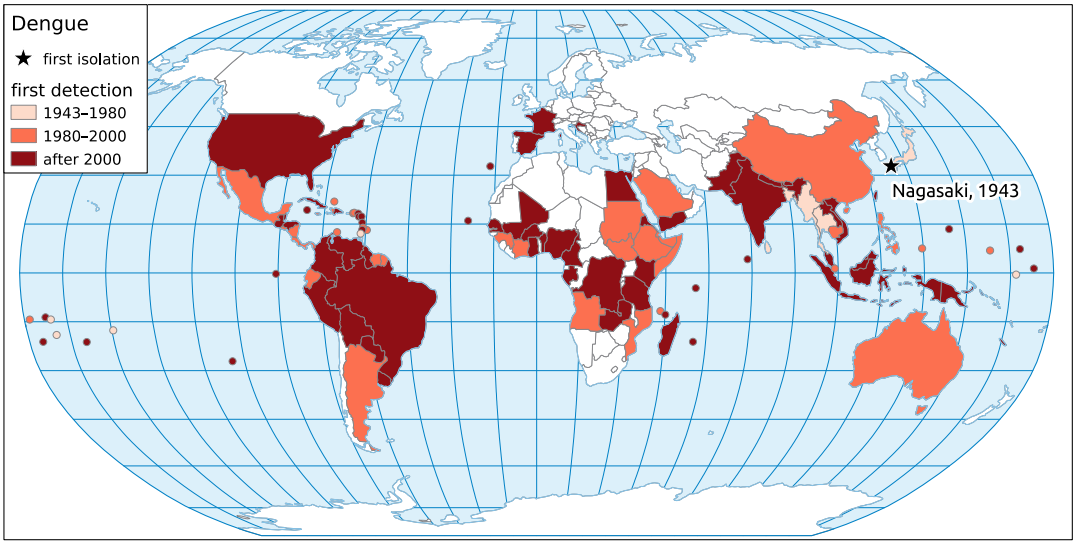

Figure 1. Global overview of the spatial distribution of dengue. Countries, islands and archipelagos reporting dengue transmission since its first isolation of the virus in Nagasaki, Japan, 1943 (black star). Colors refer to the time DENV was first detected in an area, omitting historical occurrences. Information based on Messina et al. (2014) with additions from Botros et al. (1989), Mazaba-Liwewe et al. (2014), Makiala-Mandanda et al. (2018). Records for Uruguay, Galapagos, France, Croatia, Egypt, and Spain from ProMED-Mail (Archive numbers: 20070320.0972, 20100316.0840, 20100915.3345, 20110306.0743, 20151117.3798419, and 20181021.6103066, respectively). Robinson projection (EPSG: 53030), with geodata from NaturalEarthData.com.

Consequently, dengue is described by the WHO as "the world's fastest growing vector-borne disease", with more than 40% of the global population currently being at risk (WHO, 2014b, p. 1). Currently, dengue is endemic in more than 100 countries and the number of reported cases continues to increase with "explosive outbreaks" (WHO, 2017). The WHO estimates that with more than 40% of the global population at risk of an infection, there are 50 to 100 million infections and 0.5 million cases of severe dengue each year (WHO, 2014b, p. 1).

Chikungunya

Chikungunya is an infectious disease caused by the chikungunya virus (CHIKV) that is mainly transmitted by *Ae*. *aegypti* and *Ae*. *albopictus*. Belonging to the Alphavirus genus in the family of *Togaviridae*, CHIKV is an enveloped, positive-sense, single-stranded RNA virus. It was first described by Robinson and Lumsden in 1955, following an outbreak that had occurred in today's Tanzania two years before (Lumsden, 1955; Robinson, 1955). Robinson noted that the disease was "clinically indistinguishable from dengue", given the broad range of symptoms the various forms of dengue can show. However, severe joint pains are a strong indicator for chikungunya, which is also expressed in its name. It is derived from the Kimakonde root verb "kungunyala" ("to dry up", "to become contorted", (Lumsden, 1955)), and, following Robinson (1955), usually translated as "that which bends up". Based on this characteristic, in retrospect several historic outbreaks in the 19th century that were originally attributed to DENV may actually have been caused by CHIKV (Halstead, 2015; Kuno, 2015).

From the 1950s onward until the early 2000s, chikungunya was regarded to be geographically limited to Asia and Sub-Saharan Africa (Figure 2). A peak in activity in the decades of the 1960s to 1980s was followed by a period of sporadic outbreaks in these areas (Zeller et al., 2016). A 2004 outbreak on Lamu Island, Kenya (Sergon et al., 2008), marked the beginning of a chikungunya pandemic in Central and Western Africa, in and around the Indian Ocean and in large parts of Asia. Starting in 2011 increasing numbers of cases were reported from the Pacific region and in 2013 the virus was introduced into the Caribbean (Zeller et al., 2016). This has widely been regarded as the first outbreak of chikungunya in the Americas, although some authors hypothesize earlier American chikungunya events in the 19th century (Halstead, 2015; Kuno, 2015). From its initial outbreak area on Saint Martin, the disease quickly spread across the Caribbean islands and the Central and Latin American mainland, causing millions of infections and hundreds of deaths among the population (Yactayo et al., 2016).

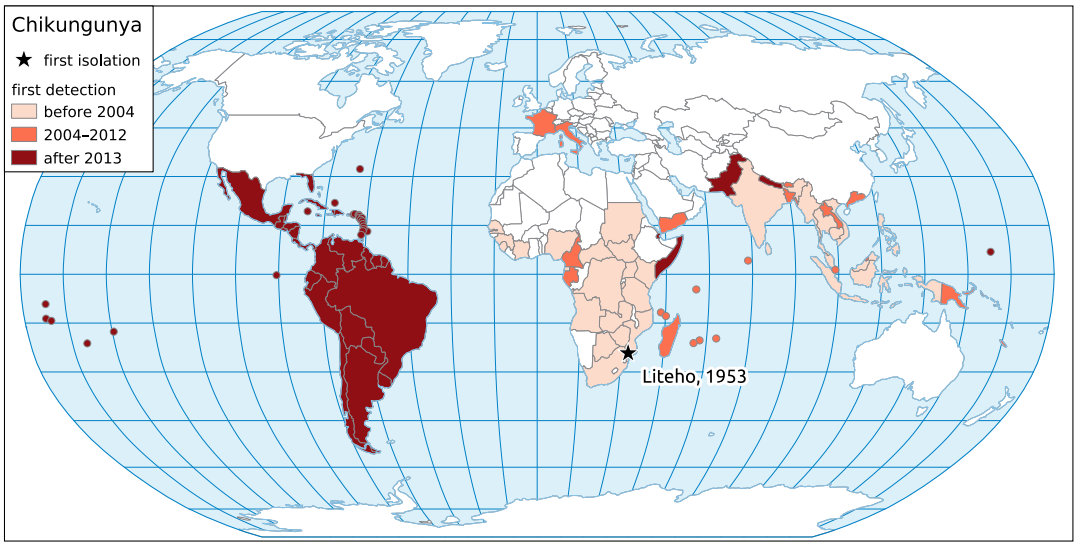

Figure 2. Overview of the spatial distribution of Chikungunya. Countries, provinces, islands and archipelagos reporting chikungunya transmission since its first isolation of the virus in Liteho, South Africa, 1953 (black star). Colors refer to the time CHIKV was first detected in a country. 2004 marks the beginning of the recent global expansion. In 2013, transmission was observed in the Americas for the first time. Information based on Zeller et al. (2016) for Africa and Eurasia, as well as PAHO (2013–2017) for the Americas. Additional data from Deller & Russell (1968); Salim & Porterfield (1973); Hayes et al. (1986); Beesoon et al. (2008); Yoosuf et al. (2009); Liew & Yung (2012); Zayed et al. (2012); Ansumana et al. (2013); Soulaphy et al. (2013); Pun et al. (2014); Tun et al. (2014); Khatun et al. (2015); Gudo et al. (2016); Humphrey et al. (2017); Wahid et al. (2017); Ryan et al. (2019). Robinson projection (EPSG: 53030), with geodata from NaturalEarthData.com.

While the vast majority of chikungunya outbreaks so far have taken place in the tropical zone, reports of autochthonous transmission from continental Europe prove that tropical climate as such is not required for the occasional transmission of the pathogen. The first outbreak in a temperate area occurred in 2007 in the region of Ravenna in northern Italy, where 205 individuals suffered from locally transmitted chikungunya (Rezza et al., 2007). This was followed by a series of limited outbreaks in France: 2010 in Fréjus, Var (Grandadam et al., 2011b), 2014 in Montpellier (Delisle et al., 2015b) and 2017 in Le Cannet-des-Maures and Taradeau, Var (Calba et al., 2017b; Calba et al., 2018). In 2017, another outbreak occurred in Lazio and Calabria, Italy (Manica et al., 2017).

Usutu

Usutu is an emerging disease caused by the Usutu virus (USUV), a single-stranded RNA virus from the family of *Flaviviridae* that is predominantly transmitted by mosquitoes of the genus of *Culex* (Roesch et al., 2019). USUV belongs to the Japanese encephalitis serocomplex and is closely related to other pathogens from that group, including West Nile virus (WNV) and Saint Louis encephalitis virus (Gaibani & Rossini, 2017). It was named after the Great Usutu River in South Africa, where it was first isolated from *Culex neavei* mosquitoes in 1959 (Williams et al., 1964; Roesch et al., 2019; CDC, 2020).

A wide range of bird species can serve as its natural host (Clé et al., 2019), with the common blackbird (*Turdus merula*) being particularly affected in Europe where significant USUV-induced events of avian mass mortality occurred in the 2010s (Gaibani & Rossini, 2017; Roesch et al., 2019). USUV has also been detected in other vertebrates, including humans, bats, horses, dogs, deer and rodents). These are generally considered to be dead-end hosts, although case data is sparse and uncertainties remain. For bats in particular, it has been speculated that they may act as reservoir hosts or even contribute to epizootics (Cadar et al., 2014; see also Fagre & Kading, 2019).

Geographically, USUV until now has been limited almost exclusively to Africa and Europe (Figure 3). After the 1959 discovery of the virus in South Africa, it was isolated in several countries across sub-Saharan Africa, including Burkina Faso, the Central African Republic, Cote d'Ivoire, Nigeria, Senegal, and Uganda (reviewed in Nikolay et al., 2011). Based on genetic analysis, it has been proposed that USUV may have been introduced to Europe through migratory birds repeatedly since the 1950s (Engel et al., 2016). The first proven occurrence of USUV outside sub-Saharan Africa however, was in Tuscany, Italy in or before 1996 (Weissenböck et al., 2013). During the following two decades, USUV or corresponding antibodies were detected in hosts and vectors in several countries across Europe and around the Mediterranean Sea, where it caused notable die-offs among blackbird populations. Most prominently, it

recurred over several years in Austria (Weissenböck et al., 2002; Meister et al., 2008), Germany (Linke et al., 2007; Ziegler et al., 2015; Ziegler et al., 2016), Hungary (Bakonyi et al., 2007), Poland (Hubálek et al., 2008b; Bażanów et al., 2018), Italy (Manarolla et al., 2010; Tamba et al., 2011; Calzolari et al., 2017) Spain (Busquets et al., 2008; Vazquez et al., 2011; Höfle et al., 2013), and Switzerland (Steinmetz et al., 2011). In single years, USUV activity was also reported from Belgium (Garigliany et al., 2014), the Czech Republic (Hubálek et al., 2008a), France (Lecollinet et al., 2016), Great Britain (Buckley et al., 2006), Greece (Chaintoutis et al., 2014), Israel (Mannasse et al., 2017), Morocco (Durand et al., 2016), Serbia (Lupulovic et al., 2011), Slovakia (Csank et al., 2018) and Tunisia (Ben Hassine et al., 2014).

2016 marks the year of the first major USUV epizootic (Clé et al., 2019). Up until then, all known USUV-related events had been limited to relatively small areas, and USUV was generally considered an "arbovirus with low zoonotic potential" (Michel et al., 2018). In 2016, however, multiple lineages of USUV showed unprecedentedly high activity in a large area across the western Europe, often in co-circulation with WNV. With cases in France, Belgium, the Netherlands and Germany, USUV-induced mass mortality of primarily blackbirds (*Turdus merula*) was observed for the first time (Rijks et al., 2016; Cadar et al., 2017; Michel et al., 2018). Two years later, in 2018, further rapid spread of USUV was observed in several Western European countries (Aberle et al., 2018; Beck et al., 2018; Carletti et al., 2019; NABU, 2019).

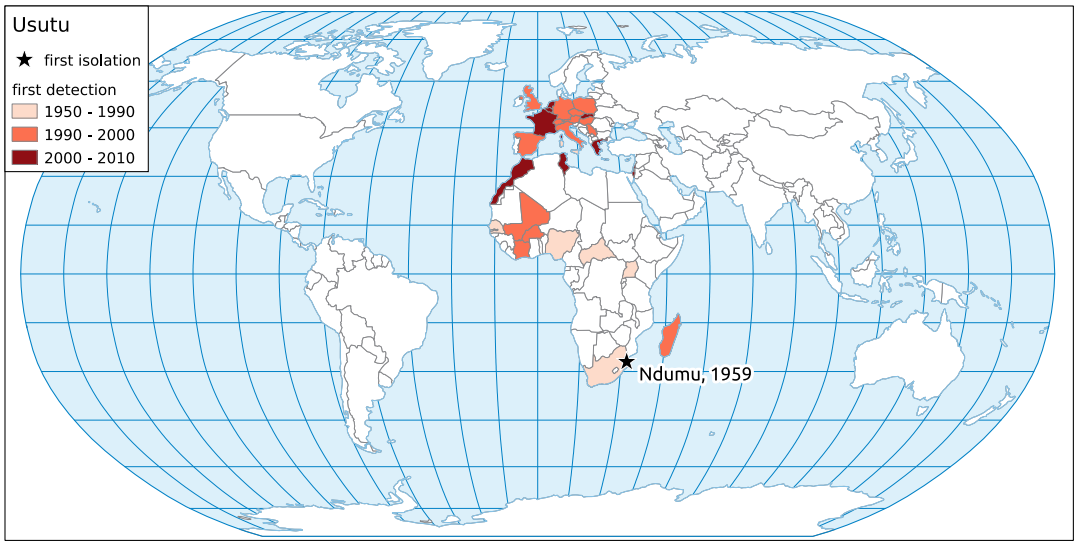

Figure 3. Global overview of the spatial distribution of Usutu. Countries reporting USUV transmission since its first isolation of the virus in Ndumu, South Africa, 1959 (black star). Colors refer to the time USUV was first detected in an area. Information based on Weissenböck et al. (2002); Buckley et al. (2006); Bakonyi et al. (2007); Linke et al. (2007); Busquets et al. (2008); Hubálek et al. (2008a); Hubálek et al. (2008b); Meister et al. (2008); Lupulovic et al. (2011); Nikolay et al. (2011); Steinmetz et al. (2011); Weissenböck et al. (2013); Ben Hassine et al. (2014); Chaintoutis et al. (2014); Garigliany et al. (2014); Durand et al. (2016); Lecollinet et al. (2016); Gaibani & Rossini (2017); Mannasse et al. (2017); Csank et al. (2018); Chevalier et al. (2020). Robinson projection (EPSG: 53030), with geodata from NaturalEarthData.com.

Human cases of USUV are rarely detected, as they tend to be asymptomatic and thus may not be noticed at all. Out of the proven 49 cases of acute infections in humans that were detected worldwide until 2019, 25 were identified only by chance in the blood of healthy donors (Clé et al., 2019). Symptomatic USUV infections, on the other hand, can manifest in several different ways. The first human cases identified in the Central African Republic in the 1981 and Burkina Faso in 2004 were rather mild, accompanied by fever, skin rash and jaundice (Nikolay et al., 2011). Severe cases of USUV-related meningoencephalitis were first detected in two hospital patients in Italy in 2009. Incidentally, both of them were immunosuppressed as receivers of an organ transplant and chemotherapy, respectively (Cavrini et al., 2009; Pecorari et al., 2009), and thus particularly susceptible to infections. However, retrospective studies focusing

on patients with neurological infections soon revealed further cases of USUV-related encephalitis and meningoencephalitis in Italy (Cavrini et al., 2011; Grottola et al., 2017) and Croatia (Santini et al., 2015; Vilibic-Cavlek et al., 2019). Finally, another retrospective study in France detected an acute human USUV infection that was unexpectedly accompanied by idiopathic facial paralysis (Simonin et al., 2018). So far, no human death has been attributed to USUV. Whether or not the virus will turn out to be a major threat for human health is currently unpredictable, as data and knowledge on USUV is even more sparse than for the other MBVD discussed in this thesis.

Climatic effects on Mosquito-Borne Viral Diseases

MBVD are, on sufficiently large spatial scales, strongly affected by climatic parameters such as temperature and precipitation. This happens in a multitude of ways, and influences a disease on multiple levels: The climatic niche of a mosquito species governs its geographical distribution. Temperature can affect various parameters of the disease's transmission cycle. Short-term effects of weather on MBVD also exist, and they are affected by climate on larger scales. For example, the frequency and intensity of extreme weather events such as droughts or heavy-rain days are likely to increase in large parts of the world due to climate change (Gallant et al., 2014; Stott, 2016).

Impacts on vector distributions and populations

Climate is one of the major factors governing the spatial distribution of insect species such as mosquitoes on global, continental, regional, and to some degree even landscape scales (Hortal et al., 2010). Especially temperature strongly affects individuals and populations of these ectotherm species in multiple ways. Although the temperature optimum varies by species, in general warm water and air temperatures are beneficial for the aquatic and adult stages of mosquitoes, as they accelerate development and increase fecundity (e.g. Ciota et al., 2014; Eisen et al., 2014). This is to some degree countered by an increase in mortality and a decrease of body size at higher temperatures (e.g. Bayoh & Lindsay, 2004; Kirby & Lindsay, 2009; Ciota et al., 2014). Large fluctuations in temperature tend to have adverse effects on various life-history traits of *Ae. aegypti* (Lambrechts et al., 2011; Carrington et al., 2013c).

It has been shown that frost can significantly reduce the hatching success of *Aedes sp.* eggs (Thomas et al., 2012). However, in these experiments individuals from tropical populations were found to be more susceptible to frost than those from populations adapted to temperate climate, and diapausing eggs were still more robust. This potential for adaption has enabled mosquito species originating from the tropics to gain a foothold in temperate regions. The latest

example for this is the recent discovery of several populations of *Ae. albopictus* overwintering in the warmer parts of Germany (Pluskota et al., 2016; Walther et al., 2017).

As all mosquito species require access to some form of surface water for their larval and pupal stages, precipitation is another important climatic factor governing their potential geographic distribution. Especially for species that breed in tree holes, rock pools or other small containers, rainfall is required to create and maintain larval habitats in natural environments. In human surroundings, however, lack of rain may not be an issue if it leads to water being stored in open containers (Trewin et al., 2013). Floodwater mosquitoes like *Aedes vexans* are also affected by precipitation regimes, as they lay their eggs in the ground along rivers and other water bodies in areas that will later be flooded temporarily (Becker et al., 2003). However, in the absence of natural flooding agricultural irrigation systems can serve as a viable substitute (Garzón et al., 2014). Heavy rainfall events can have oppositional effects on mosquito abundance. On the one hand, they can create new temporary water bodies that can serve as larval habitats. On the other hand, they can also flush larvae out of existing breeding grounds (Koenraadt & Harrington, 2008; Ahmed & Memish, 2017) or reduce development rates by removing nutrient-rich materials (Dieng et al., 2003). In addition to these effects of the precipitation regime, it has been suggested that the sea-level rise associated with global climate change may facilitate the occurrence of mosquito-borne diseases in coastal areas: Ramasamy & Surendran (2012) hypothesize that the increased extent of brackish and saline coastal waters will provide new habitats for salinity-tolerant mosquitoes, and expect that species like *Ae. aegypti* and *Ae. albopictus* will be able to adapt to saline conditions.

Impacts on disease dynamics

Climate can affect several components of disease outbreaks directly or indirectly. First and foremost, the duration of the extrinsic incubation period (EIP) of MBVD shortens with rising ambient temperature, leading to potentially

faster transmission in warmer regions (e.g. Reisen et al., 2006; Carpenter et al., 2011; Chan & Johansson, 2012; Manuscript 3).

Westbrook et al. (2010) found that adult *Ae. albopictus* were more susceptible to infection with chikungunya virus when the larvae had been reared at 18°C as opposed to 24 or 32°C. For dengue, lower temperatures and larger diurnal temperature ranges during adult life lead to lower virus dissemination in *Ae. albopictus* (Lambrechts et al., 2011; Alto & Bettinardi, 2013). As successful infection of the vector followed by dissemination is a prerequisite for further transmission, this means that vector competence can indeed be affected by temperature. However, as the above examples show, several seemingly conflicting observations have been made regarding the direction of this effect (reviewed by Samuel et al., 2016). Some studies even found complex interactions between temperature, virus and mosquitoes, suggesting that evolution and local adaption can modify the response to temperature (Zouache et al., 2014; Gloria-Soria et al., 2017).

Finally, vectorial capacity can be affected by weather (and thus, by extension, climate) in a number of ways. Drought, for example, can increase the probability of non-human vertebrate hosts visiting the same water holes that mosquitoes use for breeding, increasing the risk of ongoing transmission (Shaman et al., 2005). Both the seasonal and circadian activity patterns of host-seeking mosquitoes have been linked to ambient temperature (Roiz et al., 2010; Gray et al., 2011). Garzón et al. (2014) found that in different habitat types temperature, wind and cloud cover had different effects on the activity patterns of *Aedes albifasciatus*.

Climate- and weather-based models for MBVD risk mapping

Risk and risk maps

All manuscripts presented in this thesis ultimately refer to the following question: "How does the environment affect the risks associated with certain MBVD at a certain point in space and time?" It is thus worth considering what the word "risk" means in this context in the first place. Intuitively, the answer may seem obvious, but in practice a useful definition heavily depends on the context. Within the over-arching topic of Natural Hazards, Marre (2013) lists a collection of 23 different definitions of the term, from a multitude of disciplines (covering disaster relief, natural and social science, engineering and the insurance industry, among others). The basic concept, that has also been adopted by the United Nations (2016), is that the risk posed by a certain threat is governed by three major aspects. First, there is the *hazard*, an existing phenomenon or substance with the potential to cause harm. Second, there is *vulnerability*, an indication for how susceptible an individual, population or entire society is towards the hazard. Third, *exposure* describes the points of contact between the hazard and those that are potentially affected by it. In an over-simplified example, a pothole on a road can illustrate *hazard* as a potential threat for cyclists, and that hazard may increase as the pothole deepens over time. *Vulnerability* towards this hazard varies among cyclists: while a healthy biker may easily cope with it, a visually impaired or elderly person may be more likely to fall and get injured. Finally, *exposure* is much higher for the group of commuters that make daily use of the street than it is for mountain bikers who prefer the forest over city roads. Based on this, risk can (theoretically) be quantified and expressed as 1) the probability that a hazard will have harmful consequences or 2) the expected number of losses (lives, livelihoods, property, etc.) caused by a hazard (Marre, 2013).

While this underlying concept based on *hazard, vulnerability* and *exposure* certainly applies to epidemiology, definitions of risk still vary considerably within the field. For instance, the *Dictionary of Epidemiology* defines risk broadly as "the probability of an adverse or beneficial event in a defined population over a specified time interval" (Porta, 2014). The *Handbook of Epidemiology,* on the other hand, focuses on the individual by defining risk as "the probability that an individual who is initially disease-free will develop a given disease over a specified time or age interval" (Ahrens & Pigeot, 2007). Following this definition, the personal risk for a specific individual can indeed be calculated for "simple" diseases where risk is governed by a limited number of well-understood factors. An example for this is breast cancer, where the personal risk of an individual can indicate whether prophylactic medication should be considered (Ahrens & Pigeot, 2007).

In the context of MBVD, however, the term "risk" is predominantly used at the scale of populations (or "typical" or "average" members thereof) rather than individual persons. As MBVD are transmitted among the human population through mosquitoes, factors on individual level – such as genetic predispositions or dietary habits – play a minor (if any) role in the transmission cycle. Consequently, there is limited value in calculating risk for specific individuals. Furthermore, the transmission of MBVD depends on complex interactions between multiple factors (environmental, biological and societal), and the knowledge about these factors is often incomplete (compare Manuscripts 3 & 5). As a consequence, simplifications and generalizations have to be made that dictate a more population-focused view.

Moreover, different factors affect MBVD risk at different spatial and temporal scales. In terms of risk assessment, the importance of each factor varies depending on the status of the respective disease in a given area as well. For example, while long-term climatic conditions govern whether a species of mosquito vectors can sustain a local population in general, short- to medium-term weather conditions affect how large the population will be in a given year.

As long as no vector species occurs locally, risk assessment for a human MBVD will focus on the likelihood of mosquitoes being introduced and establishing local populations, while even large numbers of infected travelers carrying the virus into the area would not affect the risk for the local population. The conditions of course change dramatically as soon as an established vector population exists. This demonstrates how different situations call for different modes of risk assessment, where certain divers of risk are investigated more or less thoroughly, depending on the current needs. For this, different kinds of tools and models have been developed that focus on different aspects of risk and can be useful for different purposes and scenarios.

Risk maps are an important tool in epidemiology, as they can be used to illustrate and analyze geographical patterns of disease-related risks. For the reasons mentioned in the previous sections, and despite the name, these maps typically do not show risk in the strict sense of any of the above definitions. Instead, they often focus on one or more risk factors that can be used as an indicator or proxy for the actual risk. One rather simple example are the continental dengue risk maps by Jentes et al. (2016), where countries were classified into three classes of risk based on past incidence and expert opinion. Maps of actual or potential distributions of vector species are commonly used as an indicator for disease transmission risk from global to regional scales. On a very local scale, You et al. (2013) used socio-environmental characteristics to create a map of cholera risk for individual neighborhoods in Kolkata, India.

The two most commonly applied methods for creating such risk maps for MBVD based on environmental factors originate from two very different scientific disciplines: Correlative Ecological Niche Models are a standard tool used in biogeography and ecology for assessing species' distributions, while mechanistic disease transmission models are a core tool in epidemiology.

Ecological Niche Models of species' distributions

Over the last decades, Species Distribution Models (SDMs) have, become a central tool in biogeography, ecology, and nature protection. More recently, their usefulness for risk mapping of MBVD has been recognized increasingly (see Manuscript 5). On a conceptual level, the vast majority of SDM can be classified as correlative Ecological Niche Models (ENMs, also commonly called Environmental Niche Models), and indeed the terms SDM and ENM are often used interchangeably in practice (Peterson & Soberón, 2012).

Underlying principles: niche theory

ENMs are based on niche theory, an ecological concept that can be traced back to the beginning of the 20th century. Since then, several different definitions for (and interpretations of) the term *ecological niche* have been proposed and continue to co-exist (reviewed in Pocheville, 2015). ENM are based on the classical Hutchinsonian niche concept (Hutchinson, 1957), where a species' *fundamental* niche is defined as the n-dimensional hyper volume in environmental space (sometimes called *niche space*) within which the species is able to persist indefinitely in the absence of competition. The *realized* niche is then defined as that part of the fundamental niche where competition with other species does not prevent persistence. The different dimensions of environmental space consist of environmental parameters that are relevant for the species in question, such as soil pH or temperature (Pearson, 2010). Any real-world location's environmental conditions then correspond to a single point within this environmental hyperspace. Conversely, the environmental conditions at any single point in environmental space may be found at a number of different geographical locations in the real world. If the hyper volume – describing a species' niche in environmental space – is known, it can be used to map out areas of potential occurrence in geographical space. Note that this potential, often expressed as *environmental suitability*, merely describes a possibility for the species to exist under the environmental conditions at a given

location. By default, it does not take into account the limiting effects of negative biotic interactions or dispersal barriers.

Workflow

The general workflow for the creation of an ENM is as follows: First, *occurrence records*, geographical locations of a species' presence, are gathered. Ideally, these occurrence records are based on a randomized sampling scheme that is applied consistently across an entire study area. In practice, modelers often have to rely on records extracted from scientific publications, museum records, herbaria, and citizen science databases – making thorough data cleaning and pre-processing a necessity (Graham et al., 2004; Yu et al., 2010; Feldman et al., 2020). Many methods also require *absence records*, a second set of locations that represent areas where the species in question does *not* occur. However, this kind of *true absence* data is typically not available, so that they are substituted by *pseudo-absence* (or: *background*) locations drawn (semi-) randomly from within the study area (VanDerWal et al., 2009).

Second, environmental parameters relevant to the species' occurrence are identified, based on previous knowledge about its biology and ecology. Environmental data representing these parameters is then acquired, typically in the form of geographical raster data layers (stored as GeoTIFF, netCDF or similar), covering the study area.

In a third step, the geographical locations of presence and (pseudo-) absence records are superimposed upon the raster layers of environmental data. For each of these locations, the corresponding values in the environmental layers are extracted. This combination of presence/absence status and environmental conditions is the basis of the fourth step, the training of the correlative model.

For this, a multitude of different algorithms is available and applied in practice, ranging from simple multiple logistic regression to advanced machine-learning techniques like generalized boosted models (Ridgeway, 1999), random forests (Breiman, 2001), or Maxent (Phillips et al., 2006). Although

every algorithm has its individual strengths and weaknesses (Elith et al., 2006), Maxent has become the de-facto standard for this kind of studies, as it combines consistently good performance with an easy-to-operate graphical user interface (Qiao et al., 2015).

Regardless of the modelling algorithm employed, the next major step is to make a *prediction* of environmental suitability within the study area (Pearson, 2010). At this point, the correlation-based model of the associations between presence/absence status at the sampled locations and environmental parameters represents the species' niche in environmental space. Applying the model to the spatial raster layers of environmental data yields a map of environmental suitability in geographical space. If a binary map of potential presence and absence is required, a threshold measure needs to be applied to the continuous, relative suitability values (Liu et al., 2013; Liu et al., 2016).

The last obligatory step is model *validation*, using measures like Cohen's kappa (Cohen, 1960), true skill statistics (TSS, Allouche et al., 2006) or partial ROC testing (Peterson et al., 2008). Ideally, this is done with a second set of independently sampled occurrence records. Given the difficulties in obtaining such records, however, alternative methods including bootstrapping and elaborate data partitioning are commonly used (Araújo et al., 2005; Muscarella et al., 2014).

Finally, *projections* of the model in space or time can be made. For instance, it may be interesting to assess whether a species native to the study area A could potentially occur in another area B. Then another prediction would be made, where the environmental layers for A would be replaced by an equivalent set of environmental layers representing the same parameters in B. Similarly, the potential future distribution of a species under various climate change scenarios can be estimated using environmental data for the future based on climate models (see Manuscripts 1 & 2).

Risk mapping of MBVD using ENMs

In the context of MBVD, ENMs are commonly used to assess the potential spatial distribution of mosquito vectors. One of the earliest examples is the *Ae. albopictus* model by Benedict et al. (2007) that helped raise awareness for the ongoing global invasion of the species. One decade later, Manuscript 2 aims to do the same on a much finer spatial scale.

The usage of ENMs for estimating the potential spatial distribution of diseases themselves is a relatively new development. Here, evidence of autochthonous transmission of the disease is used as occurrence records for the pathogen and referred to environmental variables that can affect the disease and its vectors (Peterson, 2014). This approach is only applicable if there are clear connections between disease and environment that significantly affect its spatial distribution. For example, attempts to apply ENMs to the 2020 COVID-19 pandemic in its early stages have been criticized strongly because the observed correlations of disease occurrence and climate lacked evidence of causation (Carlson et al., 2020). For most MBVD, however, it is clear that climate plays a major role for the potential of vector and disease occurrence. Consequently, a series of ENM for MBVD have been successfully implemented like this in the more recent past (reviewed in Manuscript 5, and performed in Manuscripts 1 & 4).

Epidemiological disease transmission models

Epidemiological Models (EM) typically aim to depict the progression of infectious diseases in a population. Based on a number of different concepts, there is a variety of epidemiological modelling approaches available (compare e.g. Thrusfield, 2018a). Which approach is chosen for a study, primarily depends on the research questions and mode of disease transmission.

Underlying principles: R_0

EMs built for general risk assessment of MBVD are typically focused on the basic reproduction number R_0 (the average number of secondary infections

arising from a single infected individual in a completely susceptible population) as a measure for the transmissibility of a certain viral disease. Such models usually divide the populations of vectors and hosts into compartments of susceptible, exposed, infectious and/or recovered individuals (abbreviated as "SI", "SIR", or "SEIR models", depending on the compartments used). Based on ordinary differential equations or a probabilistic survival function, these models calculate the number of individuals in each compartment throughout a real or simulated epidemic.

The history of this branch of modern mathematical epidemiology is deeply rooted in theoretical ecology. Its foundations were laid down in the early twentieth century by Alfred Lotka (1880–1949) and Sir Ronald Ross (1857–1932) and expanded upon in the 1950s by George Macdonald (1903–1976). However, the full potential of R_0 was not recognized until the late 1970s, when groundbreaking work was done by Klaus Dietz, Robert May, Roy Anderson, and others (reviewed in Heesterbeek, 2002; Smith et al., 2012). The usefulness of R_0 in epidemiology lies in its role as a simple threshold measure: If $R_0 > 1$, an outbreak can persist, whereas it will fade out if $R_0 < 1$.

While it is theoretically possible to directly measure R_0 of newly emerging diseases during the early stages of an outbreak (i.e. before any immunity exists in the population), the reporting systems in place are usually not able to provide the data necessary for that (Delamater et al., 2019). It is worth noting that during an outbreak like the currently ongoing COVID-19 pandemic, the closely related effective reproduction number R_t may be easier to estimate from case numbers, as R_t does not assume a completely susceptible population.

As a mathematical concept, R_0 for an infectious disease is defined as:

$$R_0 = \beta \cdot \kappa \cdot d \qquad (1)$$

where β denotes the probability of transmission per contact, κ the number of contacts per unit time, and d the time contagiousness lasts after a host becomes infectious (Thrusfield, 2018b; Delamater et al., 2019). In practice, however, the

exact determination of R_0 for MBVD is far from being straightforward. One reason is, that the transmission cycle of MBVD is more complex (especially when multiple species of vectors and/or hosts are involved), so that a series of additional mechanisms and parameters need to be included in the models. In a simple transmission model for a mosquito-borne disease with a single host and a single vector species, the final equation for the calculation of R_0 can look like the following example from Martcheva (2015):

$$R_0 = \frac{\beta_{vh} \cdot \beta_{hv} \cdot a^2 \cdot N_v \cdot N_h}{\mu \cdot \alpha} \quad (2)$$

where β_{vh} and β_{hv} are the probabilities of vector–host and host–vector transmission per bite, a is the biting rate of mosquitoes, N_v and N_h are the vector and host population sizes, μ is the death rate of mosquitoes and α is the recovery rate of humans. With the introduction of further parameters, additional species, or time delays, the math necessary to deduce the equations quickly becomes more complicated (Martcheva, 2015). Due to that, several methods have been developed to simplify the mathematical procedures. But while they all result in a model with a threshold at $R_0 = 1$, technically spoken, several of these approaches do not calculate the average number of secondary infections (Li et al., 2011). It is thus apparent that numerical values of R_0 are not comparable across models based. However, the main use of R_0 as a threshold is not affected by that. In other words, models that follow different approaches (but are based on the same parameters and their respective values) should give consistent answers to the question "is R_0 larger or smaller than 1?". They will, however, in many cases give different results for the related question "how much does R_0 differ from 1?" (Li et al., 2011). Acknowledging this problem, Mordecai et al. (2017) recently published an EM with a simplified approach, where no attempt to calculate absolute values of R_0 is being made at all. Instead the authors only calculate whether or not R_0 is larger than 1, focusing on the general question of whether or not transmission is possible.

Parameterization

Once a model has been formulated for a MBVD, the next major hurdle to overcome is parameterization. Especially for new or rare viral diseases that have not yet been studied in depth, reliable information about parameters like transmission probability in unlikely to exist. Even for more common diseases such as dengue or chikungunya, knowledge may be unexpectedly sparse or heavily outdated (compare Manuscript 3). It is anything but uncommon to find values for parameters being extrapolated from knowledge about other, related viruses and vector species. Sometimes single parameter values in EMs are not more than just an "educated guess", as this may be the only way to proceed (Delamater et al., 2019). Unfortunately, not much improvement can be expected for the near future. Experiments required to yield the required data would be complicated, tedious and expensive, and the capacity of laboratories with appropriate security standards is very limited. It is thus crucial for modelers to not only acknowledge these imperfections in parameters, but also to provide a measure for the uncertainties arising from them in the workflow of a simulation study (see Mordecai et al., 2017, for an example).

Risk mapping of MBVD using Epidemiological Models

For a simple infectious disease, R_0 can be thought of as an "estimate of contagiousness" that depends on pathogenic features and behavioral patterns of the hosts (Delamater et al., 2019). It is thus always being determined for a specific outbreak situation (explicitly or implicitly, real or hypothetical) and can vary considerably depending on societal structure, disease control measures, etc. (Viceconte & Petrosillo, 2020). For MBVD, the temperature-dependence of several important parameters (see previous chapters) introduces additional variation in time and space. Temporal variations in temperature for major cities is easily derived from weather station data, so that time series of modelled R_0 over the course of an outbreak are commonly found in the literature. First spatial estimations of R_0 based on remotely sensed or spatially interpolated temperature data, however, have been popularized since approximately one

decade ago (e.g., Racloz et al., 2008; Hartemink et al., 2009). In the face of recently emerging global threats through MBVD in a connected world, the need for risk assessment is growing. The advantage of R_0-based approaches lies in the possibility to integrate spatial risk assessment with the analysis of temporal trends and patterns. Options for this and the joint use of EM and ENM are explored in Manuscript 4.

Synopsis of the following manuscripts

In the following, I will give a short overview of the manuscripts included in thesis, summarizing their methods, results and how they contribute to the current state of knowledge in MBVD risk mapping and related fields.

In **Manuscript 1**, a global, hazard-based risk assessment for chikungunya under current and future climatic conditions is presented. To map the climatic suitability of chikungunya, an Ecological Niche Model (ENM) was built upon locations of autochthonous CHIKV transmission and climatic variables. Future projections of the model were made for the IPCC CMIP5 scenarios RCP 4.5 and RCP 8.5, using climate data from an ensemble of 5 global climate models. Based on this, a "hazard index" was calculated, incorporating information on human population density as an indicator for potential exposure. Over all, the model retrodicts past spatial patterns of chikungunya transmission well, and in many areas, it performs noticeably better than comparable approaches published before. Future projections suggest that, due to climate change, the potential for chikungunya transmission will increase in many areas around the world. However, for some of the current hot spots of chikungunya transmission potential in India and South America, climatic suitability may decrease due to the climate becoming too extreme for the mosquito vectors. This work is the first study that provides a global risk assessment for chikungunya under the CMIP5 climate change scenarios.

Manuscript 2, following a similar approach as Manuscript 1, assesses the potential risk for MBVD transmission by the vector species *Ae. albopictus* in Germany. So far, Germany has not seen any local transmission of diseases by this species. However, *Ae. albopictus* has repeatedly been introduced into the country, and it was able to establish several persisting populations. At the same time, for which *Ae. albopictus* is a competent vector are frequently carried into the country by international travelers. Based on European occurrence records and relevant climatic variables, a series of different ENM algorithms was applied, and the one with the best performance (generalized boosted models,

GBM) was selected as the basis for further analysis. The map of climatic suitability derived from this model confirms, that under current climatic conditions, the Upper Rhine Valley must be considered as a hot spot for *Ae. albopictus* establishment. Future projections suggest that with climate change, large areas of western Germany will become suitable for *Ae. albopictus*. Spatial analysis of travel-related DENV and CHIKV infections over the years 2011–2017 reveals elevated incidence rates in the South of the country, partially intersecting with areas that are highly suitable for vector occurrence. This manuscript demonstrates that autochthonous transmission of DENV and CHIKV in Germany is currently unlikely but not impossible, and that the risk is likely to increase in the future due to climate change. In order to prevent long-term establishment of *Ae. albopictus*, mosquito surveillance needs to be intensified in the areas identified as suitable, so that new populations can be detected and controlled as early as possible.

Manuscript 3 puts a spotlight on the extrinsic incubation period (EIP) of dengue virus (DENV) in its mosquito vectors. As the duration of the EIP is strongly affected by ambient temperature, it is one of the main links between environment and disease transmission. This review reveals how limited the knowledge about this important factor still is. Most of the published studies focus on *Ae. aegypti* alone, neglecting *Ae. albopictus* as a competent vector. The methodology varies considerably across different studies, with several older studies delivering unrealistic results due to the methods used for infecting mosquitoes. Especially for temperatures around and below 20°C, data coverage is sparse and unreliable. Knowledge about the duration of the EIP at the lower end of the temperature spectrum could be tremendously useful for assessing the transmission potential of DENV in temperate climates. Especially R_0-based Epidemiological Models could benefit from this. Thus, suggestions for improving future experiments are given, along with the urgent plea for more research in this direction.

Manuscript 4 focuses on Usutu, a viral disease that recently caused mass mortality events in blackbird populations in Central Europe. Compared to dengue and chikungunya, knowledge about Usutu is very limited in many aspects. To make up for this, spatio-temporal risk assessment was based on the parallel application of two fundamentally different models. On the one hand, an ENM was built upon climate data and occurrence records of USUV-positive birds that were found dead and reported to the authorities. On the other hand, a previously published R_0-based Epidemiological Model was adopted for spatial risk assessment using rastered temperature data at a daily resolution. Both models are able to retrodict past outbreaks in Italy, Austria and Hungary. However, the Epidemiological Model apparently fails to predict a major outbreak in Germany and the Benelux states. The manuscript reveals unresolved difficulties in the interpretation of R_0-based risk maps. If the desired end result is a single map, daily values of R_0 need heavy temporal aggregation. There are several possible ways of doing this that mainly differ in whether R_0 is treated as a numerical value that can be averaged or whether it is considered purely as a binary threshold. The resulting maps can vary considerably, and so far no "best practice" approach has been defined. The results suggest, that for a newly emerging MBVD with largely unknown properties, correlative approaches like ENM are the more reliable tool for initial, rapid risk assessments. However, different approaches should be combined whenever possible, as a method for independent evaluation of results.

Finally, **Manuscript 5** reviews the current state-of-the-art of models of mosquito-borne diseases in the context of climate change. For both correlative ENM and mechanistic EM, it provides an overview of the basic principles, common methods, advantages, disadvantages and recurring problems. Major challenges for the modelling community as a whole are identified. Data quality and availability is common problem, both in terms of occurrence records for ENM and parameterization of EM. Standardized and thorough validation of results is another point where both disciplines need to make improvements. There is still a major gap between the two modelling communities, making the

parallel use of ENM and EM in Manuscript 4 a rare exception. Over-all, international transfer of knowledge, methods and data across all disciplines and sectors needs to be facilitated.

Summarizing discussion and emerging research challenges

MBVD risk assessment based on Ecological Niche Models

ENMs have become a standard method across ecological sub-disciplines, and their popularity in epidemiological contexts is steadily increasing. Nevertheless, there are still many problems unsolved. For instance, one of the fundamental assumptions of any correlative ENM is that the modelled species' niche is fully occupied. When this is not the case, the model may underestimate the size ("breadth") of the niche in environmental space, and thus the extent of its potential distribution in geographical space (Pearson, 2010). This can become problematic when a species that experiences strong competition in its native range invades another area where no competitors occur, as the species' realized niche then is considerably smaller than its fundamental niche (compare the Enemy Release Hypothesis from plant ecology, e.g. Keane & Crawley (2002)). In that case, an ENM built on information from the native range would potentially under-estimate the species' potential range in the invaded area considerably. Similarly, a *niche shift* – a rapid adaption to new environmental conditions – may occur during an invasion, making the potential distribution in the invaded area less predictable (Medley, 2010; Medley et al., 2019).

On the other hand, models that have been fit on occurrence records that predominantly originate from the tropics, may not be able to adequately predict real-life transmission in temperate climates due to the vastly different climatic characteristics (compare Manuscript 1). For instance, in the tropics, the commonly used bioclimatic variable "mean temperature of the wettest quarter" refers to temperature values in the rainy season. Outside of the tropics, it may refer to a temperature in summer or winter, depending on which time of the year brings more precipitation. Obviously, a variable that represents different things in different parts of the study area should be avoided. However,

problems like this are often more difficult to detect than in this example. Another way to avoid this kind of problem is to limit the study area to areas that have sufficiently similar. A manuscript that aims to overcome the shortcomings of the model in Manuscript 1 is currently in preparation (working title: "Chikungunya beyond the tropics: Where and when do we expect disease transmission in Europe?"). In order to be able to better predict the real-life outbreaks of chikungunya in Europe, this new model completely omits all tropical data, thus avoiding the issues mentioned above.

Availability and quality of occurrence records is a recurring problem, as explained in Manuscript 5. In particular, notifiable diseases in humans are recorded in a systematic manner, but usually summarized for entire districts. In the absence of more precise occurrence records, ENMs are often built using the geographical centroids of such districts as a substitute (e.g. data for Bhutan, India and Thailand in Manuscript 1). How much this affects ENMs in context with the spatial resolution of the environmental variables is being analyzed in a manuscript entitled "Centroid data in Ecological Niche Modelling: Effects on model performance in context with grain size", that is currently under review at *Global Ecology and Biogeography.*

MBVD risk assessment based on Epidemiological Models

R_0-based Epidemiological Models are a well-established tool for risk assessment in epidemiology. As they are deeply rooted in theory, the links between disease transmission and environment are formulated much more explicitly than in the correlation-based ENMs. However, elaborate EMs that are calibrated to closely resemble a specific outbreak or region (e.g., Guzzetta et al., 2016) often lack in terms of transferability, limiting their use for predictive risk assessment.

Proper parameterization of EM in practice is often hindered by a lack of data. Unfortunately, since the publication of Manuscript 3 in 2013, only few advancements have been made regarding the temperature-depence of dengue

EIP. While several articles have been published that investigate temperature effects on dengue transmission (e.g., Alto & Bettinardi, 2013; Carrington et al., 2013a; Liu-Helmersson et al., 2014; Christofferson & Mores, 2016), most of them do not meet the requirements lined out in the manuscript. A notable exception is an article by Xiao et al. (2014), in which the EIP of dengue in *Ae. albopictus* was investigated at different incubation temperatures. Future studies on temperature effects on the EIP of MBVD should also consider potential effects of daily temperature fluctuations in addition to the constant temperatures typically used in the lab (compare e.g., Carrington et al., 2013b; Sharmin et al., 2015).

EMs for MBVD are typically run on time series of daily temperature for single locations, but they can easily be adapted to use a time series of spatial raster layers instead. In a similar manner, spatial variations in vector and host populations can be implemented. This is an opportunity for an interdisciplinary use of EM and ENM, as the ENM could provide information on vector presence to the EM. This is not common practice yet, partially because EMs require values of absolute vector abundance or density, and these are difficult to derive from the relative environmental suitability provided by the ENMs.

As Manuscript 4 reveals, the translation of daily values of R_0 into summarizing maps is not trivial and warrants further investigation and standardization. This is complicated by the fact that there are different interpretations of R_0 (see above) that need to be considere. As a first step, a manuscript entitled "Deriving risk maps from epidemiological models of vector borne diseases: state-of-the-art and suggestions for best practice" is currently under review at *Epidemics*, that compares and discusses the different approaches that are currently in use for such transformations.

Concluding remarks

"Since all models are wrong the scientist must be alert to what is importantly wrong. It is inappropriate to be concerned about mice when there are tigers abroad." — Box (1976)

So, which kind of model is the best choice for spatial risk mapping of infectious diseases? Obviously, there is not single right answer to this question, as there is a number of factors that need to be considered depending on the situation. Is the disease purely vector-borne, transmitted directly, or a combination of both? Do populations of competent vectors already exist locally? Is the disease already endemic or just a hypothetical threat? Based on the specific situation, different components of risk need to be prioritized, and the choice of model differs accordingly.

For instance, in areas where vectors are consistently abundant with only minor spatial variability and transmission already occurs regularly, seasonal weather patterns (e.g., Wongkoon et al., 2013) and socio-economic drivers (e.g., Mmbando et al., 2011) may be the most useful predictors for spatial and temporal patterns of local disease transmission. An ENM of vector distributions will likely not be able to contribute much new information here.

The manuscripts in thesis, on the other hand, focus on MBVD at the very edges of their current spatial distribution, both in time (Manuscripts 1 & 5) and space (Manuscripts 2 & 3). Here, the primary question to be answered is whether or not transmission is possible at all. For instance, the fact that *Ae. albopictus* was able to establish a small number of populations in Germany raises the question of where else in the country it could survive. As vector presence is a necessary condition for most MBVD, assessment of potential vector distribution has the highest priority in this case, making ENMs the method of choice.

Over-all, ENMs are most useful on relatively coarse (global to regional) spatial scales and for MBVD where detailed knowledge about the parameters of transmission is sparse. EMs, on the other hand, can cover temporal aspects much better, provided that sufficient information on relevant parameters is available.

List of manuscripts and declaration of own contribution

Manuscript 1

Title: **Modelling the effects of global climate change on Chikungunya transmission in the 21st century**

Published in: Scientific Reports, 7: 3813, 2017

Authors: Nils B. Tjaden, Jonathan E. Suk, Dominik Fischer, Stephanie M. Thomas, Carl Beierkuhnlein, Jan C. Semenza

Personal contribution: idea & concept: 25%, data acquisition 40%, analysis: 70%, figures & tables: 90%, writing: 25%, editing: 60%

Manuscript 2

Title: **Areas with High Hazard Potential for Autochthonous Transmission of *Aedes albopictus*-Associated Arboviruses in Germany**

Published in: International Journal of Environmental Research and Public Health, 15(6): 1270, 2018

Authors: Stephanie M. Thomas, Nils B. Tjaden, Christina Frank, Anja Jaeschke, Lukas Zipfel, Christiane Wagner-Wiening, Mirko Faber, Carl Beierkuhnlein, Klaus Stark

Personal contribution: idea & concept: 10%, data acquisition 70%, analysis: 65%, figures & tables: 90%, writing: 20%, editing: 30%

Manuscript 3

Title: **Extrinsic Incubation Period of Dengue: Knowledge, Backlog, and Applications of Temperature Dependence**

Published in: PLoS Neglected Tropical Diseases, 7(6): e2207, 2013

Authors: Nils B. Tjaden, Stephanie M. Thomas, Dominik Fischer, Carl Beierkuhnlein

Personal contribution: idea & concept: 50%, data acquisition 80%, analysis: 90%, figures & tables: 90%, writing: 70%, editing: 65%, Corresponding author

Manuscript 4

Title: **Evaluating the Risk for Usutu virus circulation in Europe: Comparison of Environmental Niche Models and Epidemiological Models**

Published in: International Journal of Health Geographics, 17: 35, 2018

Authors: Yanchao Cheng, Nils B. Tjaden, Anja Jaeschke, Renke Lühken, Ute Ziegler, Stephanie M. Thomas, Carl Beierkuhnlein

Personal contribution: idea & concept: 30%, data acquisition 10%, analysis: 50%, figures & tables: 10%, writing: 30%, editing: 40%

Manuscript 5

Title: **Mosquito-borne diseases: Advances in Modelling Climate-Change impacts**

Published in: Trends in Parasitology, 34(3): 227–245, 2017

Authors: Nils B. Tjaden, Cyril Caminade, Carl Beierkuhnlein, Stephanie M. Thomas

Personal contribution: idea & concept: 50%, data acquisition 10%, analysis: 50%, figures & tables: 40%, writing: 30%, editing: 60%

Declaration of changes made to the manuscripts

While adopting the published manuscripts for use in this dissertation, a number of minor edits has been made. These are mostly corrections of typing errors and necessary adoptions of electronic supplements that originally were not intended to be printed. For the sake of transparency, these changes are listed in the following sections.

Across all manuscripts, "Worldclim" is being treated as a proper noun consistently.

Manuscript 1

The headings for sections "Abstract" and "Introduction" that are omitted from the print/PDF version of the published manuscript but present in the online version at the publisher's website are present in this dissertation as well. A misspelt "Chikungunya" was corrected in the second paragraph of the *Results* section. The Supplementary Data was adopted for print by splitting the two table sheets of the original Excel-file (occurrence records and references) into two separate tables. The "Remarks" column was omitted, source IDs abbreviated, higher order administrative units removed from the "Location/District" column, coordinates rounded to three decimals and columns and rows re-ordering.

Manuscript 2

In the two first paragraphs of the *Results* section, "current" was corrected to "currently". Repeated use of the full-length "*Aedes albopictus"* in figure legends was shortened to "*Ae. albopictus"*. The descriptive text at the bottom of Figure S1 was moved to the figure legend. The mountain range labels in the figure were edited for better readability. The separate reference list from Figure S2 was merged with the main reference list of the manuscript. This introduces additional references [58–62] that do not appear in the main text. Table S1 was formatted for printing.

Manuscript 3

Table S1 was adopted for printing: Columns were rearranged and relabeled, *Author* and *Year* columns were merged, and some rows were sorted by dengue strain instead of temperature for a more compact and informative layout. The mostly empty column *Remarks* was omitted.

Manuscript 4

The header of the right column of Table 1 was changed from "Variables" to "Variable Description". Tables 2 received minor changes in layout and typography for better readability. The figure in Additional File 2 was edited for aesthetics and readability, and a description was added. Additional File 3 was edited for layout and grammar.

Manuscript 5

The heading "Abstract" was added to the first paragraph. In the description of Figure I in Box 1, an error was introduced in the final phase of publishing: the original "between 2065–2085 and 1961–1999" was erroneously changed by the publisher to "between 2065 and 2085, and between 1961 and 1999" in an attempt to clarify the meaning. In order to eliminate any ambiguities, this was corrected to "between the 2065–2085 period and the 1961–1999 reference period" in this dissertation. In the same description, the singular "global climate model" was corrected to "global climate models". In the "Health and Vector Data Availability" section, last paragraph, second sentence, "communicable diseases" was replaced with the more appropriate "notifiable diseases".

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Manuscript 1: Modelling the effects of global climate change on chikungunya transmission in the 21st century

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Abstract

The arrival and rapid spread of the mosquito-borne viral disease Chikungunya across the Americas is one of the most significant public health developments of recent years, preceding and mirroring the subsequent spread of Zika. Globalization in trade and travel can lead to the importation of these viruses, but climatic conditions strongly affect the efficiency of transmission in local settings. In order to direct preparedness for future outbreaks, it is necessary to anticipate global regions that could become suitable for Chikungunya transmission. Here, we present global correlative niche models for autochthonous Chikungunya transmission. These models were used as the basis for projections under the representative concentration pathway (RCP) 4.5 and 8.5 climate change scenarios. In a further step, hazard maps, which account for population densities, were produced. The baseline models successfully delineate current areas of active Chikungunya transmission. Projections under the RCP 4.5 and 8.5 scenarios suggest the likelihood of expansion of transmission-suitable areas in many parts of the world, including China, sub-

Saharan Africa, South America, the United States and continental Europe. The models presented here can be used to inform public health preparedness planning in a highly interconnected world.

Introduction

Chikungunya is a mosquito-borne arboviral disease transmitted by *Aedes* species mosquitoes, notably *Aedes aegypti* and *Aedes albopictus.* Historically endemic in tropical climates such as in Africa, Southeast Asia and the Indian subcontinent, events of the past decade have led to a substantial geographic expansion of the disease. In 2005-06, an outbreak with nearly 1.4 million reported cases occurred in India[1], and another large outbreak on La Réunion led to over 250,000 reported cases[2]. Thereafter, autochthonous transmission by *Ae. albopictus* was recorded in temperate continental Europe for the first time in northern Italy in 2007[3], followed by southern France in 2010[4] and 2014[5]. Chikungunya transmission has recently also occurred in China[6], Papua New Guinea and New Caledonia[7]. In December 2013, Chikungunya arrived in the Americas on the Caribbean island of St. Martin[8, 9], from which it subsequently spread to at least 45 countries and territories, leading to at least 1.7 million suspected cases. This illustrates how the disease continues to disperse internationally and pose a threat to public health.

Numerous factors played a role in the global spread of Chikungunya. Adaptive mutations in the Chikungunya genome enabled the East/Central/South African (ECSA) strain to be more easily transmitted by *Ae. albopictus*, contributing to the outbreak in La Réunion[10] and, subsequently, to outbreaks in south Asia and Italy. Globalization in trade and travel, meanwhile, have facilitated the geographic expansion of *Ae. albopictus*[11] and have increased the possibility that travellers infected with Chikungunya could come into contact with competent *Aedes* mosquito vectors[12, 13].

Although global interconnectivity ensures a continued risk for importations of Chikungunya into regions with competent mosquito vectors, until very

recently there were no global distribution models for this viral disease, and comparatively little research identifies global regions of climatic suitability for Chikungunya transmission. It is, however, well known that climate affects growth, survival and abundance of the two primary vectors for Chikungunya, *Ae. aegypti* and *Ae. albopictus*[14]. Both field and laboratory experiments demonstrate that survival of both of these mosquito species is affected by lower and upper temperature thresholds[15]. Precipitation is another important factor influencing the availability of microhabitats for oviposition and larval development: heavy rainfalls – which are increasing in frequency due to climate change in some areas – have increased the abundance of *Ae. albopictus*, thereby increasing the risk of Chikungunya transmission in southern France in 2014[5]. Projections of the global distribution of *Ae. albopictus* and *Ae. aegypti* under climate change scenarios generally anticipate expansions in eastern North America, Central Africa, northern and eastern Australia, and East Asia[14]. Regional European models of *Ae. albopictus* under climate change scenarios suggest that climatic suitability will generally increase and populations expand northwards in the upcoming decades[16–18].

While several epidemiological models exist for Chikungunya, global climate change models for the disease so far solely focus on vector distribution (with one exception[19]). One limiting factor is the knowledge gap about the effect of temperature on the extrinsic incubation period (EIP) of Chikungunya in both *Ae. albopictus* and *Ae. aegypti*. Present-day models for Chikungunya in Europe and the United States overcame this challenge through approximations based on field data[19] or drawing parallels to similar diseases such as dengue[20]. One alternative approach that obviates the need to model the complex interactions of extrinsic and intrinsic factors related to Chikungunya transmission is correlative niche modelling, which treats the disease as a species with a specific environmental niche. This includes environmental effects on the pathogen (such as ambient temperature affecting the virus' replication rate in the ectothermic vector's body) as well as vector distribution. Commonly applied for

species distribution models of disease vectors[18] as well as in conservation biology, this approach has successfully been applied to dengue[21], Chikungunya[22], Zika[23] and other diseases[24-26].

In this study, geospatially reported cases of Chikungunya were related to climatic factors so as to deduce the most influential climatic variables governing Chikungunya transmission. The characteristics of this niche were then used to assess the current global suitability for Chikungunya. Thereafter, the RCP 4.5 and RCP 8.5[27] climate change scenarios were used to project how the global suitability for Chikungunya transmission might change in the future. In this context, high "climatic suitability" indicates an increased potential for Chikungunya transmission to occur but does not necessarily mean that actual outbreaks will take place, as public health control measures and overall levels of socioeconomic development could serve as mitigating measures.

The models developed in this study focus solely on the climatic suitability of Chikungunya transmission based upon five explanatory variables identified during the modelling process: Annual mean temperature, minimum temperature of the coldest month, mean temperature of the wettest quarter, mean temperature of the warmest quarter and annual precipitation. Present-day (or baseline) models for climatic suitability for Chikungunya transmission were developed (top-left panel, Figs 1–5) based on climate data from worldclim.com[28].

Under the RCP 4.5 and RCP 8.5 climate change scenarios, climate suitability maps for Chikungunya transmission were developed for the time periods of 2021–2040, 2041–2060, and 2061–2080 (Figs 1–5 and S1–S5, left panels) based on data from 5 different global climate models. In addition, maps of Chikungunya hazard, which additionally account for human population densities, were developed (RCP 8.5 depicted in Figs 1–5, right panels).

Results

Our models reflect the current global distribution of Chikungunya (Fig. S8), but also identify areas suitable for transmission that have not suffered from larger outbreaks in the past. These include regions in northern and southern Italy, southwest France, northeast Spain, large areas of sub-Saharan Africa, northern Australia and the southernmost tip of Florida in the United States.

Projections for two contrasting climate change scenarios (RCP 4.5, RCP 8.5) show rather similar global patterns in the suitability- and hazard maps that were generated in this study. However, the modelling results for the high emission scenario, RCP 8.5 indicate areas of higher climatic suitability and larger expanse of suitable areas. Nevertheless, we also find areas with declining suitability as well as spatial contraction of suitable areas. In Asia, the models suggest that both climatic suitability and Chikungunya hazard will generally increase in large parts of China, which had been largely free of autochthonous Chikungunya transmission until the 2010 outbreak in the Guangdong Province[6] (Figs 1, S1). India shows a gradual decrease in climatic suitability in its central regions, with persistently strong suitability continuing in the southern regions. Southeast Asia and northern Australia demonstrate strong transmission suitability throughout all time periods, with considerably lower hazard in much of Australia due to low population densities.

In Sub-Saharan Africa, climatically suitable areas are projected to increase within the 2021–2040 timeframe and remain relatively stable thereafter under both climate change scenarios (Figs 2, S2). Highly suitable regions include the Atlantic coast from Senegal through to mid Angola, and a belt beginning in West Africa and continuing through to South Sudan. Most of the Indian Ocean coastline is also projected to be suitable for Chikungunya, with the exception of the Horn of Africa and South Africa. The risk of autochthonous transmission will be principally restricted to the more populated coastal areas of Somalia, Tanzania, and Mozambique (Fig. 2, right panels).

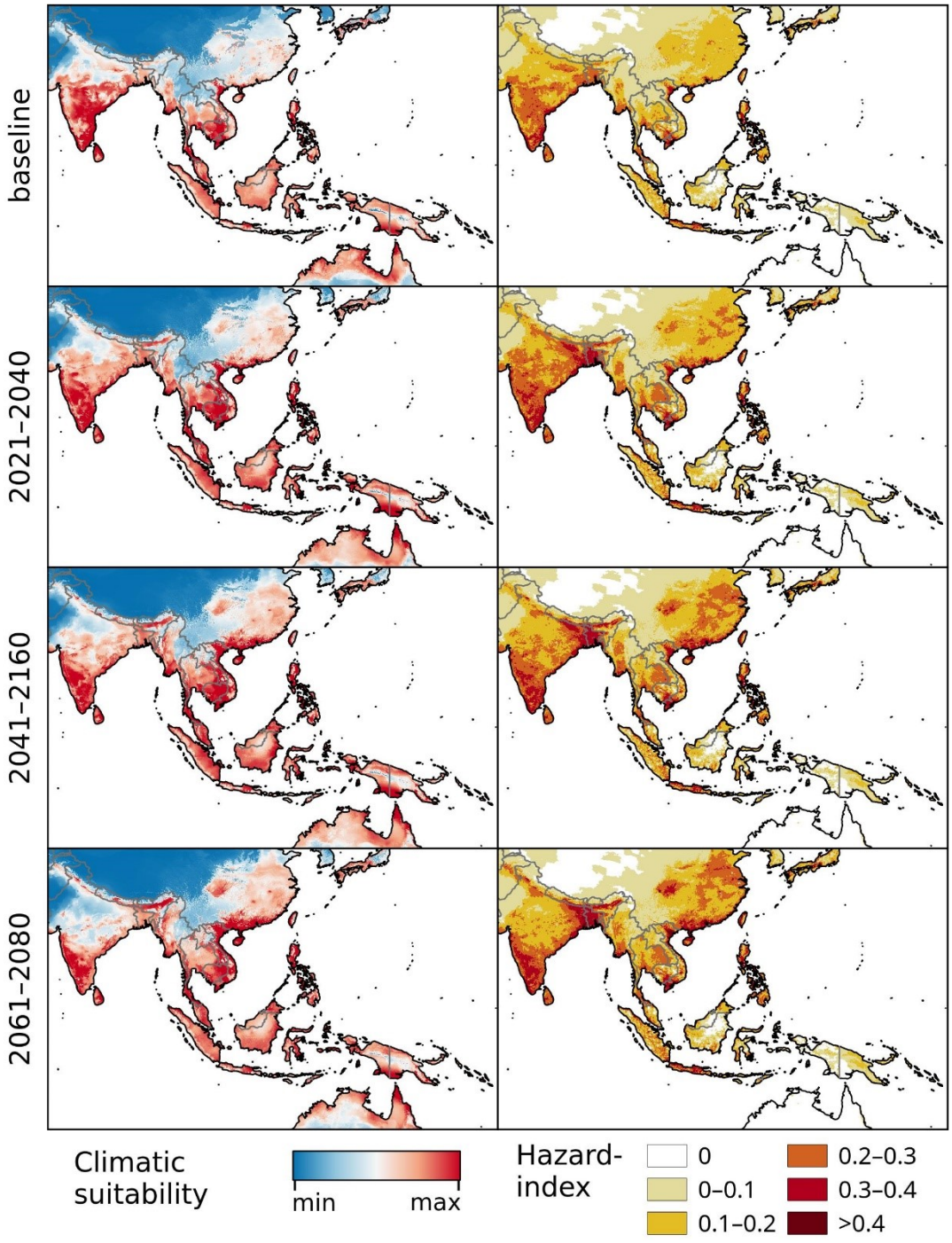

Figure 1. Chikungunya under the baseline and RCP 8.5 climate change scenarios in Asia and Australasia. Left: Climatic suitability, right: hazard index. Climate change scenarios represent the mean model output obtained through the 5 GCMs. Climatic suitability output is scaled to the over-all global minimum (0) and maximum (0.623) values observed in any model. Maps were generated using the "raster" package in R 3.3.2 (https://www.r-project.org/) and QGIS 2.8.1 (https://www.qgis.org/).

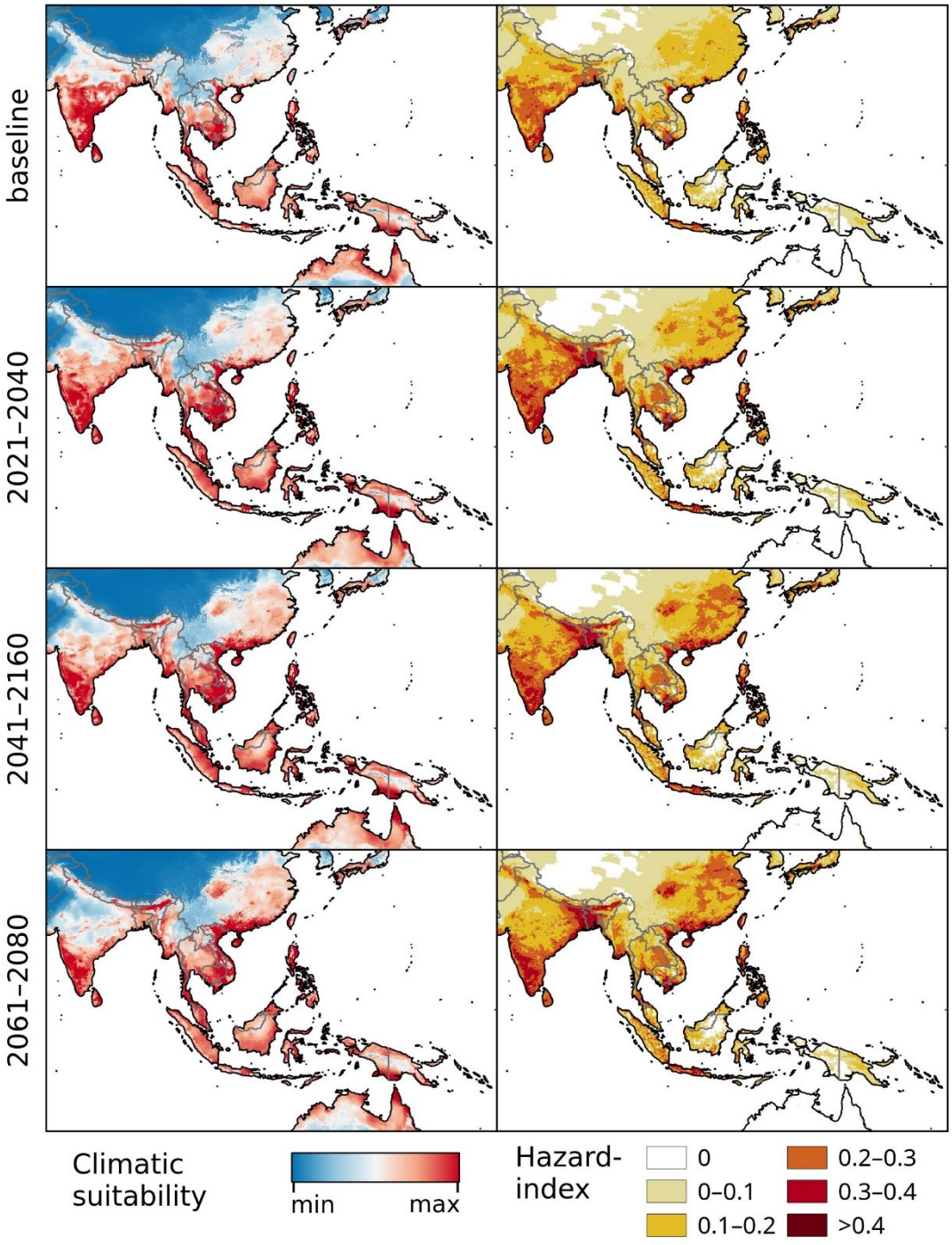

Figure 2. Chikungunya under the baseline and RCP 8.5 climate change scenarios in Africa. Left: Climatic suitability, right: hazard index. Climate change scenarios represent the mean model output obtained through the 5 GCMs. Climatic suitability output is scaled to the over-all global minimum (0) and maximum (0.623) values observed in any model. Maps were generated using the "raster" package in R 3.3.2 (https://www.r-project.org/) and QGIS 2.8.1 (https://www.qgis.org/).

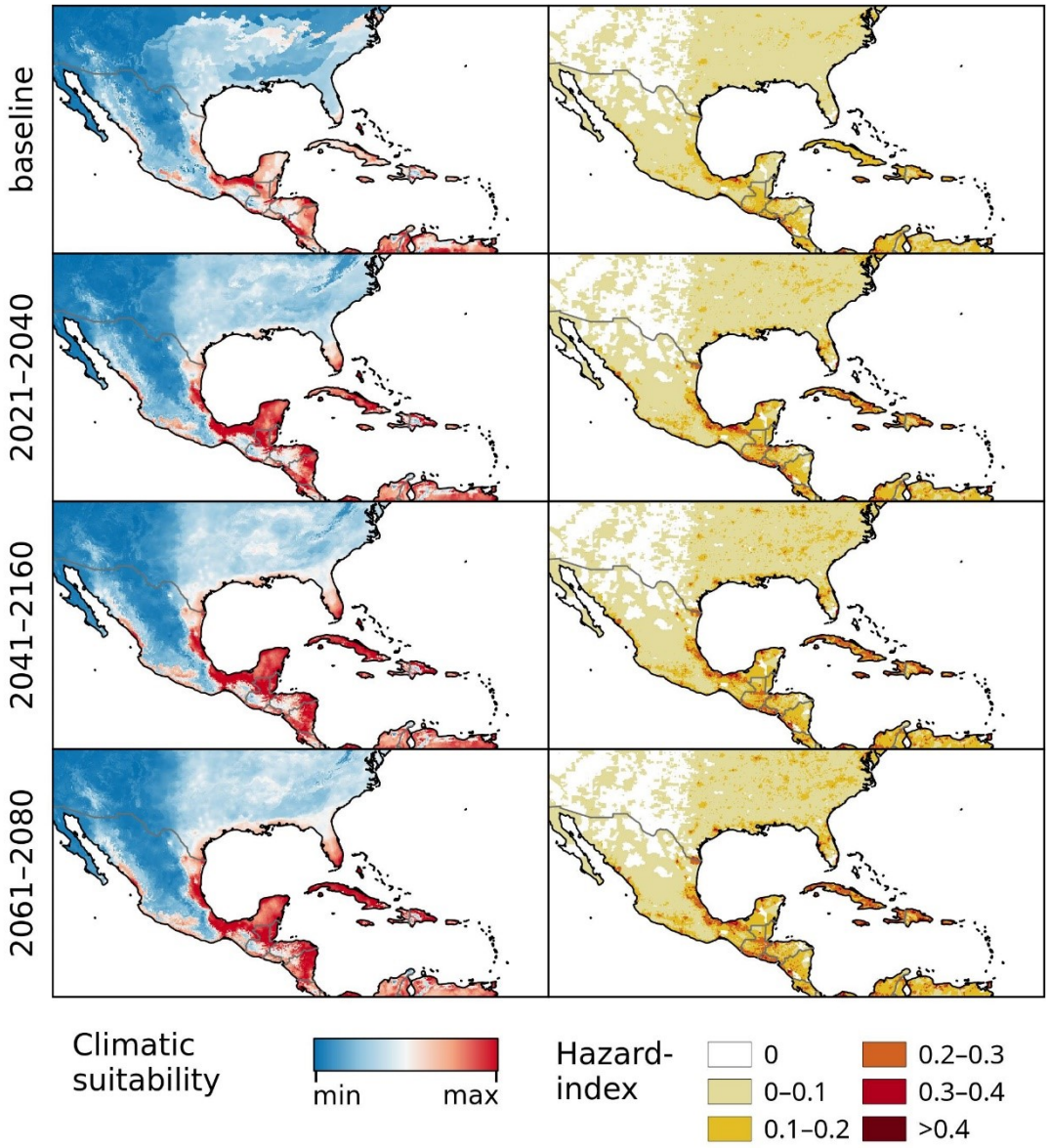

Figure 3. Chikungunya under the baseline and RCP 8.5 climate change scenarios in North- and Central America. Left: Climatic suitability, right: hazard index. Climate change scenarios represent the mean model output obtained through the 5 GCMs. Climatic suitability output is scaled to the over-all global minimum (0) and maximum (0.623) values observed in any model. Maps were generated using the "raster" package in R 3.3.2 (https://www.r-project.org/) and QGIS 2.8.1 (https://www.qgis.org/).

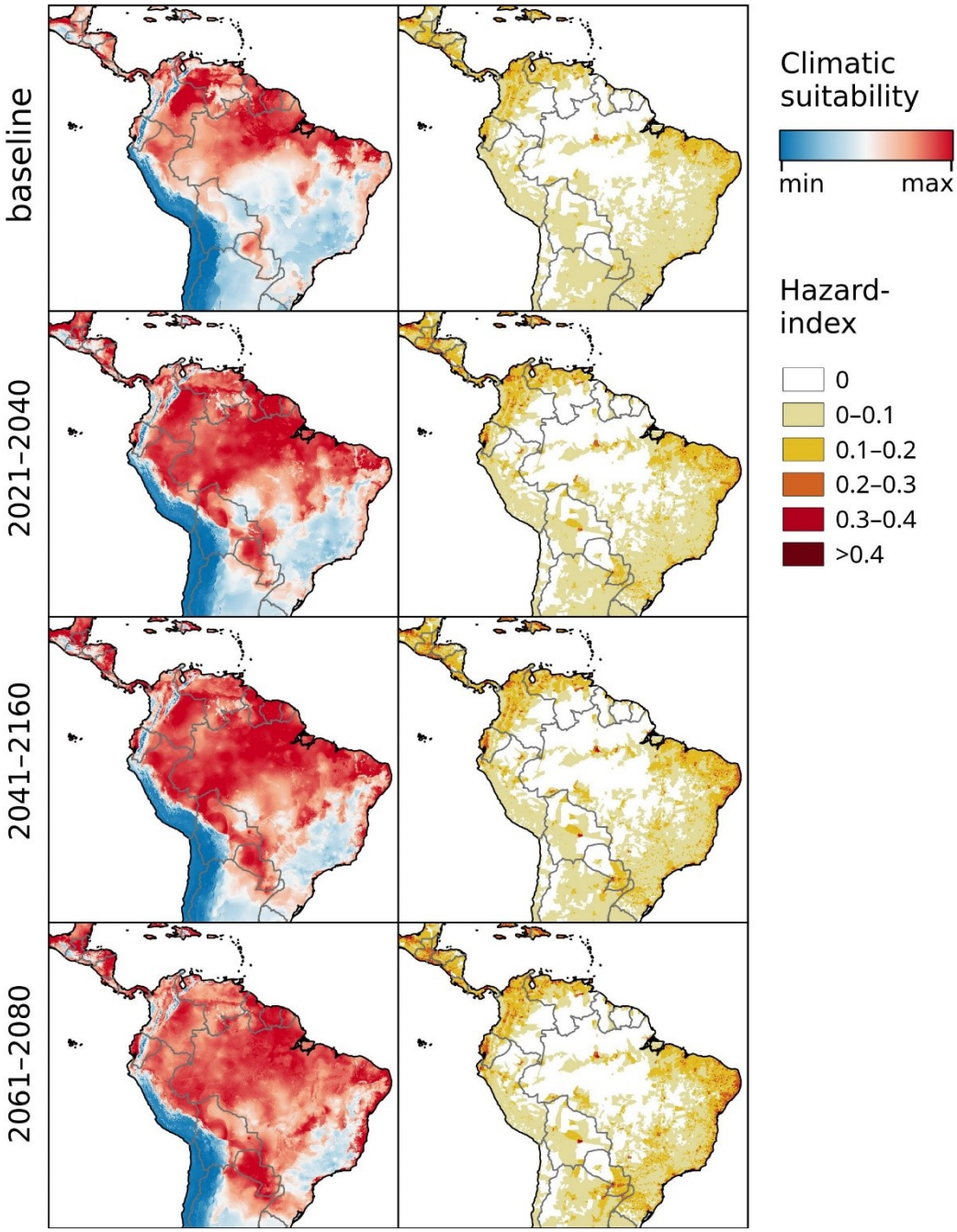

Figure 4. Chikungunya under the baseline and RCP 8.5 climate change scenarios in South America. Left: Climatic suitability, right: hazard index. Climate change scenarios represent the mean model output obtained through the 5 GCMs. Climatic suitability output is scaled to the over-all global minimum (0) and maximum (0.623) values observed in any model. Maps were generated using the "raster" package in R 3.3.2 (https://www.r-project.org/) and QGIS 2.8.1 (https://www.qgis.org/).

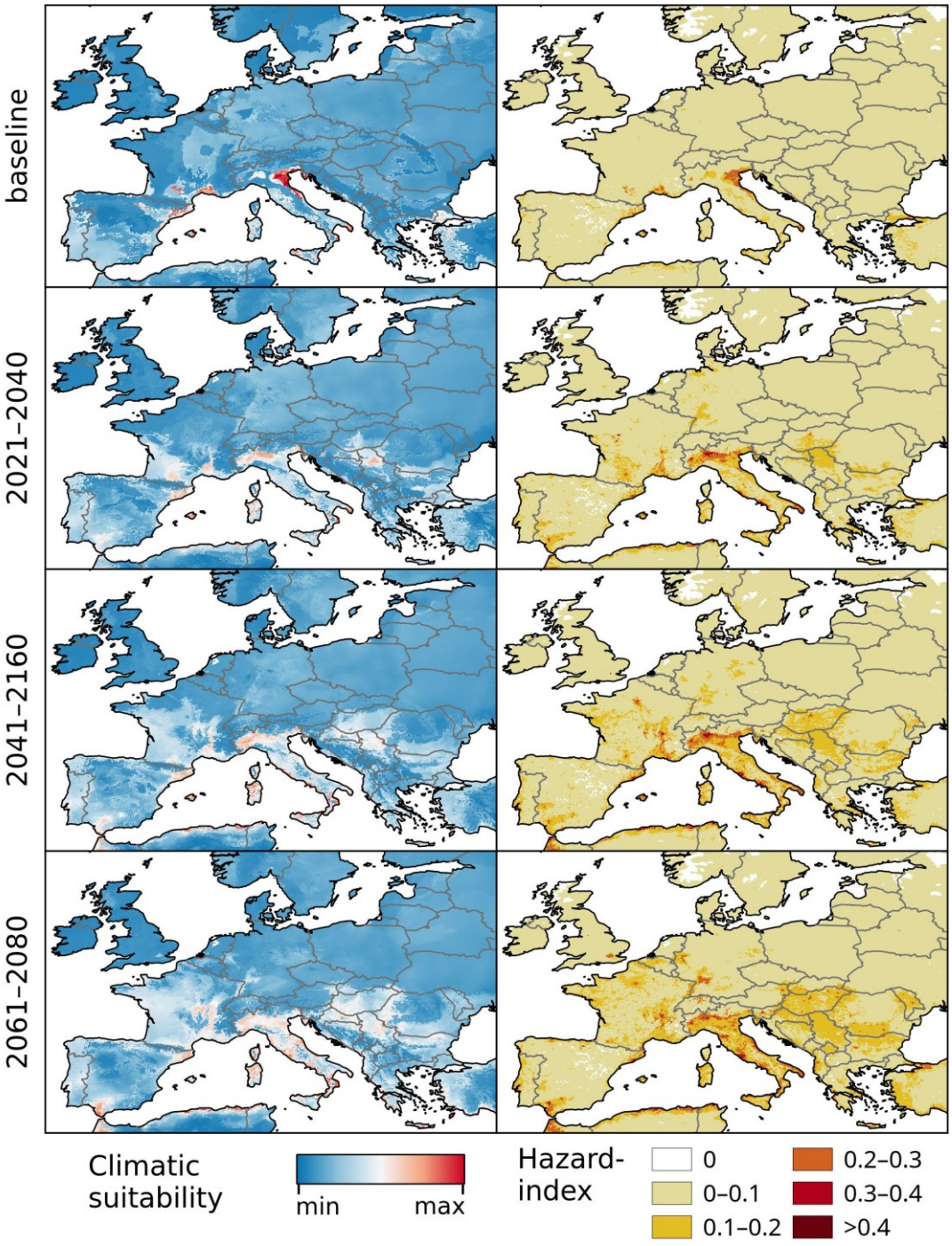

Figure 5. Chikungunya under the baseline and RCP 8.5 climate change scenarios in Europe. Left: Climatic suitability, right: hazard index. Climate change scenarios represent the mean model output obtained through the 5 GCMs. Climatic suitability output is scaled to the over-all global minimum (0) and maximum (0.623) values observed in any model. Maps were generated using the "raster" package in R 3.3.2 (https://www.r-project.org/) and QGIS 2.8.1 (https://www.qgis.org/).

The climatic suitability for Chikungunya transmission is projected to steadily increase in the Gulf Coast, southern Florida, Cuba, the Yucatan peninsula, Sinaloa, and across much of Central America under both higher and lower emission scenarios (Figs 3, S3). In South America, our models identify a southerly expansion of climatic suitability for Chikungunya transmission, with a marked increase in eastern Peru, eastern Bolivia, Paraguay, and much of central Brazil (Figs 4, S4). The high elevation areas of Chile, Bolivia, and Peru will remain unsuitable for Chikungunya transmission. Under the RCP 8.5 scenario, the overall level of climatic suitability in South America is projected to decrease by the end of the century, when the climatic conditions will be too extreme for the vector species in many regions.

In Europe, both scenarios show a moderate expansion of climatic suitability across much of central Europe, notably in France and Italy (Figs 5, S5). Large areas surrounding the Rhine and Rhone rivers in Germany and France, respectively, are also projected to increase in suitability. However, some parts of the region of highest current suitability in northern Italy near the Adriatic coast are projected to experience a decline in suitability in both scenarios due to increased probabilities of summer droughts, which will reduce the habitat suitability for the vectors.

Discussion

Neither climate change nor global interconnectivity show signs of abating[12, 29]. As such, Chikungunya is likely to remain an important public health preparedness priority in regions where it has already been introduced as well as in regions at the fringes of its current distribution.

This is, to our knowledge, the first global study on spatio-temporal patterns of potential Chikungunya transmission using the RCP 4.5 and RCP 8.5 climate change scenarios. The modelling algorithms applied in this study to generate spatially explicit hazard maps for established climate change scenarios and time steps are based upon a correlative niche modelling approach to identify

global regions that may be climatically favourable for Chikungunya transmission.

There are, broadly speaking, two key approaches for modelling vector-borne diseases. One is mechanistic modelling, which requires a detailed parameterization of numerous intricate biological processes, such as mosquito breeding and survival rates, mosquito biting rates, and the extrinsic incubation period. Although these models are thorough and based upon clear biological processes, there are important limitations to this approach. One relates to the unavailability of empirical data for the parameterization of biological processes, which may be a particular challenge for diseases such as Chikungunya which are relatively understudied. Another limitation is that modelling biological processes alone may tend to lead to overestimations (i.e. false positives) of the impacts of climate change, because they do not account for socioeconomic contexts or potential public health control measures[30–32]. In contrast, correlative modelling approaches such as the one presented here have an advantage in situations in which biological processes are incompletely parameterized[33], as the method obviates the need to model the many unknown parameters that affect the interactions between Chikungunya virus, its mosquito vectors and humans. The focus instead is *a priori* on the climatic characteristics that are common to global regions that have recorded Chikungunya transmission.

Nonetheless, as with all modelling approaches, there are limitations to correlative niche modelling as well. First, vector-borne disease transmission is very complex, involving drivers across a wide range of socioeconomic and climatic variables. In the models presented here, socioeconomic vulnerabilities and related driving forces of Chikungunya transmission are intentionally excluded because the whole array and the diversity of processes in different continents and countries cannot be feasibly modelled. The models may nonetheless be indirectly affected by socio-economic and public health factors which may either protect against or exacerbate Chikungunya transmission. For

example, there is historic evidence for Chikungunya occurring in relatively cool sub-tropical climates (such as Charleston, South Carolina, USA)[34], but due to vector control and other measures current cases in those regions are sparse. Similarly, our models do not attempt to consider future adaptive measures that might be undertaken to mitigate the risk of Chikungunya transmission. Instead, we present models that identify hazard through the combination of climatic suitability and population density (right panels, Figs 1–5 and S1–S5).

A second limitation relates to the climatic input data. While the climate data used for the baseline model and future projections represent the same climatic parameters (such as "minimum temperature of the coldest month"), the underlying input data and methods are different. The Worldclim dataset for the baseline model is interpolated from data measured by weather stations[28], whereas the data used for future projections comes from global climate models (GCM) that simulate physical processes in the atmosphere numerically. Although the approach of using those two data sources together has been widely applied, the comparability between baseline and future models is restricted nevertheless.

Finally, although calculating values for the mean climatic suitability from the climatic projections obtained from 5 different GCMs generally helps to increase confidence in the globally detected patterns (see Fig. S6 for standard deviations), small-scale differences in projected climate may lead to local under-estimations of climatic suitability (Fig. S7). Global models are only capable of displaying large-scale patterns and are best used for identifying areas of concern which could be further examined by subsequent smaller-scale models that would be better capable of representing locally relevant factors, such as the abundance of mosquito breeding sites, efforts in vector control, and local public health surveillance, preparedness, and response measures related to Chikungunya.

In comparing our baseline models with other recently-published works on Chikungunya[22, 35] and its vectors[36], there are general agreements at large scales,

albeit with smaller-scale differences. In Oceania, for example, our model (Fig. 1), the Chikungunya model by Nsoesie et al.[22] as well as the vector models by Kraemer et al.[36] all cover the same general suitability areas between India, southern Japan and northern Australia. However, the model by Nsoesie et al.[22] predicts comparably low environmental suitability in India (from where large numbers of Chikungunya cases have been reported, compare Fig. S8 and supplementary data), south-eastern China, southern Japan and northern Australia. When compared to the models by Kraemer et al.[36], our model corresponds more closely to the *Ae. aegypti* model than the *Ae. albopictus* model for this region, but with lesser projected climatic potential for Chikungunya in the northern parts of India, where Chikungunya cases are currently less common (Fig. S8).

In Sub-Saharan Africa, all of these models predict high suitability in the area between roughly Senegal, the Ethiopian Plateau, the Congo Basin and the mouth of the Congo River, as well as Madagascar and a strip along the eastern coast between Kenya and Swaziland. Suitable areas also include parts of Angola and Zambia in the two vector models by Kraemer et al.[36], while our model (Fig. 2) and the *Ae. aegypti* model[36] predict higher suitability closer to the Sahara Desert in the north.

In Central America, all models agree on the Caribbean Islands as well as the coastal regions of the mainland being suitable for Chikungunya transmission. With the exception of the models by Mordecai et al.[35], all models agree on Chikungunya or its vectors, respectively, being largely absent from the Savannahs and Steppes of inland-Mexico.

In North America, our model predicts relatively low over-all climatic potential for Chikungunya transmission. However, the areas of relatively higher suitability closely match the combined patterns of *Ae. aegypti* and *Ae. albopictus* distribution in the United States, as represented by the models by Kraemer et al.[36] While the model by Nsoesie et al.[22] appears to predict the US to be less suitable than all other models, those produced by Mordecai et al.[35] predict 3 weeks of potential transmission areas as far north as Edmonton (Canada). The

latter is probably due to the omission of low-temperature effects on mosquito survival as a modelling parameter, as even short periods of hard frost can significantly increase mortality of diapausing and non-diapausing *Aedes* eggs[37].

In South America, all models covering the region predict a wide-spread potential for Chikungunya and its vectors respectively. Complete absence of Chikungunya is predicted for the Andes, Atacama Desert and Patagonia by all models. The mechanistic models of Mordecai et al.[35] deviate from all other models by suggesting up to 5 consecutive months of potential transmission in the dry desert climates south of Trelew, Argentina as well as in a narrow strip along the western coast as far south as Los Ángeles, Chile. This is most likely due to the omission of precipitation and low-temperature limits as explanatory variables, as the very dry climate reduces availability of breeding sites for the vectors. In all other regions, Chikungunya transmission is possible in all models, though the distribution of relatively high and low suitability differs vastly among models.

In Europe, our baseline model (Fig. 5) appears to predict the locations of the recorded outbreaks in Italy and France much more accurately than the model by Nsoesie et al.[22] When compared with the *Ae. albopictus* model from Kraemer et al.[36], areas of very high climatic potential for Chikungunya transmission are more locally constrained in our model. Their vector model identifies suitable climatic conditions in Portugal and south-western Spain as well as nearly all coastal regions along the Mediterranean Sea. While many of these regions are not identified as highly climatically suitable areas for Chikungunya transmission in our model, it must be noted that they still represent a raised potential for Chikungunya transmission and should not be interpreted as low-risk areas.

To summarise, the two niche-type models based on Chikungunya occurrences, namely ours and the one by Nsoesie et al.[22], anticipate less Chikungunya transmission in temperate regions than the other ones. This may simply be a surveillance artefact: current records of Chikungunya transmission

in these areas are comparably sparse, possibly because Chikungunya is not generally expected in these regions by public health practitioners, which would mean that there is a gap in surveillance and, consequently, that our models under-estimate Chikungunya hazard in these areas. Conversely, perhaps more plausibly, it could mean that there may be additional effects of temperature that prevent Chikungunya transmission but not vector presence. It is important to note that while it is generally assumed that the Extrinsic Incubation Period (EIP) for Chikungunya is shorter than for Dengue, there are to our knowledge no systematic laboratory or field studies on how the EIP for Chikungunya changes at moderate to low temperatures. Even for Dengue, which is relatively well-studied, data on this is sparse and partially problematic[38].

The novel models presented here demonstrate projected shifts in the climatic suitability for Chikungunya globally over the next century to identify regions with comparatively high hazards of Chikungunya transmission. The models project a net global increase in climate suitability for Chikungunya transmission by 2100, albeit with some important exceptions. Given the continued expectation for rapid global viral spread of Chikungunya alongside significant projected climatic changes over the next century, the models presented here can substantially contribute to integrated planning processes linking climate change adaptation with public health preparedness for mosquito-borne diseases.

Methods

We compiled a global database of ca. 700 geo-referenced localities of confirmed autochthonous Chikungunya virus transmission from Promedmail, literature records, PAHO- and CARPHA-reports as well as global and local news outlets up until January 2015 (Fig. S8 and supplementary data). The majority of these records (73%) came from Asia, followed by the Americas (16%), Africa (9%) and Europe (2%). For some countries, we were forced to use centroids (geographical centres) of districts as geo-located regions (e.g. Bhutan, India, Thailand and Reunion Island). This may either be due to the reporting system

(in case that no detailed coordinates or cities were mentioned), or to major outbreaks affecting whole districts. After removing duplicates as well as locations with insufficiently precise coordinates or missing climatic data coverage, 615 localities remained for use in the modelling process.

Once presence records had been prepared, bioclimatic variables obtained from the "Bioclim" dataset for current climatic conditions of Worldclim[28] at a spatial resolution of 5 arcmin. Bioclimatic variables are derived from monthly temperature and rainfall values in order to generate biologically meaningful variables, representing annual trends, seasonality and extreme or limiting environmental factors. Those bioclimatic variables were referred to those sites with presence records, using the Maximum Entropy algorithm implemented in Maxent 3.3.3k[39]. Maxent is a commonly used method for predicting species distributions based on environmental variables and capable of accounting for interactions between variables. Instead of absence data, Maxent uses so-called background samples randomly drawn from the environment surrounding the presence records, accounting for the possibility of incorporating data from locations where the modelled species occurs but was not recorded. The maximum distance to the occurrence records from within which these background samples are drawn must be carefully chosen in order to avoid over- and underfitting[40]. Methods for doing this based on biological criteria exist[41], but are primarily geared towards single species of higher organisms and do not necessarily translate well for complex virus-vector-host systems. As the dispersal potential of both the pathogen and its vectors is large due to human traffic, we opted for a buffer-based approach for estimating this potential. We produced a series of test models using buffer zones with radii between 0.1 and 10°. The resulting maps were carefully examined for artefacts such as high climatic suitability being predicted for obviously unsuitable areas or being limited only to the immediate surroundings of presence records. In our case, a buffer zone with a radius of 3° gave the best results. In order to come up with the challenge of spatial autocorrelation in data and to avoid spatial clustering

in those regions with high numbers of documented cases (quantity effect) we created a spatial bias file as outlined by Elith et al.[42]

Selection of bioclimatic variables to be used in the final model was done using the "Jackknife" utility implemented in Maxent[43] on a test run with all 19 Bioclim variables offered by Worldclim. This measures the effect each input variable has on the model's training gain when a) the variable is considered in isolation and b) in combination with other variables, when this specific variable is dropped from the subset. For highly covarying variables only the one showing most influential potential in the Jackknife was considered for the final model. Based on this, the 5 most influential variables were:

- Annual mean temperature (bio 1)
- Minimum temperature of the coldest month (bio 6)
- Mean temperature of the wettest quarter (bio 8)
- Mean temperature of the warmest quarter (bio 10)
- Annual precipitation (bio 12)

The final baseline model was fit with these variables, using Maxent at default settings with a maximum of 1000 iterations. A 10-fold cross-validation was conducted for model validation, consisting of 10 separate runs with different sets of training data (used for fitting the model) and test data (used for testing model performance). Models were evaluated using partial receiver operating characteristics[44], using 1000 bootstrapping iterations on 50% of the test data using an expected error rate of 5%. AUC ratios consistently were significantly larger than 1, suggesting good model performance.

In the following step, the baseline model was used for future projections under the IPCC-5 RCP 4.5 and 8.5 climate change scenarios. RCP 4.5 represents a moderate scenario with stabilization of radiative forcing by 2100[45], while RCP 8.5 follows a "high-emission business as usual scenario"[46]. For this, additional climate data was acquired from ccafs-climate.org at a spatial resolution of 5 arcmin, covering the time steps of 2021–2040, 2041–2060 and 2061–2080. To account for uncertainties in climate modelling, data from 5 different global

climate models (CESM 1 bcg, FIO ESM, GISS e2-r, INM CM4 and MPI-ESM-lr) were used for 5 separate sets of projections, from which a mean was then calculated for each time step and scenario. Mobility-Oriented Parity analysis (MOP) was applied in order to exclude potential bias in projections due to non-analogue climatic conditions[47]. Areas of low similarity to the calibration areas and strict extrapolation were consistently restricted to climatically extreme regions such as the Sahara and Atacama deserts as well as Greenland, where harsh climatic conditions would certainly exclude chikungunya anyway.

Human population density was deliberately not included as an explanatory variable for the climate-driven distribution model. Initial test runs showed that Chikungunya occurrence was (as expected) highly correlated with human population density, which dominated the models to a degree that climate effects were completely obfuscated. Instead, a post-hoc approach was applied that combines the results of the climate-driven models and human population density into a hazard index. For that, information on human population density was acquired from the Gridded Population of the World dataset[48]. On a 2.5 arcmin resolution raster, this dataset contains the predicted population density for the year 2015. To gain meaningful results, the population data was log-transformed. Afterwards values were scaled to a range between 0 and 1 to be comparable with the scale of the output of the climate-driven models. The 5 arcmin grid of the models was up-sampled to the finer 2.5 arcmin grid of the population data using a straight-forward "nearest neighbour" approach, and the two data sets were multiplied to gain a hazard index. For all future projections, human population density was held constant, as there were no reliable future projections of population development available for the whole study period and area.

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Author Contributions

S.T. and D.F. provided the original concept of the approach and wrote parts of the text. N.T. and D.F. developed the idea for applying Chikungunya models to novel climate change scenarios (“Representative Concentration Pathways”). D.F. compiled the original Chikungunya occurrence data set and built the first test models. N.T. updated the Chikungunya occurrence data set, built the models, prepared the figures and compiled the manuscript. J.S. wrote parts of the text. C.B. and J.S. coordinated and supervised the project. All authors discussed the methodology and results, and reviewed the manuscript.

Additional Information

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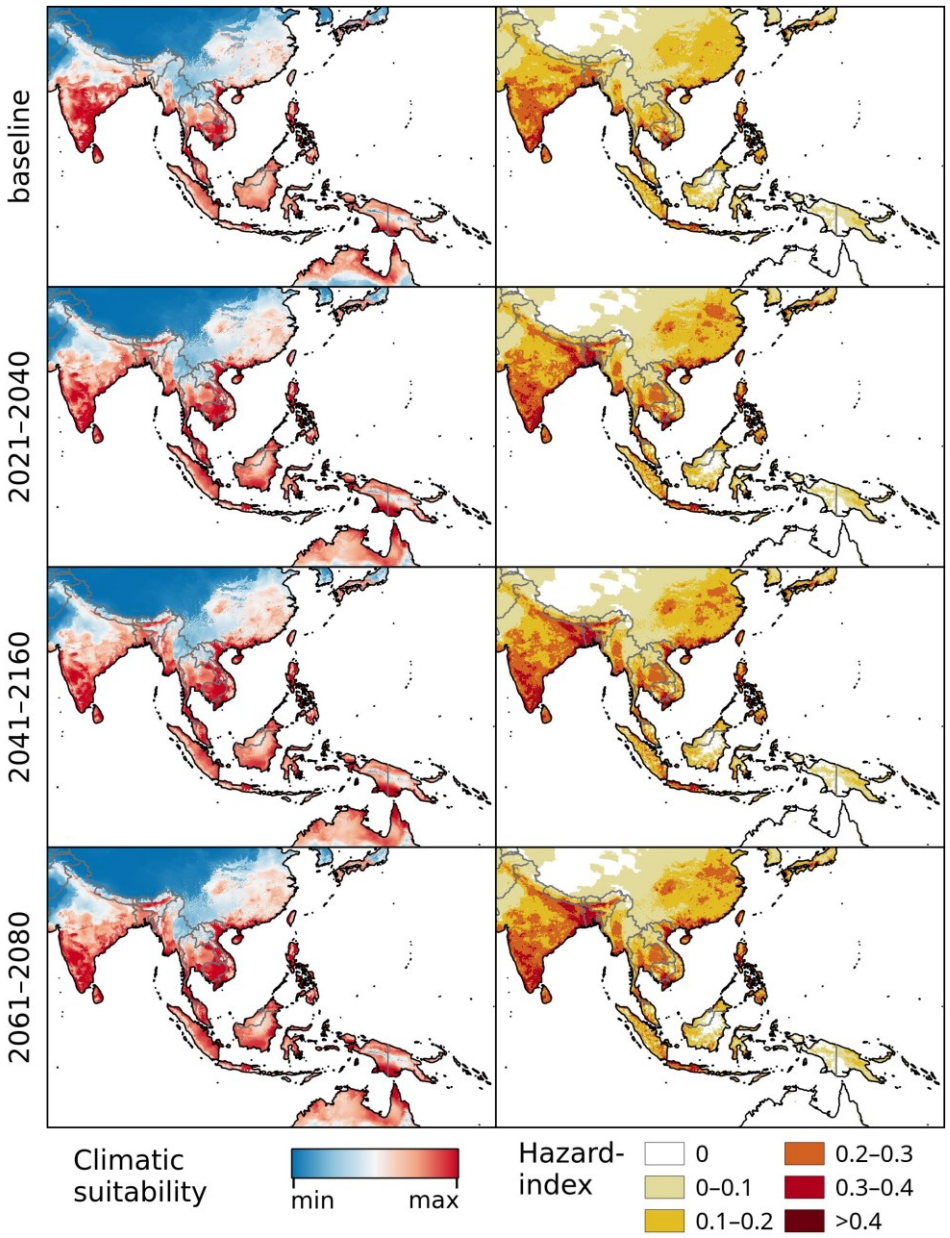
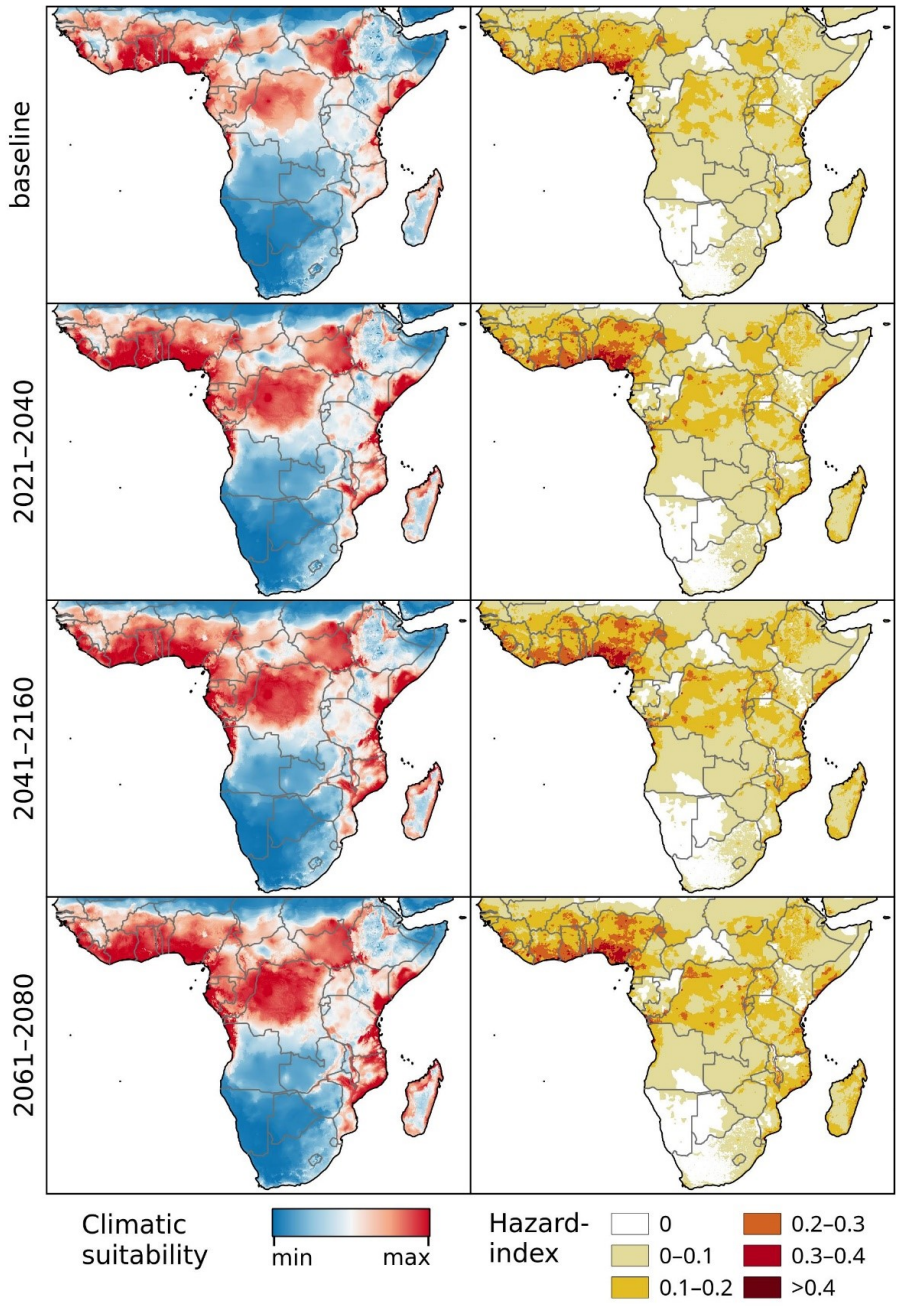
Appendix: Electronic supplementary material

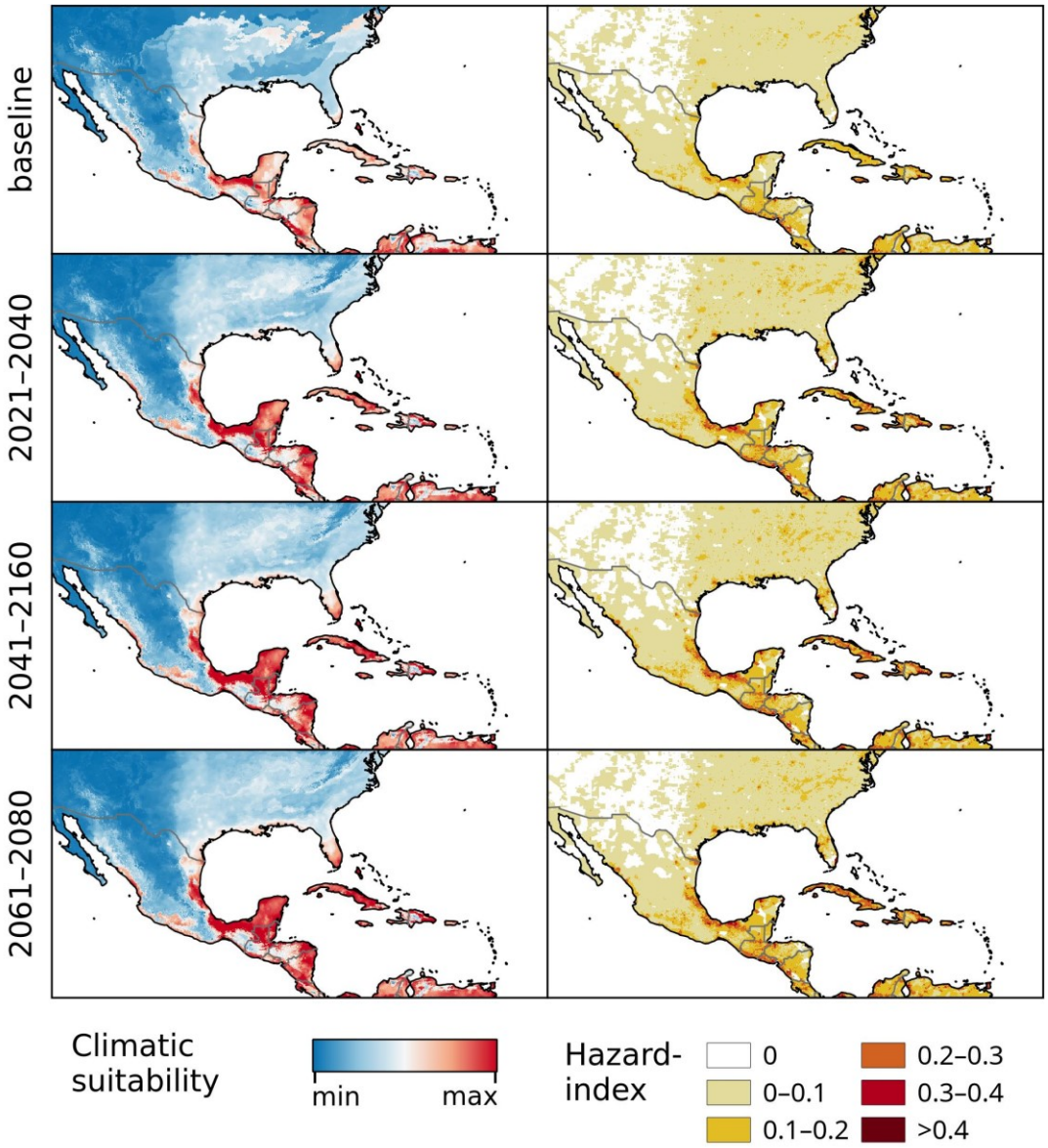
Supplementary Figures



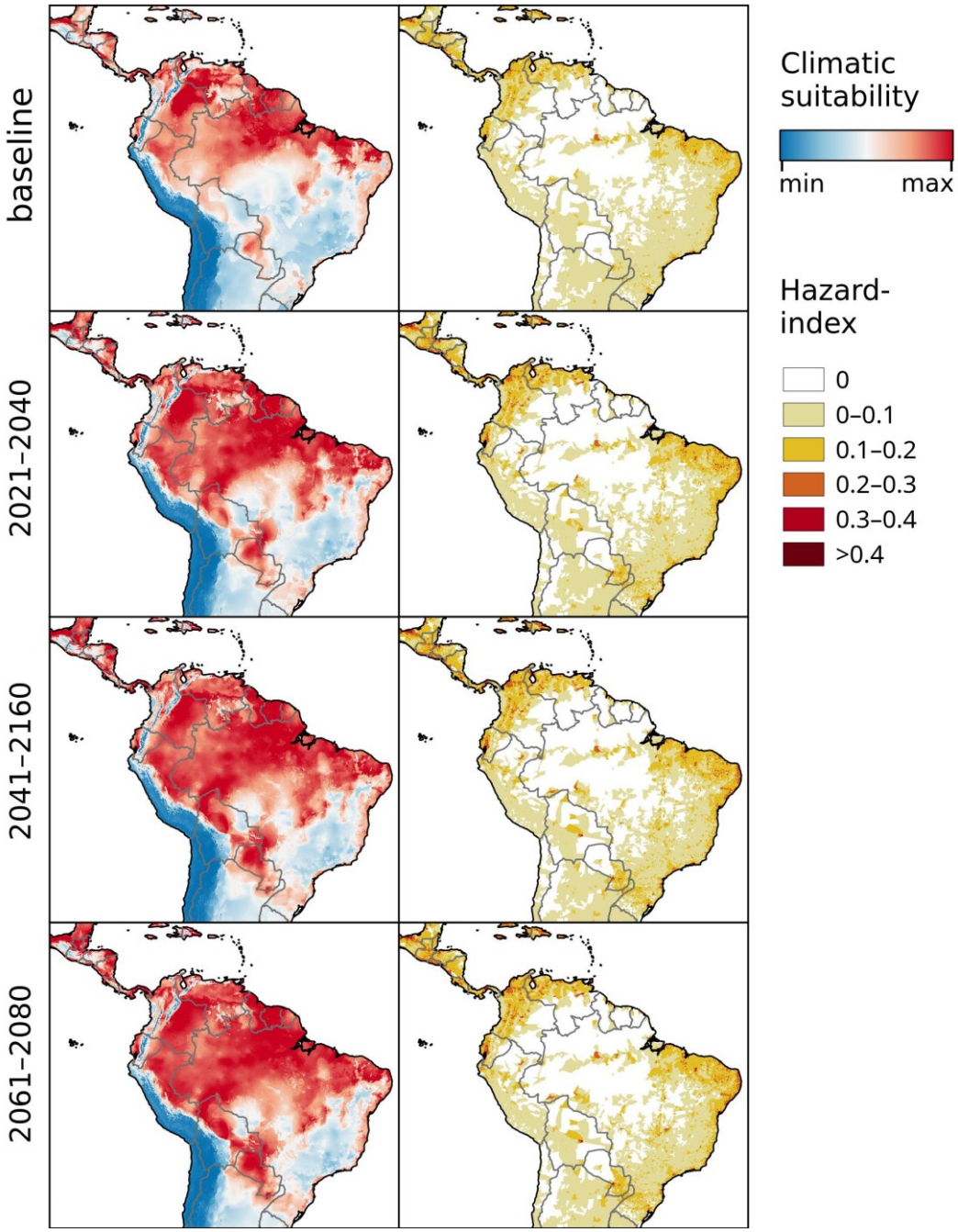
Supplementary Figure S1: Chikungunya under the baseline and RCP 4.5 climate change scenarios in Asia and Australasia. Left: Climatic suitability, right: hazard index. Climate change scenarios represent the mean model output obtained through the 5 GCMs. Climatic suitability output is scaled to the over-all global minimum (0) and maximum (0.623) values observed in any model. Maps were generated using the "raster" package in R 3.3.2 (https://www.r-project.org/) and QGIS 2.8.1 (https://www.qgis.org/).



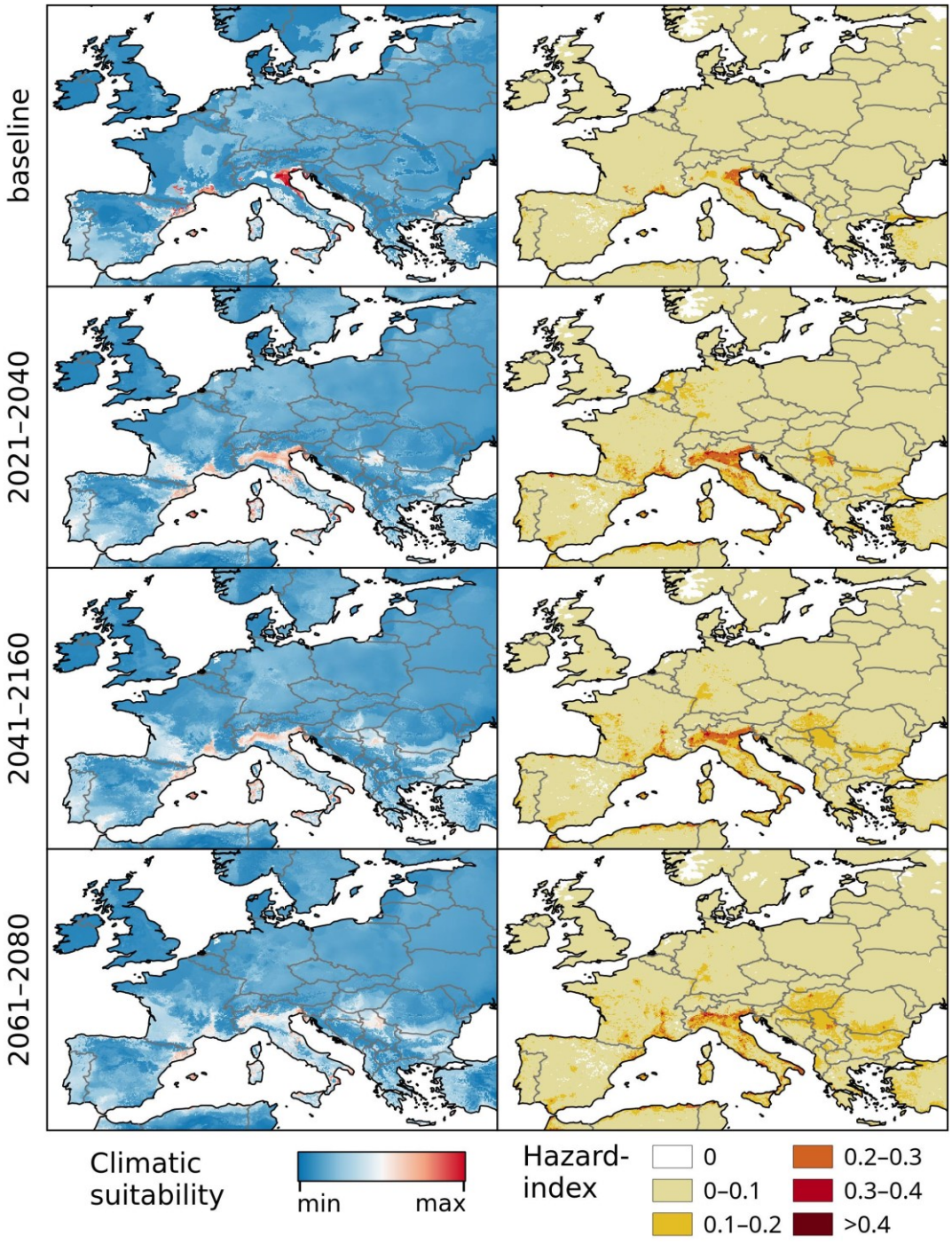
Supplementary Figure S2: Chikungunya under the baseline and RCP 4.5 climate change scenarios in Africa. Left: Climatic suitability, right: hazard index. Climate change scenarios represent the mean model output obtained through the 5 GCMs. Climatic suitability output is scaled to the over-all global minimum (0) and maximum (0.623) values observed in any model. Maps were generated using the "raster" package in R 3.3.2 (https://www.r-project.org/) and QGIS 2.8.1 (https://www.qgis.org/).



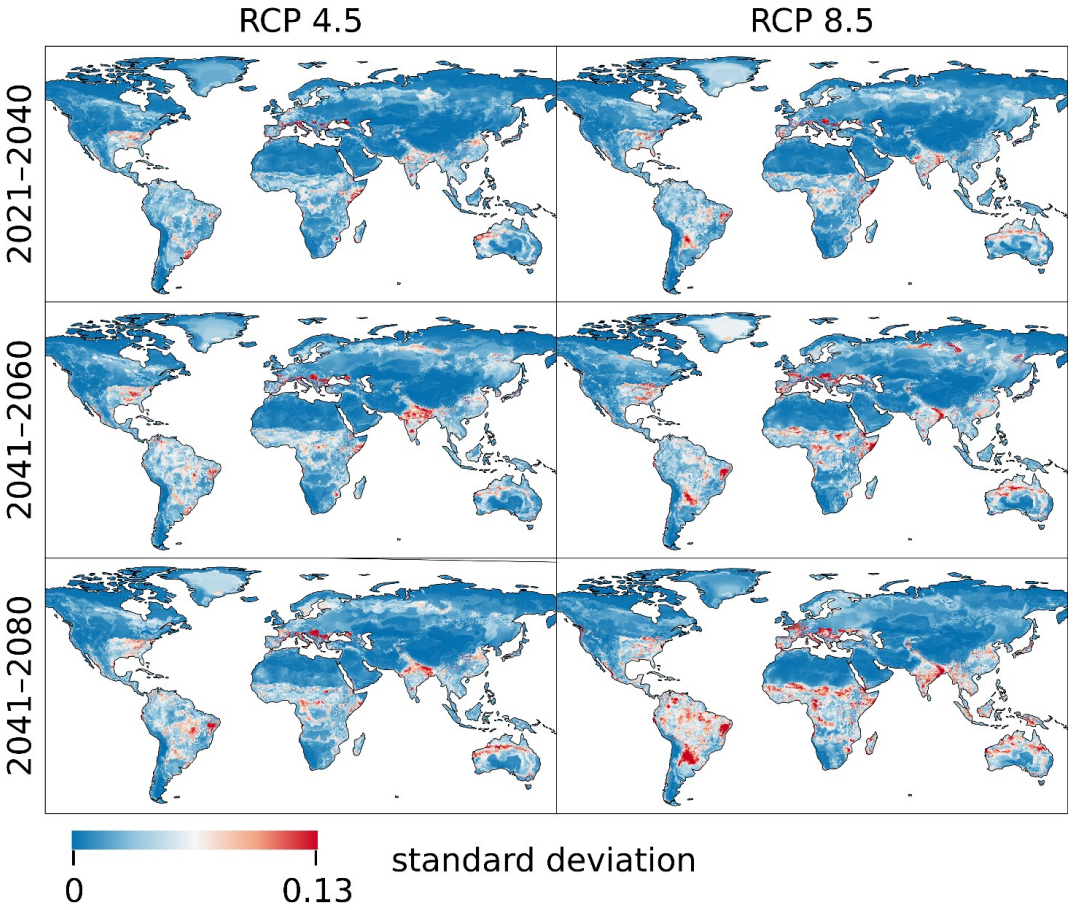
Supplementary Figure S3: Chikungunya under the baseline and RCP 4.5 climate change scenarios in North- and Central America. Left: Climatic suitability, right: hazard index. Climate change scenarios represent the mean model output obtained through the 5 GCMs. Climatic suitability output is scaled to the over-all global minimum (0) and maximum (0.623) values observed in any model. Maps were generated using the "raster" package in R 3.3.2 (https://www.r-project.org/) and QGIS 2.8.1 (https://www.qgis.org/).



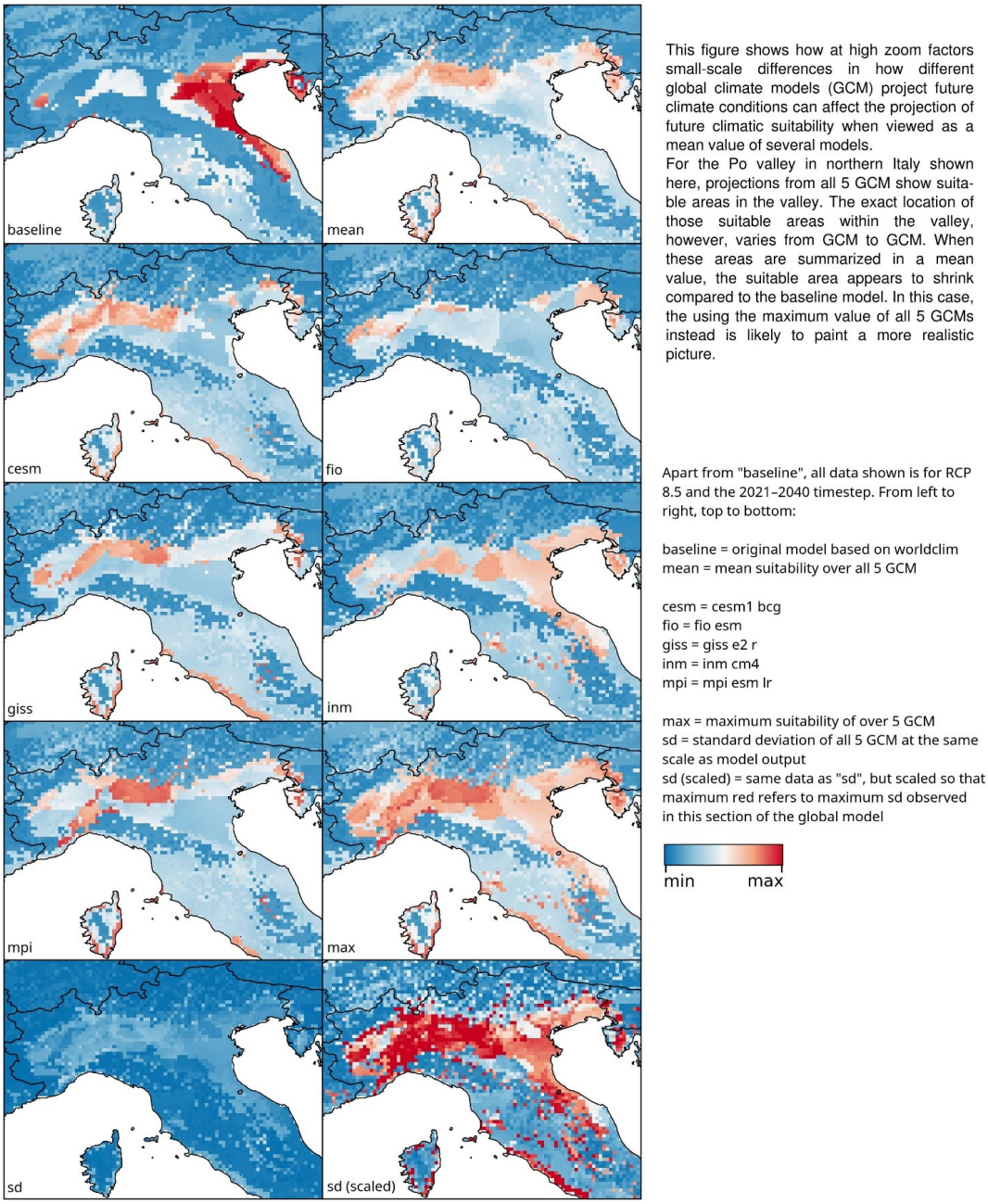
Supplementary Figure S4: Chikungunya under the baseline and RCP 4.5 climate change scenarios in South America. Left: Climatic suitability, right: hazard index. Climate change scenarios represent the mean model output obtained through the 5 GCMs. Climatic suitability output is scaled to the over-all global minimum (0) and maximum (0.623) values observed in any model. Maps were generated using the "raster" package in R 3.3.2 (https://www.r-project.org/) and QGIS 2.8.1 (https://www.qgis.org/).



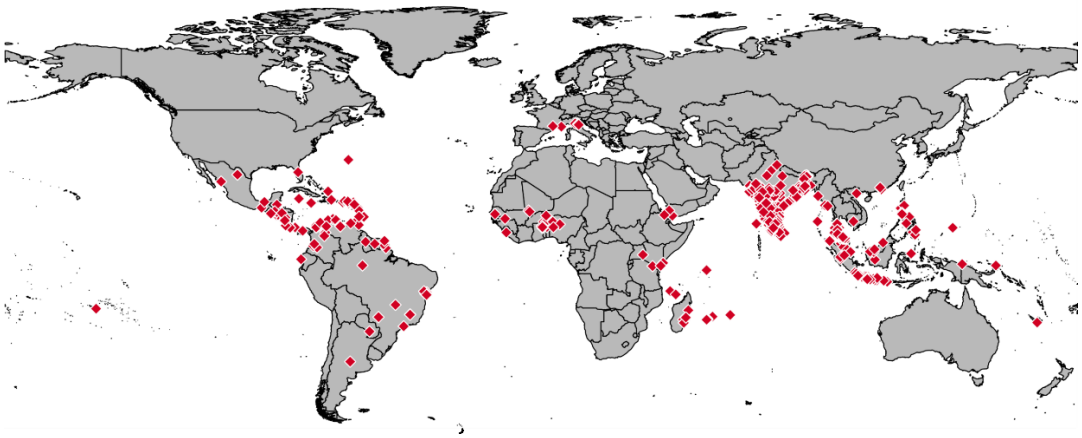
Supplementary Figure S5: Chikungunya under the baseline and RCP 4.5 climate change scenarios in Europe. Left: Climatic suitability, right: hazard index. Climate change scenarios represent the mean model output obtained through the 5 GCMs. Climatic suitability output is scaled to the over-all global minimum (0) and maximum (0.623) values observed in any model. Maps were generated using the "raster" package in R 3.3.2 (https://www.r-project.org/) and QGIS 2.8.1 (https://www.qgis.org/).



Supplementary Figure S6: Standard deviation of future projections across 5 global climate models. Maps were generated using the "raster" package in R 3.3.2 (https://www.r-project.org/) and QGIS 2.8.1 (https://www.qgis.org/).



Supplementary Figure S7: Comparison of small-scale variations in projected future climatic suitability of Chikungunya based on different climate models. Small scale differences in projected climate may lead to local under-estimations of climatic suitability. This is especially apparent for the Po Valley in northern Italy: all projections obtained from the 5 GCMs agree that there are highly suitable areas in this region, but the location of those areas within the region varies between GCMs, leading to a lower than expected mean suitability. Maps were generated using the "raster" package in R 3.3.2 (https://www.r-project.org/) and QGIS 2.8.1 (https://www.qgis.org/).



Supplementary Figure S8: Global map of Chikungunya occurrences used to train the models. The map was generated using QGIS 2.8.1 (https://www.qgis.org/).

Supplementary Data

Supplementary Table S1: Global database of CHIKV transmission with geographical co-ordinates and year of first occurrence. Source ID refers to the references listed in Supplementary Table S2.

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
Africa					
Congo, Rep.	Brazzaville	15.283	-4.267	2011	Promedmail
	Pool	14.919	-3.917	2011	Promedmail
Congo, Dem. Rep.	Kinshasa	15.314	-4.332	2012	Promedmail
	Kinshasa	15.314	-4.332	2012	Promedmail
Equatorial Guinea	Bata	9.767	1.860	2006	Collao_2010
Gabon	Franceville	13.583	1.633	2010	Promedmail
	Kango	10.108	0.170	2007	Leroy_2009
	Libreville	9.465	0.404	2007	Promedmail
	Minvoul	12.133	2.151	2007	Leroy_2009
	Mitzic	11.553	0.785	2007	Leroy_2009
	Ntoum	9.754	0.383	2007	Leroy_2009
	Oyem	11.579	1.598	2007	Leroy_2009
Kenya	Busia	0.461	34.112	NA	Mease_2011
	Lamu	-2.270	40.901	2004	Sergon_2008
	Malindi	-3.212	40.098	NA	Mease_2011
Madagascar	Ifanadiana	-21.304	47.634	2010	Promedmail
	Manakara	-22.146	48.002	2010	Promedmail
	Mananjary	-21.228	48.335	2010	Promedmail
	Nosy Varika	-20.588	48.531	2010	Promedmail
	Toamasina	-18.149	49.368	2010	Promedmail; Ratsitorahina_2008
	Vohipeno	-22.354	47.840	2011	Promedmail
Mauritius	Main island	-20.313	57.520	2005	Beesoon_EID_2008
	Moka	-20.219	57.496	2012	Promedmail
	Quatre Bornes	-20.265	57.479	2011	Promedmail
	Rodrigues	-19.716	63.429	2005	Beesoon_EID_2008
Mayotte	Mayotte	-12.851	45.140	NA	D`Ortenzio_2011
Reunion	Bras-Panon	-21.021	55.622	NA	Promedmail
	Cilaos	-21.144	55.458	NA	Promedmail
	La Plaine-des-Palmistes	-21.150	55.643	NA	Promedmail
	La Possession	-20.996	55.397	NA	Promedmail
	Le Port	-20.944	55.302	NA	Promedmail
	Le Tampon	-21.227	55.562	NA	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	L'Entre-Deux	-21.197	55.502	NA	Promedmail
	Les Avirons	-21.212	55.359	NA	Promedmail
	Les Trois-Bassins	-21.109	55.329	NA	Promedmail
	L'Étang-Salé	-21.247	55.368	NA	Promedmail
	Petite-Île	-21.340	55.568	NA	Promedmail
	Saint-André	-20.961	55.639	NA	Promedmail
	Saint-Benoît	-21.089	55.648	NA	Promedmail
	Saint-Denis	-20.931	55.447	NA	Promedmail
	Sainte-Marie	-20.946	55.532	NA	Promedmail
	Sainte-Rose	-21.189	55.753	NA	Promedmail
	Sainte-Suzanne	-20.943	55.594	NA	Promedmail
	Saint-Joseph	-21.304	55.641	NA	Promedmail
	Saint-Leu	-21.167	55.334	NA	Promedmail
	Saint-Louis	-21.233	55.422	NA	Promedmail
	Saint-Paul	-21.045	55.321	NA	Promedmail
	Saint-Philippe	-21.302	55.744	NA	Promedmail
	Saint-Pierre	-21.311	55.489	NA	Promedmail
	Salazie	-21.045	55.509	NA	Promedmail
Senegal	Kaffrine	14.103	-15.546	1996	Diallo_1999
	Kédougou	12.553	-12.176	2012	Diallo_2012
	Kédougou	12.554	-12.173	2008	Promedmail
Seychelles	Mahe	-4.684	55.483	NA	D`Ortenzio_2011
Sierra Leone	Bo	7.955	-11.741	2012	Promedmail
Tanzania	Moshi	-3.340	37.343	2011	Hertz_2012
Americas					
Anguilla	Anguilla	18.227	-63.049	NA	CDC
	Anguilla	18.216	-63.051	2014	CDC; CARPHA; PAHO
Antigua & Barbuda	Antigua & Barbuda	17.280	-61.791	2014	Herriman_2014
Argentina	Argentina	-35.376	-64.168	2014	MdS
Aruba	Aruba	12.500	-69.967	2014	CDC; CARPHA; PAHO
Bahamas	Bahamas	24.000	-76.000	2014	CDC; CARPHA; PAHO
Barbados	Barbados	13.179	-59.562	2014	Stabroek; CARPHA; PAHO
Belize	Belmopan	17.250	-88.767	2014	Jones_2014; CARPHA; PAHO
Bermuda	Bermuda	32.321	-64.757	2014	CARPHA; PAHO
Brazil	Alagoinhas - Bahia, Brazil	-12.135	-38.423	2014	Promedmail
	Amélia Rodrigues	-12.396	-38.759	2014	Promedmail
	Anápolis	-16.329	-48.953	2014	Rodrigues_2014
	Cachoeira	-12.601	-38.964	2014	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	Campo Grande	-20.443	-54.646	2014	Promedmail
	Feira de Santana	-12.267	-38.967	2014	Promedmail
	Manaus	-3.102	-60.025	2014	Dantas_2014
	Matozinhos	-19.521	-44.050	2014	Promedmail
	Mogi das Cruzes	-23.523	-46.188	2014	Globo_2014
	Oiapoque	2.708	-52.170	2014	Promedmail
	Pedro Leopoldo	-19.618	-44.043	2014	Bemparana_2014; Promedmail
	Riachão do Jacuípe	-11.806	-39.382	2014	Promedmail
	Salvador	-12.971	-38.511	2014	Promedmail
British Virgin Islands	British Virgin Islands	18.428	-64.622	2014	CARPHA; PAHO
	British Virgin Islands	18.429	-64.624	NA	CDC
Cameroon	Douala	9.706	4.047	2006	Preyrefitte_2007
	Kumbo	10.685	6.207	2006	Demanou_2010
	Yaoundé	11.517	3.867	2006	Preyrefitte_2007
Cayman Islands	Bodden Town	19.276	-81.254	2014	Bonham_2014 CARPHA; PAHO
	George Town	19.287	-81.374	2014	Bonham_2014 CARPHA; PAHO
	Newlands	19.283	-81.300	2014	Bonham_2014 CARPHA; PAHO
	West Bay	19.367	-81.417	2014	Bonham_2014 CARPHA; PAHO
Colombia	Barranquilla	10.964	-74.796	2014	El_Tiempo; PAHO
	Cali	3.417	-76.550	2014	El_Pais; PAHO
	Cartagena	10.400	-75.514	2014	Maheshwary_2014; PAHO
	Córdoba	10.333	-74.459	2014	Maheshwary_2014; PAHO
	Cúcuta	7.902	-72.498	2014	Caracol; PAHO
	La Guajira	12.072	-71.598	2014	Maheshwary_2014; PAHO
	Magdalena	9.967	-75.083	2014	Maheshwary_2014; PAHO
	Neiva	2.927	-75.282	2014	Promedmail; PAHO
	Providencia	9.667	-75.567	2014	Maheshwary_2014; PAHO
	San Andres	6.784	-72.834	2014	Maheshwary_2014; PAHO
	Santa Marta	11.247	-74.202	2014	Maheshwary_2014; PAHO
	Tuluá	4.087	-76.200	2014	El_Pais_2; PAHO
	Moroni	-11.702	43.254	2005	Sang_2008
	Ngazidja	11.618	43.324	NA	Sergon_2007
Costa Rica	Boca Barranca	9.962	-84.737	2014	TCRN; PAHO

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	Chomes	10.044	-84.908	2014	TCRN; PAHO
	Costa de Pájaros	10.100	-84.988	2014	Arias_2014; PAHO
	Esterillos Este	9.532	-84.457	2014	Promedmail; PAHO
	Manzanillo	9.634	-82.653	2014	Arias_2014; PAHO
	Miramar	10.093	-84.730	2014	TCRN; PAHO
	Parrita	9.550	-84.333	2014	TCT; PAHO
	Tamarindo	10.295	-85.839	2014	Arias_2014; PAHO
Curacao	Curaçao	12.117	-68.933	2014	CDC; CARPHA; PAHO
Dominica	Dominica	15.436	-61.356	2014	CARPHA; PAHO
	Dominica	15.417	-61.333	NA	CDC
Dominican Republic	Dominican Republic	18.894	-70.485	2014	El_Nacional; CARPHA; PAHO
Ecuador	Montecristi	-1.046	-80.659	2014	La_Hora; PAHO
El Salvador	El Salvador	13.737	-88.867	2014	El_Mundo; PAHO
French Guiana	French Guiana	4.000	-53.000	2014	PAHO; CARPHA
	Kourou	5.160	-52.650	NA	CDC/ECDC
Grenada	Grenada	12.113	-61.679	2014	Herriman_2014_2; PAHO; CARPHA
Guadeloupe	Guadeloupe	16.250	-61.583	NA	CDC
	Guadeloupe	16.250	-61.583	2014	Promedmail; PAHO; CARPHA
Guatemala	Departamento de Zacapa	15.000	-89.500	2014	Promedmail; PAHO
	Escuintla	14.305	-90.785	2014	Promedmail; PAHO
Guyana	Guyana	4.792	-58.975	2014	RHC; PAHO; CARPHA
Honduras	Departamento de Valle	13.583	-87.583	2014	El_Heraldo; PAHO
	Francisco Morazan	14.454	-87.062	2014	Promedmail; PAHO
Jamaica	Jamaica	18.151	-77.319	2014	Jamaica_Observer; PAHO; CARPHA
	Vere	17.847	-77.272	2014	The_Gleaner; PAHO; CARPHA
Martinique	Martinique	14.667	-61.000	NA	CDC
	Martinique	14.667	-61.000	2014	PAHO; CARPHA
Mexico	Arriaga	16.237	-93.902	2014	Milenio; PAHO
	Estado de Coahuila	27.333	-101.997	2014	Ideal; PAHO
	Estado de Sinaloa	25.006	-107.490	2014	Debate; PAHO
	Tabasco	18.200	-92.950	2014	Presente; PAHO
Montserrat	Montserrat	16.735	-62.187	2014	CDC; CARPHA; PAHO
Nicaragua	Chinandega	12.629	-87.131	2014	Nuevo_Diario; PAHO
	Managua	12.151	-86.268	2014	Nuevo_Diario; PAHO
	Masaya	11.967	-86.100	2014	Nuevo_Diario; PAHO
	Matagalpa	12.926	-85.917	2014	Nuevo_Diario; PAHO

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
Panama	Panama	8.507	-80.103	2014	Telemetro; PAHO
Paraguay	Asunción	-25.267	-57.667	2014	Promedmail; PAHO
Puerto Rico	San Juan	18.466	-66.106	2014	Primera_Hora; PAHO
Saint Barthélemy	Saint Barthélemy	17.900	-62.826	2014	CDC; CARPHA; PAHO
Saint Martin	Saint Martin	18.064	-63.056	2014	CDC; CARPHA; PAHO
Saint Martin (French)	Saint Martin (French)	18.067	-63.050	NA	CDC
St. Kitts & Nevis	St. Kitts	17.300	-62.733	NA	CDC
	St. Kitts & Nevis	17.326	-62.754	2014	CDC; CARPHA; PAHO
St. Lucia	St. Lucia	13.898	-60.969	2014	PAHO; CARPHA
St. Vincent & the Grenadines	St. Vincent & the Grenadines	13.255	-61.194	2014	CDC; CARPHA; PAHO
Suriname	Suriname	4.126	-55.912	2014	Promedmail; PAHO; CARPHA
Trinidad & Tobago	Trinidad & Tobago	10.469	-61.253	2014	CDC; CARPHA; PAHO
Turks & Caicos Islands	Turks and Caicos Islands	21.733	-71.583	2014	CDC; CARPHA; PAHO
US	Florida	28.150	-81.650	2014	Gilblom_2014; PAHO
US Virgin Islands	Saint Croix Island	17.736	-64.748	2014	St_Croix_1; PAHO; CARPHA
	Saint John Island	18.328	-64.738	2014	St_Croix_2; PAHO; CARPHA
	Saint Thomas	18.353	-64.937	2014	St_Croix_2; PAHO; CARPHA
Venezuela	Guarico	9.967	-67.467	2014	MPPSalud_2; PAHO
	Isla Margarita	11.000	-64.000	2014	Promedmail; PAHO
	Maracay	10.247	-67.596	2014	Promedmail; PAHO
	Zulia	10.000	-72.167	2014	MPPSalud; PAHO
Asia					
Bangladesh	Chapai Nawabganj	24.590	88.271	2008	Promedmail
	Dhaka	23.710	90.407	2011	Promedmail
	Dohar	23.618	90.119	2011	Promedmail
	Rajshahi	24.367	88.600	2008	Promedmail
	Sathia	24.007	89.244	2008	Promedmail
Bhutan	Bhalujora	26.841	89.486	NA	Promedmail
	Charghare	26.996	88.972	NA	Promedmail
	Chengmari	26.992	89.066	NA	Promedmail
	Lahireni	27.095	89.019	NA	Promedmail
	Nainetal	26.957	89.009	NA	Promedmail
	Pagli	26.851	89.183	NA	Promedmail
	Phuentsholing	26.859	89.391	2012	Promedmail
	Phuentsholing	26.918	89.401	NA	Promedmail
	Samtse	27.029	89.056	2012	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	Samtse	26.921	89.123	NA	Promedmail
	Sibsu	27.005	88.885	NA	Promedmail
	Tendruk	27.150	88.939	NA	Promedmail
Brunei	Brunei Darussalam	4.534	114.727	2012	Liew_2012
Cambodia	Trapeang Roka	11.665	104.797	NA	CDC
China	Dongguan	23.021	113.752	2010	Promedmail
	Hong Kong	22.396	114.110	2008	Promedmail
India	Adilabad	19.254	78.967	NA	Promedmail
	Ahmadabad	22.727	72.203	NA	Promedmail
	Ahmednagar	19.233	74.646	NA	Promedmail
	Akola	20.750	77.045	NA	Promedmail
	Alappuzha	9.413	76.446	NA	Promedmail
	Amravati	21.189	77.569	NA	Promedmail
	Amreli	21.421	71.264	NA	Promedmail
	Anand	22.450	72.791	NA	Promedmail
	Anantapur	14.475	77.571	NA	Promedmail
	Ariyalur	11.147	79.228	NA	Promedmail
	Aurangabad	20.023	75.276	NA	Promedmail
	Bagalkot	16.218	75.627	NA	Promedmail
	Banas Kantha	24.281	72.039	NA	Promedmail
	Bangalore Rural	12.887	77.422	NA	Promedmail
	Bangalore Urban	12.942	77.587	NA	Promedmail
	Barwani	21.790	75.023	NA	Promedmail
	Belgaum	16.118	74.828	NA	Promedmail
	Bellary	15.105	76.531	NA	Promedmail
	Betul	21.880	77.867	NA	Promedmail
	Bhandara	21.160	79.869	NA	Promedmail
	Bharuch	21.787	72.923	NA	Promedmail
	Bhavnagar	21.684	71.863	NA	Promedmail
	Bid	18.925	75.802	NA	Promedmail
	Bidar	17.950	77.224	NA	Promedmail
	Bijapur	16.792	75.953	NA	Promedmail
	Birbhum	23.952	87.662	NA	Promedmail
	Buldana	20.511	76.404	NA	Promedmail
	Burhanpur	21.374	76.369	NA	Promedmail
	Chamrajnagar	11.949	77.090	NA	Promedmail
	Chandrapur	20.117	79.438	NA	Promedmail
	Chennai	13.048	80.235	NA	Promedmail
	Chhindwara	22.123	78.850	NA	Promedmail
	Chikmagalur	13.449	75.690	NA	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	Chitradurga	14.162	76.512	NA	Promedmail
	Chittoor	13.457	79.004	NA	Promedmail
	Coimbatore	10.837	77.072	NA	Promedmail
	Cuddalore	11.525	79.445	NA	Promedmail
	Cuddapah	14.451	78.774	NA	Promedmail
	Dadra and Nagar Haveli	20.195	73.081	NA	Promedmail
	Dahod	22.910	74.020	NA	Promedmail
	Dakshin Dinajpur	25.362	88.593	NA	Promedmail
	Dakshin Kannad	12.833	75.267	NA	Promedmail
	Daman	20.414	72.842	NA	Promedmail
	Darjiling	26.914	88.392	NA	Promedmail
	Davanagere	14.352	75.931	NA	Promedmail
	Delhi	28.647	77.109	NA	Promedmail
	Dewas	22.748	76.454	NA	Promedmail
	Dharmapuri	12.296	78.097	NA	Promedmail
	Dharwad	15.386	75.156	NA	Promedmail
	Dhule	21.112	74.605	NA	Promedmail
	Dindigul	10.379	77.805	NA	Promedmail
	East Godavari	17.184	82.001	NA	Promedmail
	East Midnapore	22.027	87.774	NA	Promedmail
	East Nimar	21.939	76.570	NA	Promedmail
	Ernakulam	10.055	76.474	NA	Promedmail
	Erode	11.319	77.447	NA	Promedmail
	Gadag	15.428	75.667	NA	Promedmail
	Gandhinagar	23.208	72.700	NA	Promedmail
	Ganjam	19.622	84.659	NA	Promedmail
	Garhchiroli	19.782	80.234	NA	Promedmail
	Gondiya	21.121	80.155	NA	Promedmail
	Greater Bombay	19.145	72.923	NA	Promedmail
	Gulbarga	17.052	76.881	NA	Promedmail
	Guntur	16.291	80.081	NA	Promedmail
	Haora	22.524	88.065	NA	Promedmail
	Hassan	12.990	76.105	NA	Promedmail
	Haveri	14.734	75.419	NA	Promedmail
	Hingoli	19.615	77.117	NA	Promedmail
	Hugli	22.882	88.076	NA	Promedmail
	Hyderabad	17.386	78.464	NA	Promedmail
	Idukki	9.874	77.013	NA	Promedmail
	Jaipur	26.984	75.718	NA	Promedmail
	Jalgaon	20.937	75.491	NA	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	Jalna	19.820	75.983	NA	Promedmail
	Jalpaiguri	26.663	89.081	NA	Promedmail
	Jamnagar	22.251	69.925	NA	Promedmail
	Junagadh	20.835	70.794	NA	Promedmail
	Junagadh	21.213	70.568	NA	Promedmail
	Kachchh	23.625	69.967	NA	Promedmail
	Kancheepuram	12.681	79.936	NA	Promedmail
	Kanniyakumari	8.306	77.347	NA	Promedmail
	Kannur	11.992	75.536	NA	Promedmail
	Karimnagar	18.546	79.235	NA	Promedmail
	Karur	10.832	78.118	NA	Promedmail
	Kasaragod	12.459	75.152	NA	Promedmail
	Katni	23.704	80.335	NA	Promedmail
	Keonjhar	21.532	85.699	NA	Promedmail
	Khammam	17.590	80.679	NA	Promedmail
	Kheda	22.876	73.023	NA	Promedmail
	Khordha	20.083	85.505	NA	Promedmail
	Kodagu	12.319	75.799	NA	Promedmail
	Kolar	13.356	78.012	NA	Promedmail
	Kolhapur	16.467	74.167	NA	Promedmail
	Kolkata	22.552	88.352	NA	Promedmail
	Kollam	8.954	76.868	NA	Promedmail
	Koppal	15.558	76.220	NA	Promedmail
	Kottayam	9.628	76.649	NA	Promedmail
	Kozhikode	11.481	75.832	NA	Promedmail
	Krishna	16.550	80.793	NA	Promedmail
	Kurnool	15.528	78.000	NA	Promedmail
	Lakshadweep islands	10.865	72.196	2006	Samuel_2009
	Latur	18.373	76.760	NA	Promedmail
	Lucknow	26.847	80.897	NA	Promedmail
	Madurai	9.910	77.990	NA	Promedmail
	Mahbubnagar	16.493	78.140	NA	Promedmail
	Mahesana	23.580	72.496	NA	Promedmail
	Malappuram	11.129	76.152	NA	Promedmail
	Mandya	12.604	76.790	NA	Promedmail
	Medak	17.885	78.211	NA	Promedmail
	Murshidabad	24.161	88.227	NA	Promedmail
	Mysore	12.202	76.436	NA	Promedmail
	Nadia	23.476	88.516	NA	Promedmail
	Nagapattinam	10.864	79.736	NA	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	Nagpur	21.177	79.082	NA	Promedmail
	Nalgonda	17.062	79.281	NA	Promedmail
	Namakkal	11.305	78.122	NA	Promedmail
	Nanded	19.115	77.621	NA	Promedmail
	Nandurbar	21.547	74.220	NA	Promedmail
	Narmada	21.712	73.658	NA	Promedmail
	Nashik	20.260	74.078	NA	Promedmail
	Navsari	20.813	73.103	NA	Promedmail
	Nayagarh	20.206	84.993	NA	Promedmail
	Nellore	14.430	79.723	NA	Promedmail
	Nilgiris	11.448	76.633	NA	Promedmail
	Nizamabad	18.524	78.139	NA	Promedmail
	North 24 Parganas	22.463	88.778	NA	Promedmail
	North Goa	15.551	73.984	NA	Promedmail
	Osmanabad	18.188	76.039	NA	Promedmail
	Palakkad	10.787	76.548	NA	Promedmail
	Panch Mahals	22.853	73.609	NA	Promedmail
	Parbhani	19.286	76.682	NA	Promedmail
	Patan	23.768	71.800	NA	Promedmail
	Pattanamtitta	9.276	76.913	NA	Promedmail
	Perambalur	11.260	78.878	NA	Promedmail
	Porbandar	21.638	69.802	NA	Promedmail
	Port Blair	11.623	92.726	2007	Manimunda_2007
	Prakasam	15.611	79.510	NA	Promedmail
	Pudukkottai	10.342	78.867	NA	Promedmail
	Pune	18.571	74.077	NA	Promedmail
	Purba Singhbhum	22.579	86.447	NA	Promedmail
	Puri	19.866	85.698	NA	Promedmail
	Puruliya	23.275	86.413	NA	Promedmail
	Raichur	16.086	76.890	NA	Promedmail
	Raigarh	18.510	73.230	NA	Promedmail
	Rajkot	22.255	70.792	NA	Promedmail
	Ramanathapuram	9.443	78.680	NA	Promedmail
	Rangareddi	17.284	78.172	NA	Promedmail
	Ratnagiri	17.273	73.461	NA	Promedmail
	Rudra Prayag	30.595	79.098	NA	Promedmail
	Sabar Kantha	23.658	73.167	NA	Promedmail
	Salem	11.663	78.209	NA	Promedmail
	Sangli	17.111	74.775	NA	Promedmail
	Satara	17.668	74.181	NA	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	Shimoga	14.052	75.176	NA	Promedmail
	Sindhudurg	16.132	73.743	NA	Promedmail
	Sivaganga	9.907	78.576	NA	Promedmail
	Solapur	17.789	75.485	NA	Promedmail
	South 24 Parganas	22.114	88.416	NA	Promedmail
	South Goa	15.195	74.120	NA	Promedmail
	Srikakulam	18.571	83.979	NA	Promedmail
	Sundargarh	22.077	84.504	NA	Promedmail
	Surat	21.234	73.309	NA	Promedmail
	Surendranagar	22.795	71.552	NA	Promedmail
	Thane	19.618	73.166	NA	Promedmail
	Thanjavur	10.655	79.224	NA	Promedmail
	The Dangs	20.799	73.706	NA	Promedmail
	Theni	9.881	77.424	NA	Promedmail
	Thiruvallur	13.230	79.925	NA	Promedmail
	Thiruvananthapuram	8.606	77.005	NA	Promedmail
	Thiruvarur	10.669	79.535	NA	Promedmail
	Thoothukudi	8.877	77.988	NA	Promedmail
	Thrissur	10.466	76.312	NA	Promedmail
	Tiruchchirappalli	10.877	78.555	NA	Promedmail
	Tirunelveli Kattabo	8.790	77.523	NA	Promedmail
	Tiruvannamalai	12.419	79.154	NA	Promedmail
	Tumkur	13.514	76.941	NA	Promedmail
	Udupi	13.465	74.883	NA	Promedmail
	Uttar Dinajpur	25.874	88.157	NA	Promedmail
	Uttar Kannand	14.788	74.624	NA	Promedmail
	Vadodara	22.226	73.541	NA	Promedmail
	Valsad	20.418	73.119	NA	Promedmail
	Vellore	12.801	78.998	NA	Promedmail
	Villupuram	11.960	79.284	NA	Promedmail
	Virudhunagar	9.481	77.894	NA	Promedmail
	Vishakhapatnam	17.885	82.682	NA	Promedmail
	Vizianagaram	18.465	83.364	NA	Promedmail
	Warangal	17.950	79.792	NA	Promedmail
	Wardha	20.796	78.583	NA	Promedmail
	Washim	20.238	77.217	NA	Promedmail
	Wayanad	11.705	76.092	NA	Promedmail
	West Godavari	16.887	81.392	NA	Promedmail
	West Midnapore	22.410	87.262	NA	Promedmail
	Yavatmal	20.084	78.158	NA	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
Indonesia	Anuradhapura	8.315	80.415	2008	Promedmail
	Bakauheni	-5.862	105.746	2010	Promedmail
	Bandar Lampung	-5.428	105.243	2007	Promedmail
	Bandung	-6.915	107.610	2003	Promedmail
	Banjar Yeh Sumbul	-8.212	114.966	2008	Promedmail
	Barat	-8.584	116.101	2003	Promedmail
	Bekasi	-6.233	107.000	2002	Promedmail
	Bengkalis Regency	1.466	102.251	2008	Promedmail
	Bireuen	5.205	96.702	2001	Promedmail
	Bogor city	-6.590	106.794	2002	Promedmail
	Bolaang	0.856	124.148	2003	Promedmail
	Boyolali	-7.517	110.594	2003	Promedmail
	Brebes	-6.873	109.041	2007	Promedmail
	Brebes	-6.873	109.041	2007	Promedmail
	Cirebon	-6.720	108.551	2003	Promedmail
	Curungrejo	-8.090	112.611	2007	Promedmail
	Depok	-6.390	106.830	2012	Promedmail
	Jakarta	6.212	106.845	2008	Promedmail
	Jepara	-8.581	116.114	2003	Promedmail
	Kal Jaya village	-6.221	107.027	2002	Laras_2005
	Keagungan	-6.152	106.819	2004	Promedmail
	Kebon Pedes	-6.560	106.783	2001	Laras_2005
	Kebupaten Kebumen	-7.728	109.429	2008	Promedmail
	Kedung Badak	-6.539	106.304	2001	Laras_2005
	Kemranjen	-7.592	109.272	2009	Promedmail
	Kepanjen	-8.132	112.569	2007	Promedmail
	Klaten	-7.704	110.603	2002	Promedmail
	Kudus	-7.563	110.824	2003	Promedmail
	Loji	-6.578	106.771	2007	Promedmail
	Madiuan	-7.630	111.514	2009	Promedmail
	Magetan	-7.655	111.330	2004	Promedmail
	Makmur	5.106	96.809	2008	Promedmail
	Mesuji	-5.436	105.286	2010	Promedmail
	Padang	-0.950	100.374	2007	Promedmail
	Pakoan	-0.299	100.379	2011	Promedmail
	Pangke	-1.167	111.997	2008	Promedmail
	Pasuruan	-7.645	112.903	2003	Promedmail
	Pauh	-0.920	100.465	2008	Promedmail
	Pekalongan	-6.893	109.671	2007	Promedmail
	Pekalongan	-6.893	109.671	2007	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	Pesawahan	-7.521	109.164	2008	Promedmail
	Purbalingga	-7.390	109.361	2004	Promedmail
	Purworejo	-7.713	110.009	2002	Promedmail
	Riau	0.294	101.707	2009	Promedmail
	Somagede	-7.524	109.329	2009	Promedmail
	Sragen	-7.428	111.018	2004	Promedmail
	Sukoharjo	-7.681	110.841	2008	Promedmail
	Sumpiuh	-7.613	109.360	2009	Promedmail
	Surabaya	-7.289	112.735	2012	Mulyatno_2012
	Tanggerang	-6.178	106.632	2003	Promedmail
	Tegal	-6.875	109.135	2002	Promedmail
	Tegal	-6.871	109.137	2004	Promedmail
	Trincomalee	8.573	81.238	2007	Promedmail
	Tulungagung	-8.073	111.907	2007	Promedmail
	Yogyakarta	-7.797	110.369	2004	Porter_2004
	Yogyakarta	-7.797	110.369	1999	Promedmail
Malaysia	Bagan Panchor	4.526	100.565	2006	AbuBakar_EID_2007
	Betong	1.420	111.596	2009	Promedmail
	Ipoh	4.611	101.113	2006	Pulmanausahakul_2011
	Kampung Baru	3.161	101.707	2008	Promedmail
	Sungkap Para Kampung Ulu Choh	1.521	103.545	2008	Promedmail
	Kedah	5.883	100.530	2008	Promedmail
	Kelantan	5.115	101.889	2009	Promedmail
	Kuala Lumpur	3.134	101.687	2007	Promedmail
	Kuala Muda	5.715	100.533	2008	Promedmail
	Kuching	1.531	110.344	2009	Promedmail
	Melaka	2.210	102.257	NA	Promedmail
	Panchor	2.162	102.724	2006	Kumarasamy_2006
	Pangkor island	4.228	100.558	2012	Promedmail
	Port Klang	3.003	101.413	1998	AbuBakar_EID_2007
	Selangor	3.509	101.525	2009	Promedmail
	Sibu	2.310	111.840	2009	Promedmail
Maledives	Airport	4.114	73.529	NA	Yoosuf 2009
	Malé	4.174	73.509	NA	Yoosuf 2009
Micronesia	Yap state	9.533	138.117	NA	Promedmail
Myanmar	Ayeyarwady	17.034	95.227	2010	Promedmail
	Sittwe	20.146	92.893	2010	Promedmail
	Yangon	16.800	96.150	2010	Promedmail
New Caledonia	Nouméa	-22.270	166.460	2011	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
Papua New Guinea	Lihir Island	-3.120	152.604	NA	Promedmail
	Vanimo hospital	-2.667	141.283	NA	Promedmail
Philippines	Albay	13.178	123.528	2012	Promedmail
	Cagayan Valley	16.975	121.811	2012	Promedmail
	Calabarzon	14.101	121.079	2012	Promedmail
	Caraga	8.802	125.741	2012	Promedmail
	Davao	7.191	125.455	2012	Promedmail
	Ilocos	16.083	120.620	2012	Promedmail
	Metro Manila	14.562	121.034	2012	Promedmail
	Northern Mindanao	8.020	124.686	2012	Promedmail
	Western Visayas	11.005	122.537	2012	Promedmail
Singapore	Bah Soon Pah Road	1.409	103.817	2008	Ng_2009
	Kranji	1.423	103.762	2008	Ng_2009
	Little India	1.307	103.849	2008	Ng_2009
	Mandai	1.392	103.759	2008	Ng_2009
	Queen Street	1.298	103.851	2008	Ng_2009
	Sungei	1.417	103.751	2008	Ng_2009
	Teachers Estate	1.383	103.829	2008	Ng_2009
Sri Lanka	Batticaloa	7.718	81.700	2006	Promedmail
	Colombo	6.926	79.867	2006	Promedmail
	Deraniyagala	6.928	80.339	2008	Promedmail
	Jaffna	9.668	80.006	2006	Promedmail
	Kalmunai	9.600	80.058	2006	Promedmail
	Kuruwita-Erathna	6.832	80.422	2008	Promedmail
	Mannar	8.982	79.904	2006	Promedmail
	Puttalam	8.036	79.839	2006	Promedmail
	Ratnapura	6.693	80.387	2008	Promedmail
Thailand	Ao Luk	8.385	98.762	NA	Promedmail
	Bacho	6.546	101.649	NA	Promedmail
	Ban Na Doem	8.901	99.280	NA	Promedmail
	Ban Na San	8.806	99.401	NA	Promedmail
	Ban Ta Khun	9.106	98.675	NA	Promedmail
	Bang Kaeo	7.416	100.173	NA	Promedmail
	Bang Khan	8.012	99.485	NA	Promedmail
	Bang Klam	7.064	100.407	NA	Promedmail
	Bannang Star	6.256	101.279	NA	Promedmail
	Batong	5.864	101.229	NA	Promedmail
	Chaiburi	8.439	99.071	NA	Promedmail
	Chaiya	9.492	98.994	NA	Promedmail
	Chalermphrakiet	8.185	100.031	NA	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	Chana	6.892	100.699	NA	Promedmail
	Cha-uat	7.959	99.985	NA	Promedmail
	Chawang	8.477	99.528	NA	Promedmail
	Chian Yai	8.121	100.153	NA	Promedmail
	Cho-I-rong	6.227	101.844	NA	Promedmail
	Chulaphon	8.077	99.857	NA	Promedmail
	Don Sak	9.201	99.688	NA	Promedmail
	Hat Yai	6.966	100.429	NA	Promedmail
	Hua Sai	8.012	100.245	NA	Promedmail
	Huai Yot	7.790	99.605	NA	Promedmail
	Ja-Nae	6.047	101.617	NA	Promedmail
	K. Chang Klang	8.355	99.627	NA	Promedmail
	K. Hat Samran	7.238	99.588	NA	Promedmail
	K. Krong Pi Nung	6.400	101.255	NA	Promedmail
	K. Ma Nang	7.017	99.943	NA	Promedmail
	K. Nophi Tam	8.756	99.674	NA	Promedmail
	K. Sri Nakarin	7.564	99.903	NA	Promedmail
	K. Suk Samran	9.418	98.482	NA	Promedmail
	K. Wipawadi	9.229	98.874	NA	Promedmail
	Ka Bang	6.369	100.978	NA	Promedmail
	Ka Pho	6.610	101.542	NA	Promedmail
	Kanchanadit	9.071	99.542	NA	Promedmail
	Kantrang	7.400	99.475	NA	Promedmail
	Kapoe	9.532	98.620	NA	Promedmail
	Kapong	8.740	98.466	NA	Promedmail
	Kathu	7.918	98.313	NA	Promedmail
	Khanom	9.187	99.806	NA	Promedmail
	Khao Chaison	7.454	100.096	NA	Promedmail
	Khao Phanom	8.270	99.114	NA	Promedmail
	Khian Sa	8.738	99.112	NA	Promedmail
	Khiri Ratthanikhom	9.006	98.941	NA	Promedmail
	Khlong Hoi Kong	6.863	100.347	NA	Promedmail
	Khlong Thom	7.916	99.198	NA	Promedmail
	Khok Pho	6.703	101.124	NA	Promedmail
	Khuan Don	6.768	100.123	NA	Promedmail
	Khuan Ka Long	6.911	100.049	NA	Promedmail
	Khuan Khanun	7.757	100.043	NA	Promedmail
	Khuan Niang	7.180	100.374	NA	Promedmail
	Khura Buri	9.148	98.402	NA	Promedmail
	Ko Lanta	7.683	99.077	NA	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	Ko Phangan	9.793	99.999	NA	Promedmail
	Ko Samui	9.505	99.994	NA	Promedmail
	Ko Yao	8.052	98.584	NA	Promedmail
	Kong Ra	7.421	99.949	NA	Promedmail
	Kra Buri	10.461	98.849	NA	Promedmail
	Krasae Sinthu	7.613	100.328	NA	Promedmail
	Lam Thap	8.047	99.325	NA	Promedmail
	Lamae	9.756	99.033	NA	Promedmail
	Lan Saka	8.377	99.778	NA	Promedmail
	Lang Suan	9.938	99.048	NA	Promedmail
	Langu	6.910	99.792	NA	Promedmail
	La-Un	10.080	98.782	NA	Promedmail
	Mae Lan	6.670	101.231	NA	Promedmail
	Mai Kaen	6.616	101.675	NA	Promedmail
	Mayo	6.708	101.403	NA	Promedmail
	Muang Chumphon	10.461	99.103	NA	Promedmail
	Muang Krabi	8.147	98.864	NA	Promedmail
	Muang Nakhon Si Thammarat	8.443	99.971	NA	Promedmail
	Muang Narathiwat	6.394	101.813	NA	Promedmail
	Muang Pattani	6.853	101.265	NA	Promedmail
	Muang Phangnga	8.493	98.505	NA	Promedmail
	Muang Phatthalung	7.600	100.069	NA	Promedmail
	Muang Phuket	7.849	98.361	NA	Promedmail
	Muang Ranong	9.861	98.609	NA	Promedmail
	Muang Satun	6.624	99.916	NA	Promedmail
	Muang Songkhla	7.110	100.611	NA	Promedmail
	Muang Surat Thani	9.098	99.325	NA	Promedmail
	Muang Trang	7.609	99.621	NA	Promedmail
	Muang Yala	6.554	101.240	NA	Promedmail
	n.a	7.529	100.262	NA	Promedmail
	n.a	7.614	100.293	NA	Promedmail
	Na Bon	8.274	99.556	NA	Promedmail
	Na Mom	6.955	100.577	NA	Promedmail
	Na Thawi	6.639	100.681	NA	Promedmail
	Na Yong	7.560	99.746	NA	Promedmail
	Nong Chik	6.801	101.171	NA	Promedmail
	Nua Khlong	8.020	99.034	NA	Promedmail
	Pa Bon	7.226	100.133	NA	Promedmail
	Pa Payom	7.828	99.868	NA	Promedmail
	Pak Phanang	8.312	100.163	NA	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	Pak Phayun	7.331	100.308	NA	Promedmail
	Palian	7.231	99.791	NA	Promedmail
	Panare	6.807	101.516	NA	Promedmail
	Pathiu	10.811	99.339	NA	Promedmail
	Phanom	8.803	98.701	NA	Promedmail
	Phato	9.812	98.800	NA	Promedmail
	Phi Pun	8.600	99.592	NA	Promedmail
	Phra Phrom	8.322	99.934	NA	Promedmail
	Phrommakhiri	8.543	99.792	NA	Promedmail
	Phunphin	9.026	99.142	NA	Promedmail
	Plai Phraya	8.539	98.833	NA	Promedmail
	Prasaeng	8.552	99.105	NA	Promedmail
	Raman	6.491	101.434	NA	Promedmail
	Rangae	6.256	101.705	NA	Promedmail
	Ranot	7.814	100.282	NA	Promedmail
	Rasada	7.937	99.666	NA	Promedmail
	Rattaphum	7.075	100.196	NA	Promedmail
	Ron Phi Pun	8.192	99.893	NA	Promedmail
	Ruso	6.375	101.514	NA	Promedmail
	Saba Yoi	6.531	100.913	NA	Promedmail
	Sadao	6.672	100.424	NA	Promedmail
	Sai Buri	6.699	101.579	NA	Promedmail
	Sathing Phra	7.480	100.423	NA	Promedmail
	Sawi	10.240	99.018	NA	Promedmail
	Si Banphot	7.697	99.862	NA	Promedmail
	Si Sakhon	6.194	101.513	NA	Promedmail
	Sichon	8.946	99.810	NA	Promedmail
	Sikao	7.596	99.364	NA	Promedmail
	Singha Nakhon	7.285	100.488	NA	Promedmail
	Sukhirin	5.915	101.738	NA	Promedmail
	Su-ngai Ko Lok	6.075	101.992	NA	Promedmail
	Sungai Padi	6.105	101.894	NA	Promedmail
	Tak Bai	6.240	102.000	NA	Promedmail
	Takua Pa	8.837	98.326	NA	Promedmail
	Takua Thung	8.287	98.393	NA	Promedmail
	Tamot	7.282	100.033	NA	Promedmail
	Tha Chana	9.606	99.051	NA	Promedmail
	Tha Chang	9.343	98.948	NA	Promedmail
	Tha Phae	6.788	99.922	NA	Promedmail
	Tha Sae	10.770	99.093	NA	Promedmail

Country/Island	Location/District	Longitude	Latitude	First Year	Source ID
	Tha Sala	8.697	99.877	NA	Promedmail
	Thai Muang	8.496	98.309	NA	Promedmail
	Thalang	8.053	98.345	NA	Promedmail
	Tham Phannara	8.459	99.375	NA	Promedmail
	Than To	6.081	101.256	NA	Promedmail
	Thap Put	8.536	98.631	NA	Promedmail
	Thepha	6.790	100.912	NA	Promedmail
	Thung Song	8.117	99.661	NA	Promedmail
	Thung Tako	10.091	99.050	NA	Promedmail
	Thung Wa	7.046	99.769	NA	Promedmail
	Thung Yai	8.289	99.372	NA	Promedmail
	Thung Yang Daeng	6.640	101.450	NA	Promedmail
	Waeng	5.901	101.868	NA	Promedmail
	Wang Wiset	7.762	99.409	NA	Promedmail
	Wiang Sa	8.601	99.358	NA	Promedmail
	Yaha	6.404	101.117	NA	Promedmail
	Yan Ta Khao	7.423	99.739	NA	Promedmail
	Yarang	6.697	101.313	NA	Promedmail
	Yaring	6.835	101.390	NA	Promedmail
	Yi-ngo	6.417	101.700	NA	Promedmail
Vietnam	Hanoi	21.033	105.850	2009	Promedmail
Yemen	Al Khoka	13.827	41.307	2011	Zayed_2012
	Al Muneera	15.321	42.932	2011	Zayed_2012
	Taiz	13.570	44.015	2012	Promedmail
Europe					
France	Fréjus	43.433	6.735	2011	Grandadam_2011
	Montpellier	3.875	43.613	2014	Delisle_2015
Italy	Bologna	44.494	11.341	2007	Seyler_2008
	Castiglione di Cervia	44.266	12.264	2007	Bonilauri_EID_2008
	Castiglione di Ra-venna	44.261	12.256	2007	Bonilauri_EID_2008
	Cervia	44.263	12.346	2007	Angelini_2007
	Cervia	44.239	12.324	2007	Promedmail
	Cesena	44.140	12.246	2007	Angelini_2007
	Cesena	44.140	12.246	2007	Promedmail
	Ravenna	44.418	12.203	2007	Angelini_2007
	Ravenna	44.418	12.204	2007	Promedmail
	Rimini	44.056	12.565	2007	Angelini_2007
	Rimini	44.057	12.565	2007	Promedmail
Pacific Ocean					
French Polynesia	Tahiti	-17.617	-149.450	2014	RNZ; Aubrey_2015

Supplementary Table S2: References for Supplementary Table S1. All websites were last accessed in January 2017.

ID	Publication Year	Authors	Title	Publication details	DOI/URL
AbuBakar_EID_2007	2007	Sazaly AbuBakar, I-Ching Sam, Pooi-Fong Wong, NorAziyah MatRahim, Poh-Sim Hooi, and Nuruliza Roslan	Reemergence of Endemic Chikungunya, Malaysia	Emerging Infectious Diseases Vol. 13, No. 1, pp 147-149	https://wwwnc.cdc.gov/eid/article/13/1/pdfs/06-0617.pdf
Angelini_2007	2007	Angelini R, Finarelli AC, Angelini P, Po C, Petropulacos K, Macini P, Fiorentini C, Fortuna C, Venturi G, Romi R, Majori G, Nicoletti L, Rezza G, Cassone A.	An outbreak of chikungunya fever in the province of Ravenna, Italy	Eurosurveillance, Volume 12, Issue 36, 06 September 2007	http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=3260
Arias_2014	2014	L. Arias	Costa Rica registers 2 new cases of chikungunya virus, bringing total number to 47	The Tico Times, Dec. 14, 2014	http://www.ticotimes.net/2014/12/14/costa-rica-registers-2-new-cases-of-chikungunya-virus-bringing-total-number-to-47
Aubrey_2015	2015	Maite Aubry, Anita Teissier, Claudine Roche, Vaea Richard, Aurore Shan Yan, Karen Zisou, Eline Rouault, Véronique Maria, Stéphane Lastère, Van-Mai Cao-Lormeau, and Didier Musso	Chikungunya Outbreak, French Polynesia, 2014	Emerg Infect Dis. 2015 Apr; 21(4): 724–726.	10.3201/eid2104.141741

ID	Publication Year	Authors	Title	Publication details	DOI/URL
Beesoon_EID_2008	2008	Sanjay Beesoon, Ellen Funkhouser, Navaratnam Kotea, Andrew Spielman,Rebecca M. Robich	Chikungunya Fever, Mauritius, 2006	Emerging Infectious Diseases Vol. 14, No. 2, pp. 337-338	https://wwwnc.cdc.gov/eid/article/14/2/pdfs/07-1024.pdf
Bemparana_2014	2014	Staff Editor	Em menos de um mês, casos de febre "prima da dengue" crescem 65%	Bemparaná Brazil, 02-12-2014	http://www.bemparana.com.br/noticia/361388/em-menos-de-um-mes-casos-de-febre-prima-da-dengue-crescem-65
Bonham_2014	2014	Samantha Bonham	One new local chikungunya case confirmed	Cayman Compass, Nov. 6. 2014	https://www.caymancompass.com/2014/11/06/One-new-local-chikungunya-case-confirmed/
Bonilauri_EID_2008	2008	Paolo Bonilauri, Romeo Bellini, Mattia Calzolari, Raffaella Angelini, Luciano Venturi, Francesca Fallacara, Paolo Cordioli, Paola Angelini, Claudio Venturelli, Giuseppe Merialdi, Michele Dottori	Chikungunya Virus in Aedes albopictus, Italy	Emerging Infectious Diseases Vol. 14, No. 5, pp. 852-854	https://wwwnc.cdc.gov/eid/article/14/5/pdfs/07-1144.pdf
Caracol	2014	Staff Editor	Alerta máxima en Cúcuta por virus del chikungunya	Caracol Radio, Dec. 12, 2014	http://caracol.com.co/radio/2014/12/12/regional/1418373720_548521.html

ID	Publication Year	Authors	Title	Publication details	DOI/URL
CARPHA	2013-2014	Caribbean Public Health Agency	Countries/territories with Reported Cases of Chikungunya	weekly updates available from CARPHA website	http://carpha.org/What-We-Do/Public-Health-Activities/Chikungunya
CDC	2013-2014	Centers for Disease Control and Prevention	Chikungunya in the Caribbean	Travel notice	https://wwwnc.cdc.gov/travel/notices/watch/chikungunya-caribbean
Collao_2010	2010	Ximena Collao, Ana I. Negredo, Jorge Cano, Antonio Tenorio, Fernando de Ory, Agustin Benito, Mar Masia and María-Paz Sánchez-Seco	Different Lineages of Chikungunya Virus in Equatorial Guinea in 2002 and 2006	Am J Trop Med Hyg March 2010 vol. 82 no. 3 505-507	10.4269/ajtmh.2010.09-0435
D`Ortenzio_2011	2011	D'Ortenzio E, Grandadam M, Balleydier E, Jaffar-Bandjee M, Michault A, Brottet E, et al.	A226V Strains of Chikungunya Virus, Réunion Island, 2010	Emerg Infect Dis. 2011;17(2):309-311	10.3201/eid1702.101056
Dantas_2014	2014	Marcos Dantas	Manaus entra em estado de alerta contra dengue, aponta LIRAa	Globo.com, 06-12-2014	http://g1.globo.com/am/amazonas/noticia/2014/12/manaus-entra-em-estado-de-alerta-para-da-dengue-aponta-liraa.html
Debate	2014	Bonita Haro	Chikungunya, de la nada le dio	Debate, Dec. 23, 2014	http://www.debate.com.mx/losmochis/Chikungunya-de-la-nada-le-dio-20141223-0035.html

ID	Publication Year	Authors	Title	Publication details	DOI/URL
Delisle_2015	2015	Delisle E, Rousseau C, Broche B, Leparc-Goffart I, L'Ambert G, Cochet A, Prat C, Foulongne V, Ferre JB, Catelinois O, Flusin O, Tchernonog E, Moussion IE, Wiegandt A, Septfons A, Mendy A, Moyano MB, Laporte L, Maurel J, Jourdain F, Reynes J, Paty MC, Golliot F.	Chikungunya outbreak in Montpellier, France, September to October 2014	Euro Surveill. 2015 Apr 30;20(17). pii: 21108.	http://www.eurosurveillance.org/images/dynamic/EE/V20N17/art21108.pdf
Demanou_2010	2010	Maurice Demanou, Christophe Antonio-Nkondjio, Emmanuel Ngapana, Dominique Rousset, Christophe Paupy, Jean-Claude Manuguerra and Hervé Zeller	Chikungunya outbreak in a rural area of Western Cameroon in 2006: A retrospective serological and entomological survey	BMC Research Notes 2010 3:128	10.1186/1756-0500-3-128
Diallo_1999	1999	M Diallo, J Thonnon, M Traore-Lamizana and D Fontenille	Vectors of Chikungunya virus in Senegal: current data and transmission cycles.	Am J Trop Med Hyg February 1999 vol. 60 no. 2 281-286	
Diallo_2012	2012	Diawo Diallo, Amadou A. Sall, Michaela Buenemann, Rubing Chen, Oumar Faye,	Landscape Ecology of Sylvatic Chikungunya Virus and Mosquito Vectors in Southeastern Senegal	PLoS Negl Trop Dis 6(6): e1649	10.1371/journal.pntd.0001649

ID	Publication Year	Authors	Title	Publication details	DOI/URL
		Cheikh T. Diagne, Ousmane Faye, Yamar Ba, Ibrahima Dia, Douglas Watts, Scott C. Weaver, Kathryn A. Hanley, Mawlouth Diallo			
El_Heraldo	2014	Staff Editor	Honduras: Dengue y chikungunya toman fuerza en Valle	El Heraldo, 10.11.2014	http://www.elheraldo.hn/regionales/766473-218/honduras-dengue-y-chikungunya-toman-fuerza-en-valle
El_Mundo	2014	Staff Editor	Confirman 12.929 casos de dengue y 126 de chikunguña en el país	El Mundo, Oct. 2, 2014	http://elmundo.sv/confirman-12-929-casos-de-dengue-y-126-de-chikunguna-en-el-pais/
El_Nacional	2014	Staff Editor	Parturientas pueden infectar con chikungunya a sus bebés - See more at: http://www.healthmap.org/ai.php?2825515&trto=en&trfr=en&pid24#sthash.Xn20W3rW.dpuf	El Nacional, Oct. 2, 2014	http://www.el-nacional.com/sociedad/Parturientas-pueden-infectar-chikungunya-bebes_0_493150835.html
El_Pais	2014	Staff Editor	Confirman primer caso autóctono del virus chikungunya en Cali	El País, Nov 10, 2014	http://www.elpais.com.co/elpais/valle/noticias/autoridades-salud-confirman-primer-caso-virus-chikungunya-cali

ID	Publication Year	Authors	Title	Publication details	DOI/URL
El_Pais_2	2014	Staff Editor	Confirman primeros cuatro casos autóctonos del virus del Chikungunya en el Valle	El País, Oct. 3, 2014	http://www.elpais.com.co/elpais/valle/noticias/confirman-primeros-dos-casos-virus-chikungunya-valle-cauca
El_Tiempo	2014	Staff Editor	Proliferación de virosis en Barranquilla agota varios medicamentos	El Tiempo dec. 16. 2014	http://www.eltiempo.com/colombia/barranquilla/virus-en-barranquilla/14983477
Gilblom_2014	2014	Kelly Gilblom	Chikungunya reaches US, starting in Florida	live mint Oct. 1, 2014	http://www.livemint.com/Politics/5FzHLrLS50WIvHBc490KkL/Chikungunya-reaches-US-starting-in-Florida.html
Globo_2014	2014	Staff Editor	Alto Tietê deve ficar em alerta para chikunguya e dengue, diz veterinário	Globo.com, 24-11-2014	http://g1.globo.com/sp/mogi-das-cruzes-suzano/noticia/2014/11/alto-tiete-deve-ficar-em-alerta-para-chikunguya-e-dengue-diz-veterinario.html
Grandadam_2011	2011	Marc Grandadam, Valérie Caro, Sébastien Plumet, Jean-Michel Thiberge, Yvan Souarès, Anna-Bella Failloux, Hugues J. Tolou, Michel Budelot, Didier Cosserat, Isabelle Leparc-Goffart, and Philippe Desprès	Chikungunya Virus, Southeastern France	Emerg Infect Dis. 2011;17(5):910-913	10.3201/eid1705.101873

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Herriman_2014	2014	Robert Herriman	Colombia chikungunya cases double, Puerto Rico cases increase 1500	Outbreak News Today, October 17, 2014	http://outbreaknewstoday.com/colombia-chikungunya-cases-double-puerto-rico-cases-increase-1500/
Herriman_2014_2	2014	Robert Herriman	Chikungunya cases up in the UK in 2014	Outbreak News Today, Nov. 30, 2014	http://outbreaknewstoday.com/chikungunya-cases-up-in-the-uk-in-2014/
Hertz_2012	2012	Julian T. Hertz, O. Michael Munishi, Eng Eong Ooi, Shiqin Howe, Wen Yan Lim, Angelia Chow, Anne B. Morrissey, John A. Bartlett, Jecinta J. Onyango, Venance P. Maro, Grace D. Kinabo, Wilbrod Saganda, Duane J. Gubler, John A. Crump	Chikungunya and Dengue Fever among Hospitalized Febrile Patients in Northern Tanzania	Am J Trop Med Hyg 2012 vol. 86 no. 1 171-177	10.4269/ajtmh.2012.11-0393
Ideal	2014	Staff Editor	¡Alarma!:... Confirma Coahuila caso de chikungunya (virus) - See more at: http://www.healthmap.org/ai.php?2992446&trto=en&trfr=es&pid491#sthash.XXMpXUqH.dpuf	Ideal Digital Nov. 26, 2014	http://www.ideal.es/gente-estilo/201411/26/alarma-confirma-coahuila-caso-chikunguya-virus-20141126174839.html

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Jamaica_Observer	2014	Staff Editor	St Vincent authorities investigating two suspected Chikungunya deaths	Jamaica Observer, Dec. 29, 2014	http://www.jamaicaobserver.com/latestnews/St-Vincent-authorities-investigating-two-suspected-Chikungunya-deaths
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La_Hora	2014	Staff Editor	El virus de la chikungunya ya está en el país	La Hora, Dec. 17, 2014	http://lahora.com.ec/index.php/noticias/show/1101762461/-1/El_pa%C3%ADs_ya_no_est%C3%A1_libre_del_virus_chikungunya._El_Ministerio_de_Salud_confirm%C3%B3_ayer_el_primer_caso_de_una_persona_contagiada_en_Montecristi,_Manab%C3%AD..html
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Liew_2012	2012	C Liew, CF Yung	First detection of chikungunya infection and transmission in Brunei Darussalam	Singapore Medical Journal 53(4):e66-8	
Maheshwary_2014	2014	Pooja Maheshwary	Colombia has seen a dramatic increase in the lethal Chikungunya virus, with around 20,000 cases of infection reported in the northern region of the country since September this year.	The Bogotá Post, Dec. 11, 2014	http://thebogotapost.com/2014/12/11/chikungunya-virus-surge/
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MdS	2014	Ministerio de Salud	Argentina aún no registra casos autóctonos de chikun-guña pero se estima que en el verano pueden presentarse	via twitter @msalnacion in 17 Dec 2014	https://twitter.com/msalnacion/statuses/545330175874183168
Mease_2011	2011	Luke E Mease, Rodney L Coldren, Lillian A Musila, Trish Prosser, Fredrick Ogolla, Victor O Ofula, Randal J Schoepp, Cindy A Rossi and Nicholas Adungo	Seroprevalence and distribution of arboviral infections among rural Kenyan adults: A cross-sectional stu	Virology Journal 2011 8:371	10.1186/1743-422X-8-371
Milenio	2014	Hermes Chavéz	Confirma en Chiapas primer caso de virus chikungunya en México	Milenio, Nov. 14, 2014	http://www.milenio.com/estados/chikungunya-virus-paciente_enfermo_de_chikungunya-mosquitos_0_409159462.html
MPPSalud	2014	Ministerio de Salud (Venezuela)	Disminuyen en 50% casos de #Chikungunya en #Zulia http://ht.ly/ECNKV #LeyesSocialistasParaLaPatria	via twitter @MPPSalud_Vzla, Nov. 20, 2014	https://twitter.com/MPPSalud_Vzla/status/535545857828212736
MPPSalud_2	2014	Ministerio de Salud (Venezuela)	Incidencias del virus #Chikungunya disminuyeron en un 60% en la #Guárico http://ht.ly/EWuJP	via twitter @MPPSalud_Vzla, Nov. 26, 2014	https://twitter.com/MPPSalud_Vzla/status/537727599879790593

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Nuevo_Diario	2014	Staff Editor	Nicaragua suma 131 casos de chikungunya	El Nuevo Diario, Oct. 31, 2014	http://www.elnuevodiario.com.ni/nacionales/333657-nicaragua-suma-131-casos-chikungunya/
PAHO	2013-2015	Pan American Health Organization	Countries/territories with autochthonous transmission or imported cases of Chikungunya in the americas	weekly reports available from PAHO website	http://www.paho.org/hq/index.php?option=com_topics&view=readall&cid=5927&Itemid=40931&lang=en
Porter_2004	2004	Porter Kevin R, Tan Ratna, Istary Yunry, Suharyono Wuryadi, Sutaryo, Widjaja Susana, Ma'Roef Chairin, Listiyaningsih Erlin, Kosasih Herman, Hueston Linda, McArdle James, Juffrie Mohammad	A serological study of Chikungunya virus transmission in Yogyakarta, Indonesia: evidence for the first outbreak since 1982.	The Southeast Asian Journal of Tropical Medicine and Public Health. 2004 Jun; 35(2): 408-15	http://imsear.hellis.org/handle/123456789/34197

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Presente	2014	Isidro Jiménez	Detectan a centroameri-cano con virus de Chikungunya en Tabasco	Presente, Dec. 2, 2014	http://www.diariopresente.com.mx/section/lcapital/122195/detectan-centroamericano-virus-chikungunya-tabasco-/
Preyrefitte_2007	2007	Peyrefitte CN, Rousset D, Pastorino B, Pouillot R, Bessaud M, Tock F, et al.	Chikungunya Virus, Cameroon, 2006	Emerg Infect Dis. 2007;13(5):768	10.3201/eid1305.061500
Primera_Hora	2014	Staff Editor	Salud confirma primer caso del virus de Chikungunya en la Isla	primerahora, May 5, 2014	http://www.primerahora.com/noticias/puerto-rico/nota/saludconfirmaprimercasodelvirusdechikungunyaenlaisla-1012533/
Promedmail	2006-2015	International Society for Infectious Diseases Staff Editors	ProMED-mail	Chikungunya updates	http://www.promedmail.org/
Pulmanausahakul_2011	2011	Rojjanaporn Pulmanausahakul, Sittiruk Roytrakul, Prasert Auewarakul, Duncan R. Smith	Chikungunya in Southeast Asia: understanding the emergence and finding solutions	International Journal of Infectious Diseases , Volume 15 , Issue 10 , e671 - e676	10.1016/j.ijid.2011.06.002
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RNZ	2014	Staff Editor	15 cases of Chikungunya found in French Polynesia	RNZ Oct. 13, 2014	http://www.radionz.co.nz/international/pacific-news/256684/15-cases-of-chikungunya-found-in-french-polynesia
Rodrigues_2014	2014	Yago Rodrigues	Com 7 mil casos de dengue registrados, município inicia campanha de prevenção	Jornal Opção 02-12-2014	http://www.jornalopcao.com.br/colunas-e-blogs/anapolis/com-7-mil-casos-de-dengue-registrados-municipio-inicia-campanha-de-prevencao-22717/
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St_Croix_2	2014	Susan Ellis	St. Croix at Peak of Chikungunya Outbreak; St. Thomas Cases Decline	St. Croix Source, Dec. 2, 2014	http://stcroixsource.com/content/news/local-news/2014/12/02/st-croix-peak-chikungunya-outbreak-st-thomas-cases-decline
Stabroek	2014	Staff Editor	Chikungunya rising rapidly in Barbados	Stabroek News October 3, 2014	http://www.stabroeknews.com/2014/news/regional/10/03/chikungunya-rising-rapidly-barbados/
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TCT	2014	Staff Editor	1st indigenous case of chikungunya in Costa Rica reported	The Costa Rican Times, Nov. 19, 2014	http://www.costaricantimes.com/1st-indigenous-case-of-chikungunya-in-costa-rica-reported/32452
Telemetro	2014	Viola Guevara Gallimore	Autoridades hacen llamado por casos de hantavirus, dengue, chikungunya y leptospirosis	Telemetro, Oct. 1, 2014	http://www.telemetro.com/nacionales/Autoridades-llamado-hantavirus-chikungunya-leptospirosis_0_739426661.html
The_Gleaner	2014	Shanique Samuels	Vere remembers teachers, student who died from chikungunya complications	The Gleaner, Oct. 30, 2014	http://jamaica-gleaner.com/article/lead-stories/20141030/vere-remembers-teachers-student-who-died-chikungunya-complications
Yoosuf 2009	2009	Abdul Azeez Yoosuf, Ibrahim Shiham, Ahmed Jamsheed Mohamed, Geela Ali, J.M. Luna, R. Pandav, G.N. Gongal, Ananda Nisaluk, Richard G. Jarman, Robert V. Gibbons	First report of chikungunya from the Maldives	Transactions of the Royal Society of Tropical Medicine and Hygiene, Volume 103, Issue 2, February 2009, Pages 192-196	10.1016/j.trstmh.2008.09.006

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Manuscript 2: Areas with high hazard potential for autochthonous transmission of *Aedes albopictus*-associated arboviruses in Germany

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Abstract

The intensity and extent of transmission of arboviruses such as dengue, chikungunya, and Zika virus have increased markedly over the last decades. Autochthonous transmission of dengue and chikungunya by *Aedes albopictus* has been recorded in Southern Europe where the invasive mosquito was already established and viraemic travelers had imported the virus. *Ae. albopictus* populations are spreading northward into Germany. Here, we model the current and future climatically suitable regions for *Ae. albopictus* establishment in Germany, using climate data of spatially high resolution. To highlight areas where vectors and viraemic travellers are most likely to come into contact, reported dengue and chikungunya incidences are integrated at the county level. German cities with the highest likelihood of autochthonous transmission of *Aedes albopictus*-borne arboviruses are currently located in the

western parts of the country: Freiburg im Breisgau, Speyer, and Karlsruhe, affecting about 0.5 million people. In addition, 8.8 million people live in regions considered to show elevated hazard potential assuming further spread of the mosquito: Baden-Württemberg (Upper Rhine, Lake Constance regions), southern parts of Hesse, and North Rhine-Westphalia (Lower Rhine). Overall, a more targeted and thus cost-efficient implementation of vector control measures and health surveillance will be supported by the detailed maps provided here.

Introduction

The dengue, chikungunya, and Zika fevers are emerging viral diseases of significant global public health concern [1–5]. Transmission of these diseases requires the presence of competent vectors and viraemic humans or primates. In non-endemic areas, infected travellers returning from endemic countries can start the chain of infection if vectors are present and environmental conditions are appropriate.

The invasive vector mosquito *Aedes albopictus*, closely associated with human settlements [6, 7], is now established in large areas of Southern Europe [8]. The low-temperature-tolerant mosquito [9] is a known or suspected vector for more than 20 arboviruses [10, 11] for which often neither vaccinations nor specific antiviral treatments are available [7]. Autochthonous transmissions of dengue (DENV) and chikungunya virus (CHIKV) by *Ae. albopictus* were recently recorded in Southern Europe for the first time (Table 1).

The hazard potential of autochthonous transmission now applies to Germany, with at least four factors coming together. Firstly, *Ae. albopictus* continues to spread further north and into Germany. While the species has been present in the Mediterranean region since 1979 [8], it took years for it to move towards more temperate climates. First found in 2007 in southwestern parts of Germany in the state of Baden-Württemberg [21], larvae were discovered in 2011 at the Czech–Austrian border [22] and in Austria in the Inn valley in 2012

[23]. In 2014, *Ae. albopictus* populations were found in the Upper Rhine Valley in south-western Germany near Freiburg, suggesting locally occurring reproduction of the mosquito [24]. Further single-specimen findings on parking lots near motorways confirm the repeated introduction of this species by the long-distance transport from Southern Europe over the German–Austrian and German–Swiss borders [25, 26]. A sharp increase in the number and size of detected *Ae. albopictus* populations along motorways was recorded in the summers of 2015 and 2016 in the German states of Baden-Württemberg, Hesse, and Rhineland Palatinate [27]. With the recent discoveries of overwintering populations in Freiburg, Heidelberg, and Jena [28, 29], the species must be considered to be established in Germany.

Table 1. European cases of *Aedes albopictus*-associated virus transmission. CHIKV: chikungunya virus; DENV: dengue virus.

Virus	Year	Region	Number of Cases	Reference
CHIKV	2007	Ravenna region, Italy	ca. 200	(Angelini et al., 2007)
	2010	Var, France	2	(Grandadam et al., 2011a)
	2014	Montpellier, France	14	(Delisle et al., 2015a)
	2017	Var, France	9	(Calba et al., 2017a)
	2017	Rome and Anzio, Italy	ca. 400	(European Centre for Disease Prevention and Control, 2017)
DENV	2010	Nice, France	2	(La Ruche et al., 2010a)
	2010	Croatia	1	(Gjenero-Margan et al., 2011a)
	2013	Bouches-du-Rhône, France	1	(Marchand et al., 2013a)
	2015	Nîmes, France	7	(Succo et al., 2016a)

Secondly, German infrastructure for mosquito surveillance, monitoring, and control is severely under-developed in large portions of the country. While the Kommunale Aktionsgemeinschaft zur Bekämpfung der Schnakenplage (KABS,

the German Mosquito Control Association) has been performing mosquito control along the Upper Rhine since 1976, similar organizations do not exist in other parts of the country (see Figure S2). Larger-scale surveillance and monitoring projects like the recent CuliMo (a country-wide monitoring project coordinated by the Friedrich-Loeffler-Institute running since 2015) only receive funding for limited amounts of time.

Thirdly, the global intensity and extent of transmission of arboviruses such as DENV, CHIKV, and Zika virus (ZIKV) has increased markedly [2, 30, 31], and global travel is rapidly expanding [32]. Travel between Germany and tropical areas where these viruses are endemic continues to increase (the number of passengers arriving in Germany from tropical countries increased by 23% from 2011 to 2016 [33]). This trend increases the probability and frequency of the presence of viraemic returnees in Germany [34].

Fourthly, at least in some areas of Germany, summer conditions may already be suitable for vector-borne transmission of DENV and CHIKV. For ZIKV, the local transmission potential of *Ae. albopictus* is less clear under current German conditions, but may increase with rising temperatures [11]. Most outlooks on the effects of climate change in Germany signal increasing temperatures in decades to come.

In order to implement appropriate infection prevention measures and to be able to quickly react to developing situations, areas where such autochthonous transmissions may occur need to be identified. Here, we model the current and future climatically suitable regions for *Ae. albopictus* establishment in Germany on the basis of current data on the European occurrence of *Ae. albopictus*, using climate data of spatially high resolution. Reported DENV and CHIKV incidences at the county level are then combined with climate suitability for vector establishment to highlight areas where vector and viraemic travellers are most likely to come into contact. This identification of current areas showing a hazard potential supports public administrations to effectively plan vector control

measures and health surveillance to avoid autochthonous transmission of *Aedes*-associated arboviruses in Germany.

Materials and methods

Estimation of the potential spatial distribution of vector species is an essential step for assessing areas potentially affected by a vector-borne disease [35]. Here, we used European occurrence records of *Ae. albopictus* to calibrate our models, in order to project the environmental niche of the invasive species within the European environment as accurately as possible. Records on the presence of *Ae. albopictus* at the European scale were taken from Kraemer et al. [36]. Additionally, scientific articles and reports of mosquito surveillance published between 1979 (the year *Ae. albopictus* was first discovered in Europe [37]) and January 2018 were scanned for additional records of infestations. Records where no long-term establishment of populations (specimens found over at least 2 years or overwintering otherwise suggested) could be inferred were discarded, resulting in a total of 1336 observed records (Figure 1).

Bioclimatic variables with a spatial resolution of 2.5 arcmin (≈ 5 km) were taken from the global climatic dataset *Worldclim*, comprising 19 variables [39]. Out of these 19 variables a pre-selection of variables based on expert knowledge on the ecology of *Ae. albopictus* was carried out. Here we mainly focused on upper and lower environmental limits (maximum and minimum temperature) as well as temperature and precipitation periods (e.g., mean temperature of warmest quarter, precipitation of driest quarter). With the remaining eleven variables we conducted hierarchical partitioning (R package "hier.part", version 1.0-4) [40] to assess the influence of the single variables and to further reduce the set of variables to the most important ones. Six variables remained after the hierarchical partitioning and were used for modelling: annual mean temperature, minimum temperature of the coldest month, mean temperature of the warmest quarter, mean temperature of the coldest quarter, precipitation of the driest month, and precipitation of the driest quarter.

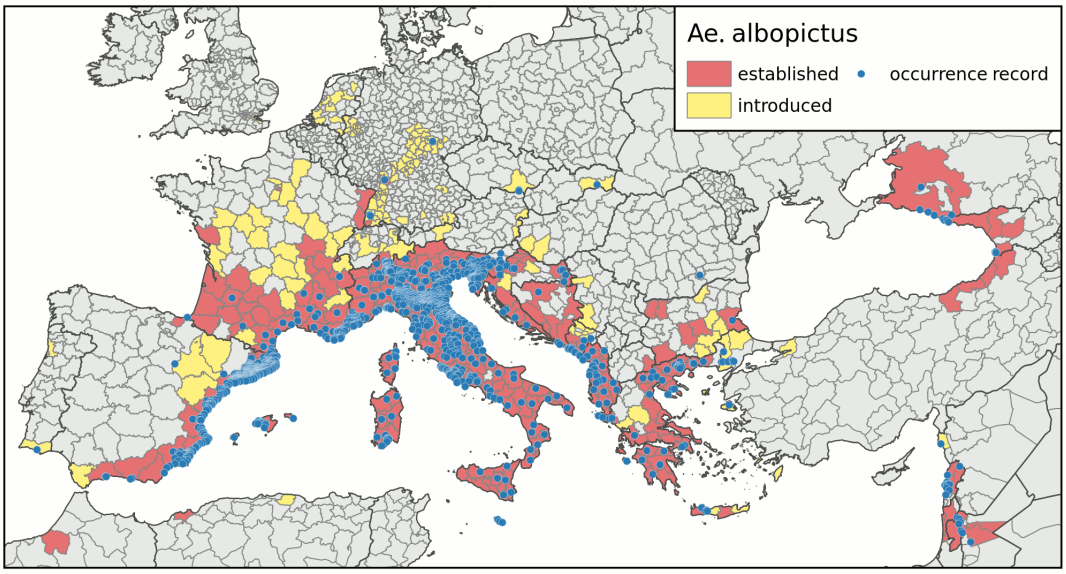

Figure 1. European distribution of *Aedes albopictus* as of January 2018. Blue dots: high-precision occurrence records derived from the literature and used for modelling (n = 1336). Red and yellow areas: administrative units with established populations and introduced specimens, respectively, according to the European Centre for Disease Prevention and Control [38]. Areas are level-3 administrational units following the nomenclature des unités territoriales statistiques (nomenclature of territorial units for statistics, NUTS) as used by the European Union. For Germany, this corresponds to the district (Kreis) level.

The model of the current and future climatic suitability of *Ae. albopictus* was based on four different model algorithms (generalized boosted model – GBM, generalized additive model – GAM, maximum entropy – Maxent and random forest – RF). All model runs were performed using the biomod2 package (version 3.3-7) [41] implemented in R (version 3.4.2) [42]. The current European distribution was best depicted by the GBM (AUC: 0.98, TSS: 0.86). Subsequently, only the GBM was used to project the potential future distribution. We used observed occurrences and randomly generated pseudo-absences within Europe where the number of pseudo-absences corresponds to the number of occurrences in Europe (N = 1336), which is the most suitable method for GBMs [43]. A database with confirmed absence points of *Ae. albopictus* in Europe was not available; only administrative units with absences (e.g. distribution map of *Ae. albopictus* from ECDC [38]). However, this

information is not sufficient for modelling as the exact locations of absence within these administrative units are missing.

The model of the current and future climatic suitability of Ae. albopictus was based on four different model algorithms: the generalized boosted model (GBM), the generalized additive model (GAM), maximum entropy (Maxent), and random forest (RF). All model runs were performed using the biomod2 package (version 3.3-7) [41] implemented in R (version 3.4.2) [42]. The current European distribution was best depicted by the GBM (area under the curve (AUC): 0.98, total sum of squares (TSS): 0.86). Subsequently, only the GBM was used to project the potential future distribution. We used observed occurrences and randomly generated pseudo-absences within Europe where the number of pseudo-absences corresponds to the number of occurrences in Europe (N = 1336), which is the most suitable method for GBMs [43]. Databases with confirmed absence points of *Ae. albopictus* in Europe were not available, only administrative units with absences (e.g., the distribution map of *Ae. albopictus* from the European Centre for Disease Prevention and Control ECDC [38]). However, this information is not sufficient for modelling as the exact locations of absence within these administrative units are missing.

For future projections of climatically suitable areas in the near future (2021–2040) we used data from the Earth system model of the Max Planck Institute for Meteorology (MPI-ESM-lr), downloaded from the website of the Consortium of International Agricultural Research Centers CGIAR program on Climate Change, Agriculture and Food Security (CCAFS) [44]. From the various available emission scenarios based on the Intergovernmental Panel on Climate Change IPCC [45], representative concentration pathway RCP 8.5 was selected as an extreme scenario (radiation force of 8.5 W/m^2 in 2100 versus 1850) with an expected increase in temperature of about 4.3 °C by the end of the century in comparison to the pre-industrial times [46].

Infections with DENV and CHIKV have been legally notifiable infections in Germany for years, with a general arbovirus notification requirement

(including ZIKV) only coming into force in May 2016 [47]. Laboratories have to notify diagnoses of acute infections to local health departments who investigate further information such as travel history. Suitable areas for a likely establishment of *Ae. albopictus* in Germany were combined with the incidence of (potentially viraemic) travel-associated CHIKV and DENV infection cases at the county level over the years 2011–2017 (from the Robert Koch Institute RKI-hosted national-level database on notifiable diseases SURVNET [48]). As a spatial reference for the German counties, data provided by the German Federal Agency for Cartography and Geodesy was used [49]. The data product vg1000-ew also contains the official number of inhabitants per county as of 31 December 2016, which was used to calculate the incidence rate (cases per 100,000 inhabitants). In order to carry out a classification of the hazard potential for virus transmission, first the spatial average of climatic suitability was calculated for each county based on the rasterized output of the GBM. Then, both climatic suitability and incidence rate data were re-scaled to values between 0 and 1, and the two layers were multiplied with each other to gain an estimate of over-all hazard potential per county. Continuous values were divided into three classes using Jenks natural breaks. Seasonal coupling of vector occurrence and viral disease incidences was not considered, since the incidences were summarized for 7 years. All analyses were made using R version 3.4.2 [42].

Results

Current and future climatically suitable areas for the establishment of *Aedes albopictus*

The federal states of Baden-Württemberg, the Saarland, Rhineland-Palatinate, Hesse and North Rhine-Westphalia currently show the highest values of climatic suitability for *Ae. albopictus* (Figure 2a, see Figure S1 for geographical reference). Thus far, established populations (long-term presence, locally reproducing, overwintering) have been found in Baden-Württemberg (Heidelberg, Freiburg) and Thuringia (Jena). The two locations where single

specimens of the mosquito have been found in North Rhine-Westphalia lie in an area that is classified as climatically suitable by the model, suggesting that surveillance activities should be intensified in order to avoid unnoticed establishment of populations. The same is currently not true for the locations of introduced specimens in Bavaria and eastern Baden-Württemberg, but this may change sooner rather than later.

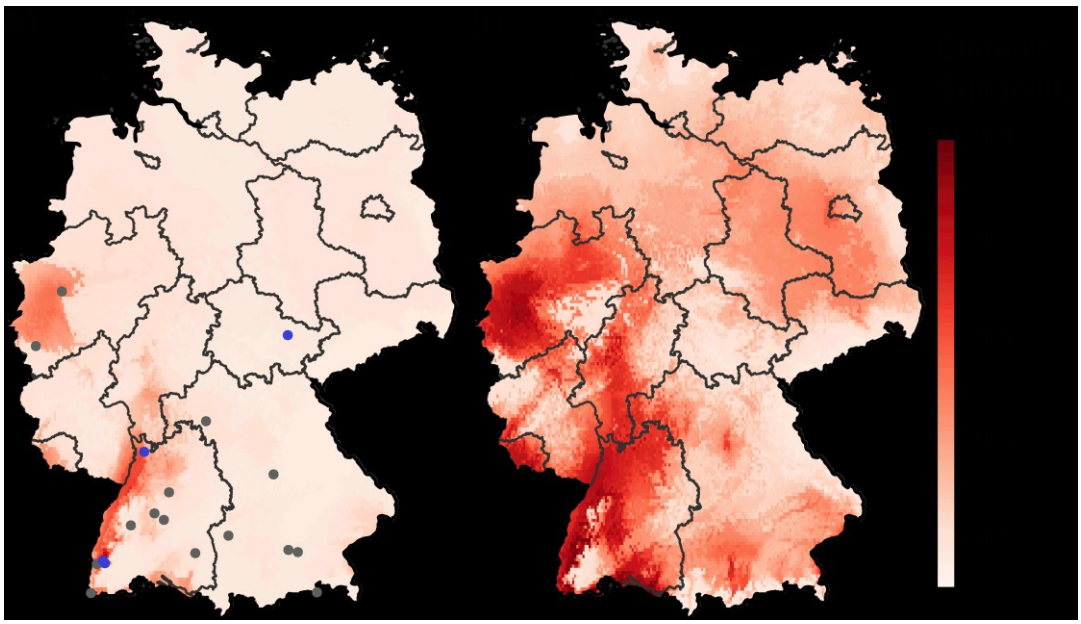

Figure 2. (a) Relative climatic suitability for the establishment of *Aedes albopictus* in Germany. Circles: high-precision occurrence records derived from the literature for both single introduction events (grey) and established (overwintering) populations (blue); only the latter were used for modelling. (b) Projected future suitable climates for the establishment of *Ae. albopictus* in Germany (near future 2021–2040, climate model mpi-esm-lr, climate scenario RCP 8.5). (a, b) global climatic dataset Worldclim with spatial resolution of 2.5 arcmin (≈ 5 km). Lines delineate level-2 administrational units (federal states) of Germany.

In the near future (2021–2040), the area climatically suitable for the mosquitoes strongly extends into Germany and reaches high values of suitability all over the western and southern parts of the country, excluding the extreme North-West and low mountain landscapes (Figure 2b). Increasing climatic suitability is found in Lower Saxony, Saxony-Anhalt, Brandenburg, northern regions of Saxony, and the cities of Berlin, and Hamburg, as well as in

north-western and southern parts of Bavaria. The altitudinal pattern of Germany is reflected in the temperature and precipitation variables used in our model: *Ae. albopictus* is less likely to establish in higher elevations such as the Black Forest, Swabian Jura hills, the Bavarian forest, Ore Mountains, and the Rothaar Mountains in Germany.

German counties and population showing a hazard potential for autochthonous transmission of dengue and chikungunya viruses

When the climatic suitability is averaged on county level, Baden-Württemberg, Hesse and North Rhine-Westphalia currently show the highest number of counties and cities climatically suitable for *Ae. albopictus* (Figure 3a).

Autochthonous mosquito-borne DENV and CHIKV cases have not been identified in Germany so far. Travel-associated CHIKV and DENV infections in Germany are most frequently diagnosed in large cities such as Berlin (number of cases 2011-2017: 511), Munich (405), Hamburg (234), Cologne (149), and Frankfurt am Main (114) (Figure 3b, Table S1). Counties in the direct neighbourhoods of these metropolitan areas also show an elevated incidence of DENV and CHIKV cases (Rhein-Neckar-Kreis county (65), Munich county (57), Hannover county (55), and Karlsruhe county (47)). Overall, southern states of Germany appear more affected than others, with the highest incidences found in Bavaria and Baden-Württemberg. DENV cases are more frequent than CHIKV cases.

German counties and cities showing a high hazard potential for autochthonous transmission of *Ae. albopictus*-borne arboviruses in case of further establishment of the vector are the cities of Freiburg im Breisgau, Speyer, and Karlsruhe (Figure 3c, Table S1). The species formed at least two separate, reproducing populations in Freiburg, that were able to overwinter in 2015–2016 [28, 29, 50].

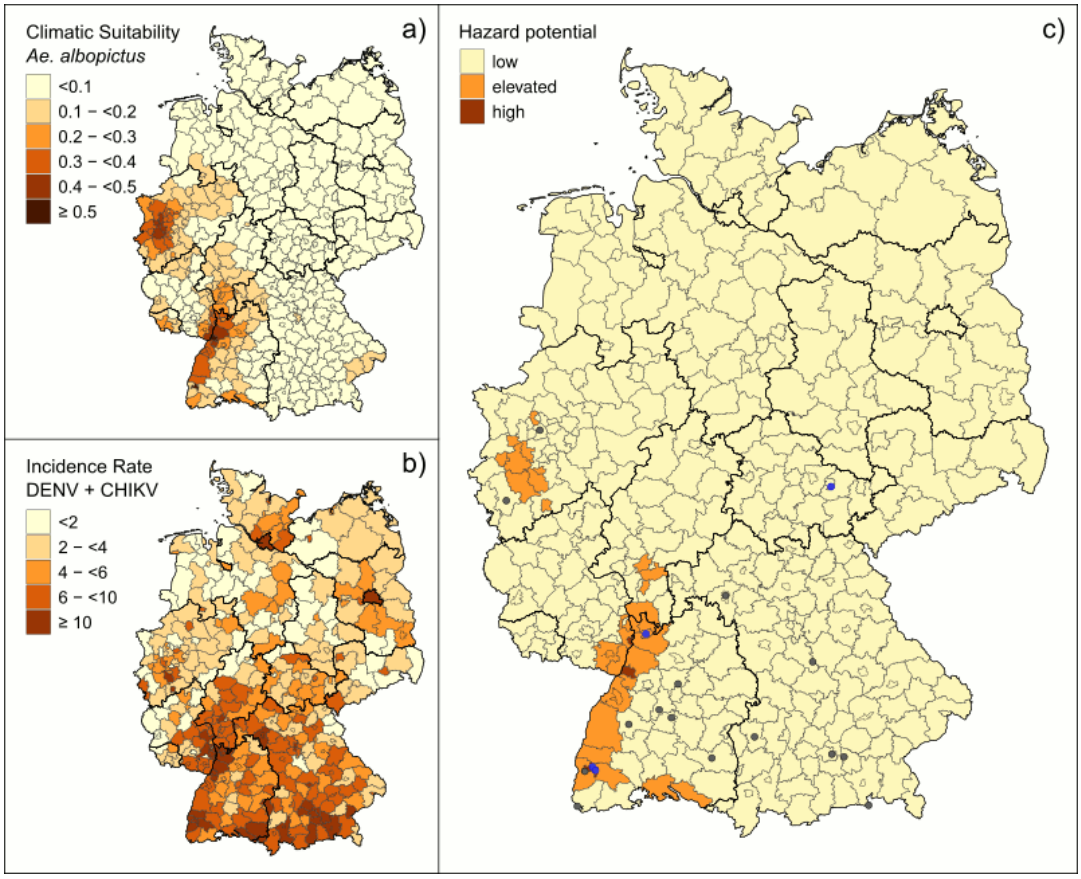

Figure 3. (a) Current climatic suitability for the establishment of *Aedes albopictus* in Germany, averaged over the county level in Germany. (b) Incidence of (potentially viraemic) travel-associated CHIKV and DENV infection cases at the county level (cases per 100,000 population by county over the years 2011–2017, from the RKI-hosted national-level database on notifiable diseases SURVNET). (c) Likelihood of *Ae. albopictus* meeting viraemic returning travellers, potentially leading to transmission, shown as a combination of the modelled climatic suitability for *Ae. albopictus* at the county level, and DENV and CHIKV incidence in returning travellers. Circles: high-precision occurrence records derived from the literature for both single introduction events (grey) and established (overwintering) populations (blue) of *Ae. albopictus*; only the latter were used for modelling. Black and grey lines respectively indicate level-2 and level-3 administrational units (federal states and "Kreis") of Germany. Administrative units provided by the Federal Agency for Cartography and Geodesy in Germany BKG: © GeoBasis-DE / BKG 2013.

An elevated hazard potential of transmission becomes apparent mainly along the Rhine river valley and adjacent portions of its tributaries in Baden-Württemberg, southern parts of Hesse, and North Rhine-Westphalia as far

north as Duisburg. Within this category, the cities Mannheim, Cologne, Heidelberg, Frankfurt am Main, and Ludwigshafen, and the counties Karlsruhe, Emmendingen, Rhein-Pfalz-Kreis, Rhein-Neckar-Kreis, and Germersheim show the highest relative values. While most of the counties, cities and districts along the Upper Rhine are potentially covered by mosquito control (Figure S2), no comparable permanent infrastructure exists in the densely populated North Rhine-Westphalia.

Applying the previously described categorization, currently about 0.5 million people are living in Germany in areas that have a high hazard potential for an autochthonous transmission of DENV or CHIKV during the active season of the vector mosquito. In addition, 8.8 million people live in regions showing an elevated hazard potential if vector establishment continuous to progress in climatically suitable areas. Of all these, 1.7 million people live in administrative units that are members of the German Mosquito Control Association.

Discussion

Mosquito-borne diseases such as DENV, CHIKV and Zika have spread and expanded globally during the last decades. At the same time, an increase of established populations of the competent vector *Ae. albopictus* in Germany creates an emerging health hazard potential for seasonal autochthonous transmission of non-endemic mosquito-borne viral diseases. For the first time, spatially explicit information on DENV and CHIKV incidence found in travellers in Germany is combined with the current climatic suitability for vector establishment. This identification of areas with transmission potential on the county level supports public administrations to effectively plan adequate vector control measures and to intensify surveillance and raise awareness to avoid autochthonous transmission of *Ae. albopictus*-associated arboviruses. Beside the public health hazards, the daytime biter *Ae. albopictus* is also known to be a significant biting nuisance and thus may negatively impact tourism and outdoor activities, leading to economic loss [51].

The limitations of the model approach used here should be taken into account. The strength of a species distribution model depends on the quality and quantity of the occurrence records as well as the environmental data [52]. Aside from further areas rendered suitable by climate change, *Ae. albopictus* is likely not yet occupying all currently suitable areas in Europe. In Southern Europe, *Ae. albopictus* may not yet have been forced to apply its full cold adaptation capacity. In this case, our model would underestimate the potential areas of suitability in Germany. However, we expect only a minor influence on our modelling results due to the large amount of already available data in Europe as well as the good model performance.

To fit our models, environmental variables with a spatial resolution of 2.5 arcmin (≈5 km) are used. This is still quite coarse for an insect species and does not account for suitable microclimatic conditions allowing spatial and temporal windows of opportunity for establishments of *Ae. albopictus*. This was the case in at least one sheltered valley in Thuringia: Jena is one of the most climatically favourable regions in Germany. Reflected solar radiation on the steep slopes and heat storage of the shell limestone are responsible for mild springs, hot summers, long and warm autumns, and mild winters. Due to the warm microclimate, the region near Jena is also called the "Tuscany of the East". Here, vector monitoring discovered a locally reproducing population of *Ae. albopictus* in 2015 [53], but this area was too small to be recognized as having a suitable climate by the model.

Aside from data-related issues, the choice of model algorithm is a major source of uncertainty in correlative species distribution modelling [54]. To reduce the uncertainty in model projections, we initially used four model algorithms and reduced the set later to the one algorithm that performed best regarding the AUC/TSS and reasonably reflected the observed data.

For the selection of pseudo-absences, the application of different methods influences the modelling results [55]. We used a random pseudo-absence selection with the same number of pseudo-absences as the number of

presences [43]. As *Ae. albopictus* continues to spread in Europe and niche shifts are likely [56], we intended to avoid the exclusion of areas likely to be suitable by defining minimum or maximum distances around occurrences for the pseudo-absence selection.

Besides the vector´s climatic suitability, temperature also directly impacts the transmission process of viruses, as the extrinsic incubation period (defined as the period between infection of the insect vector and its ability to transmit the virus to other susceptible hosts) depends on the ambient temperature (see e.g., [57]). Accounting for the extrinsic incubation period can add a temporal aspect in the description of vector-borne disease risk especially in temperate regions.

The numbers of diagnosed and notified cases of DENV and CHIKV infection underestimate the true number of imported (symptomatic and asymptomatic) infections, mostly because not every infected traveller will make use of medical counselling. There still may be residually better access to diagnostics in urban as compared to rural areas (e.g., by easy access to centres for tropical medicine) resulting in an underestimation of hazard in rural areas. At the same time, the notified case numbers overestimate the number of viraemic returnees because a proportion of patients notified as cases is already non-viraemic upon return to Germany. Nevertheless, as an indicator for relative and geographic frequency of import of travel-associated infections, notified infections represent the best available data source. The resulting categories consider the distribution of the available data on travel-associated infections as well as the range of modelled suitability values and observed incidences and thus can serve as an indicator for the spatial patterns of hazard potential.

Long-term mosquito control can reduce the number of invasive mosquito populations and/or mosquito abundance which in turn will lower a potential disease transmission risk. However, currently barriers exist for implementation and expansion of mosquito control and surveillance programs. Unclear responsibilities among the various authorities involved (such as

environmental authority, public health authority, and local authorities), and a lack of standardized procedures for monitoring and intervention plans as well as different interpretations of the existing legal basis hamper rapid and successful implementation.

Most counties in Germany are not experienced in getting to terms with establishing container-breeding vector mosquitoes. Until recently, large-scale vector control measures conducted by the German Mosquito Control Association have focused primarily on *Aedes vexans* and similar species that lay their eggs in the moist soils of the floodplains and riparian forests around the Rhine river. After flood events, large areas are treated with *Bacillus thuringiensis israelensis* (BTI) on foot and from helicopters. While this method has proven to be effective against those species, *Ae. albopictus* poses a different challenge. As it prefers small water bodies (such as rain barrels or flower vases) as breeding sites, surveillance and monitoring efforts need to be directed towards different kinds of habitats. Similarly, control of *Ae. albopictus* requires a much more targeted approach. When the first mass development of *Ae. albopictus* in Germany occurred in an allotment garden in Freiburg, control measures included the removal of breeding sites and deployment of BTI tablets. For the future, release of sterilized or *Wolbachia*-infected males has been considered as an additional measure [27].

Vector abundance data is not sufficiently available yet but will improve future model approaches. Assuming at least similar numbers of infected travellers returning to Germany over the upcoming two decades and taking into account the increasing climatic suitability for vector establishment especially in western and southern parts of the country, a further increase in the size of the population at risk can be expected.

Conclusions

Despite its limitations, the model is an important step forward, because for the first time spatially explicit information about travel-related arbovirus

infections in Germany is combined with data on the vector's climatic suitability. Overall, a more targeted and thus cost-efficient implementation of adequate vector control measures, health surveillance, and awareness raising are supported by the detailed maps provided here. At a national scale, besides Baden-Württemberg, Hesse, and Rhineland-Palatinate, the federal state of North Rhine-Westphalia appears to require the most urgent attention, as several hazard factors come together there. Future approaches should also include additional vector species such as *Aedes japonicus* and the diseases they transmit. The establishment of vectors and introduction of infectious diseases not known yet in Germany is a very dynamic process which requires permanent adaptation and improvement of projections based on new data on vector control, vector occurrence, vector ecology, and arbovirus incidence in returnees.

Supplementary materials

The following are available online at http://www.mdpi.com/1660-4601/15/6/1270/s1, Table S1: Current climatic suitability for the establishment of *Aedes albopictus* in Germany, incidence of travel-associated CHIKV and DENV infections (cases per 100,000 population over the years 2011–2017), and hazard potential classes at the county level, Figure S1: Map of Germany with geographical units (federal states, counties, cities and mountain ranges) mentioned in the main text, Figure S2: Overview about the current situation regarding *Aedes albopictus* in Germany.

Author contributions

S.M.T. developed the research idea and concept. N.B.T. and A.J. modelled the species distribution and applied the climate models. L.Z. supported species distribution modelling and the overlay of incidences. N.B.T. produced the maps. C.F., K.S. provided incidences. A.J., C.F., C.W.-W., K.S., M.F., N.B.T., and S.M.T. wrote parts of the paper and reviewed the paper. C.B. reviewed the paper.

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Conflicts of interest

The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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Appendix: Supplementary materials

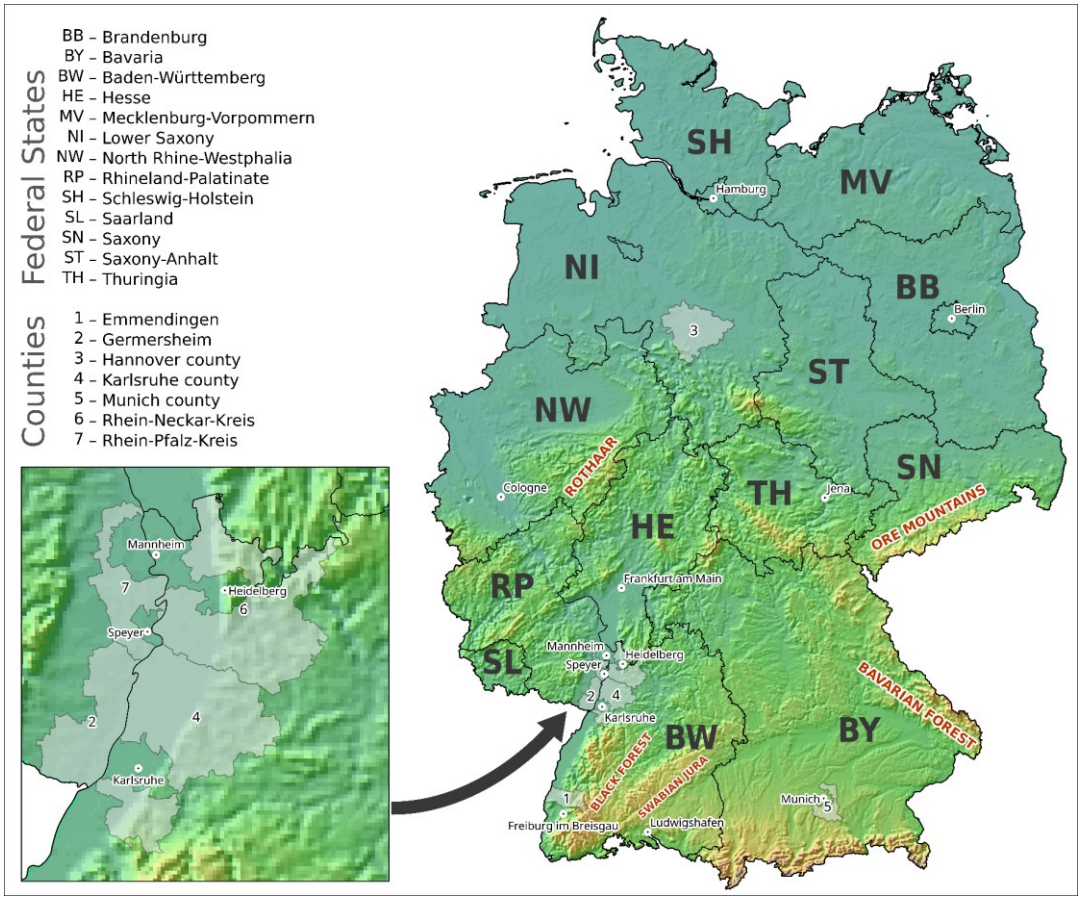

Figure S1. Overview map of Germany including cities, counties and mountain ranges mentioned in the main text, as well as all (non-city) Federal States. Administraional units and digital elevation model © GeoBasis-DE / BKG 2018.

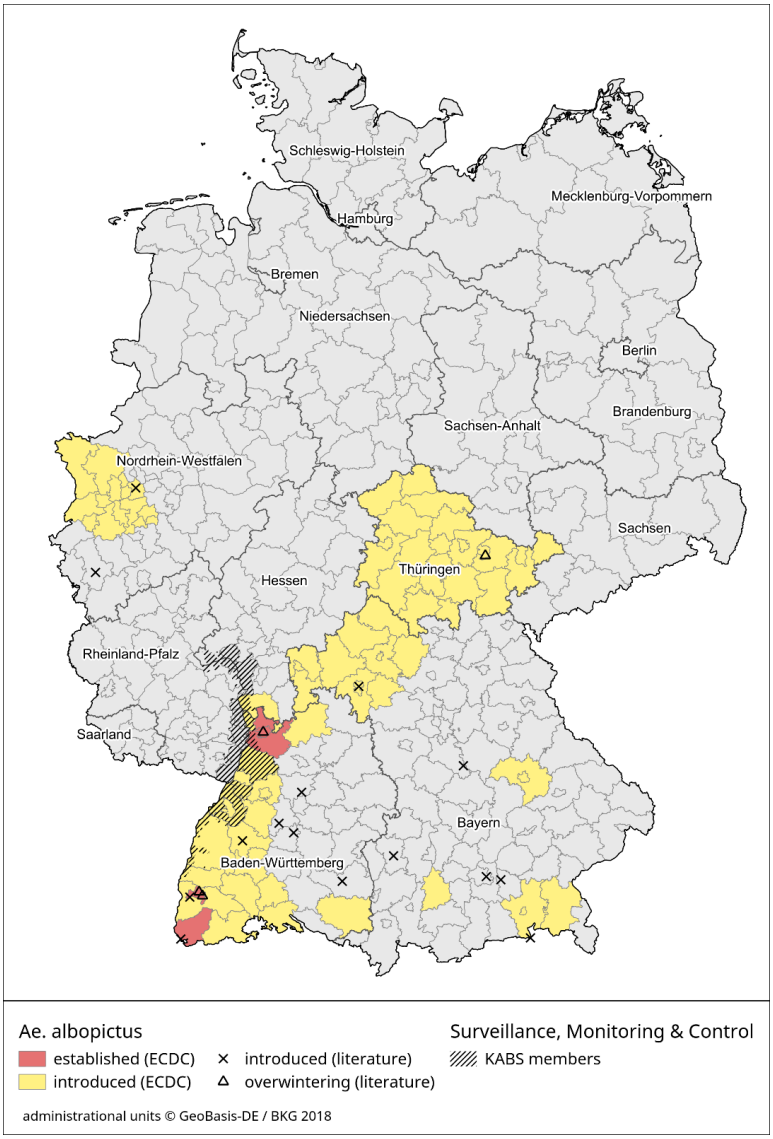

Figure S2. Overview about the current situation regarding *Ae. albopictus* in Germany. The colored areas give the status according to the European Centre for Disease Prevention and Control (ECDC) for German districts ("Landkreis" or "Stadtkreis", equivalent to NUTS level 3 on a European scale) [58]. Precise locations or data sources are not available for these areas. Crosses and triangles show point locations that are publically available from the scientific literature (2008–2018) [36, 50, 59, 60]. Precision varies from precise site descriptions to rough maps. Hatched areas show municipalities and districts that are members of the German Mosquito Control Association KABS [61]. The Federal States of Baden-Württemberg and Rheinland-Pfalz support KABS as well. Neither the trapping locations of the currently running CuliMo project nor data from the Mückenatlas citizen science project [62] are publicly available yet. Administraional units © GeoBasis-DE / BKG 2018.

Table S1. Current climatic suitability for the establishment of *Aedes albopictus* in Germany, incidence of travel associated CHIKV and DENV infections (cases per 100,000 population over the years 2011–2017), hazard potential classes on county level. SK = Stadtkreis (city), LK = Landkreis (rural district).

Kreis-kennziffer	NUTS-ID	Name	incidence rate	climatic suitability	hazard potential	hazard class
1001	DEF01	SK Flensburg	3.43	0.07	0.01	low
1002	DEF02	SK Kiel	6.47	0.07	0.01	low
1003	DEF03	SK Lübeck	5.54	0.07	0.01	low
1004	DEF04	SK Neumünster	5.02	0.07	0.01	low
1051	DEF05	LK Dithmarschen	3.74	0.07	0.01	low
1053	DEF06	LK Herzogtum Lauenburg	7.18	0.07	0.01	low
1054	DEF07	LK Nordfriesland	3.03	0.07	0.01	low
1055	DEF08	LK Ostholstein	4.98	0.07	0.01	low
1056	DEF09	LK Pinneberg	6.12	0.07	0.01	low
1057	DEF0A	LK Plön	3.88	0.07	0.01	low
1058	DEF0B	LK Rendsburg-Eckernförde	2.94	0.07	0.01	low
1059	DEF0C	LK Schleswig-Flensburg	0.50	0.07	0.00	low
1060	DEF0D	LK Segeberg	4.04	0.07	0.01	low
1061	DEF0E	LK Steinburg	3.79	0.07	0.01	low
1062	DEF0F	LK Stormarn	5.38	0.07	0.01	low
2000	DE600	SK Hamburg	12.93	0.07	0.02	low
3101	DE911	SK Braunschweig	3.62	0.07	0.01	low
3102	DE912	SK Salzgitter	1.93	0.07	0.00	low
3103	DE913	SK Wolfsburg	3.23	0.08	0.01	low
3151	DE914	LK Gifhorn	4.58	0.07	0.01	low
3153	DE916	LK Goslar	0.72	0.08	0.00	low
3154	DE917	LK Helmstedt	1.09	0.07	0.00	low
3155	DE918	LK Northeim	2.99	0.08	0.01	low
3157	DE91A	LK Peine	5.26	0.07	0.01	low
3158	DE91B	LK Wolfenbüttel	2.48	0.07	0.00	low
3159	-----	LK Göttingen	4.28	0.08	0.01	low
3241	DE929	Region Hannover	4.79	0.08	0.01	low
3251	DE922	LK Diepholz	0.93	0.09	0.00	low
3252	DE923	LK Hameln-Pyrmont	2.02	0.09	0.01	low
3254	DE925	LK Hildesheim	1.80	0.08	0.00	low
3255	DE926	LK Holzminden	0.00	0.09	0.00	low
3256	DE927	LK Nienburg (Weser)	1.65	0.08	0.00	low
3257	DE928	LK Schaumburg	1.27	0.09	0.00	low
3351	DE931	LK Celle	2.24	0.07	0.00	low
3352	DE932	LK Cuxhaven	0.50	0.07	0.00	low
3353	DE933	LK Harburg	3.20	0.07	0.00	low
3354	DE934	LK Lüchow-Dannenberg	0.00	0.08	0.00	low
3355	DE935	LK Lüneburg	3.30	0.07	0.01	low
3356	DE936	LK Osterholz	0.89	0.08	0.00	low
3357	DE937	LK Rotenburg (Wümme)	2.45	0.07	0.00	low
3358	DE938	LK Heidekreis	0.72	0.07	0.00	low
3359	DE939	LK Stade	2.98	0.07	0.00	low

Kreis-kennziffer	NUTS-ID	Name	incidence rate	climatic suitability	hazard potential	hazard class
3360	DE93A	LK Uelzen	5.38	0.07	0.01	low
3361	DE93B	LK Verden	1.47	0.07	0.00	low
3401	DE941	SK Delmenhorst	2.60	0.08	0.01	low
3402	DE942	SK Emden	5.94	0.08	0.01	low
3403	DE943	SK Oldenburg	3.62	0.08	0.01	low
3404	DE944	SK Osnabrück	7.92	0.11	0.03	low
3405	DE945	SK Wilhelmshaven	2.62	0.08	0.01	low
3451	DE946	LK Ammerland	0.00	0.08	0.00	low
3452	DE947	LK Aurich	2.10	0.08	0.00	low
3453	DE948	LK Cloppenburg	2.41	0.09	0.01	low
3454	DE949	LK Emsland	1.24	0.09	0.00	low
3455	DE94A	LK Friesland	1.02	0.08	0.00	low
3456	DE94B	LK Grafschaft Bentheim	1.47	0.09	0.00	low
3457	DE94C	LK Leer	0.59	0.08	0.00	low
3458	DE94D	LK Oldenburg	1.54	0.08	0.00	low
3459	DE94E	LK Osnabrück	3.38	0.11	0.01	low
3460	DE94F	LK Vechta	0.00	0.10	0.00	low
3461	DE94G	LK Wesermarsch	2.24	0.08	0.00	low
3462	DE94H	LK Wittmund	1.76	0.08	0.00	low
4011	DE501	SK Bremen	5.66	0.08	0.01	low
4012	DE502	SK Bremerhaven	1.77	0.08	0.00	low
5111	DEA11	SK Düsseldorf	9.46	0.41	0.24	elevated
5112	DEA12	SK Duisburg	1.20	0.42	0.03	low
5113	DEA13	SK Essen	3.26	0.37	0.07	low
5114	DEA14	SK Krefeld	4.41	0.41	0.11	elevated
5116	DEA15	SK Mönchengladbach	4.60	0.40	0.11	elevated
5117	DEA16	SK Mülheim a.d.Ruhr	2.34	0.40	0.06	low
5119	DEA17	SK Oberhausen	3.31	0.39	0.08	low
5120	DEA18	SK Remscheid	3.62	0.12	0.02	low
5122	DEA19	SK Solingen	1.89	0.22	0.02	low
5124	DEA1A	SK Wuppertal	2.55	0.11	0.01	low
5154	DEA1B	LK Kleve	1.93	0.21	0.02	low
5158	DEA1C	LK Mettmann	5.57	0.31	0.10	low
5162	DEA1D	LK Rhein-Kreis Neuss	4.25	0.41	0.11	elevated
5166	DEA1E	LK Viersen	2.35	0.35	0.05	low
5170	DEA1F	LK Wesel	2.82	0.31	0.05	low
5314	DEA22	SK Bonn	11.49	0.20	0.12	elevated
5315	DEA23	SK Köln	13.85	0.33	0.27	elevated
5316	DEA24	SK Leverkusen	4.90	0.35	0.10	elevated
5334	DEA2D	StadtRegion Aachen	6.70	0.16	0.05	low
5358	DEA26	LK Düren	1.53	0.28	0.02	low
5362	DEA27	LK Rhein-Erft-Kreis	5.80	0.35	0.12	elevated
5366	DEA28	LK Euskirchen	2.09	0.11	0.01	low
5370	DEA29	LK Heinsberg	1.98	0.34	0.04	low
5374	DEA2A	LK Oberbergischer Kreis	3.66	0.11	0.01	low
5378	DEA2B	LK Rheinisch-Bergischer Kreis	8.82	0.18	0.08	low
5382	DEA2C	LK Rhein-Sieg-Kreis	3.85	0.17	0.03	low
5512	DEA31	SK Bottrop	5.11	0.37	0.11	elevated
5513	DEA32	SK Gelsenkirchen	1.14	0.36	0.02	low

Kreis-kennziffer	NUTS-ID	Name	incidence rate	climatic suitability	hazard potential	hazard class
5515	DEA33	SK Münster	9.62	0.10	0.04	low
5554	DEA34	LK Borken	2.43	0.12	0.01	low
5558	DEA35	LK Coesfeld	3.20	0.11	0.01	low
5562	DEA36	LK Recklinghausen	1.78	0.25	0.03	low
5566	DEA37	LK Steinfurt	3.15	0.10	0.01	low
5570	DEA38	LK Warendorf	3.24	0.11	0.01	low
5711	DEA41	SK Bielefeld	5.70	0.11	0.02	low
5754	DEA42	LK Gütersloh	3.32	0.11	0.01	low
5758	DEA43	LK Herford	1.99	0.11	0.01	low
5762	DEA44	LK Höxter	1.40	0.10	0.01	low
5766	DEA45	LK Lippe	4.59	0.11	0.02	low
5770	DEA46	LK Minden-Lübbecke	2.57	0.10	0.01	low
5774	DEA47	LK Paderborn	3.28	0.11	0.01	low
5911	DEA51	SK Bochum	6.58	0.25	0.09	low
5913	DEA52	SK Dortmund	3.24	0.15	0.02	low
5914	DEA53	SK Hagen	2.12	0.11	0.01	low
5915	DEA54	SK Hamm	0.56	0.13	0.00	low
5916	DEA55	SK Herne	0.64	0.34	0.01	low
5954	DEA56	LK Ennepe-Ruhr-Kreis	5.84	0.14	0.04	low
5958	DEA57	LK Hochsauerlandkreis	2.67	0.09	0.01	low
5962	DEA58	LK Märkischer Kreis	3.14	0.10	0.01	low
5966	DEA59	LK Olpe	2.96	0.09	0.01	low
5970	DEA5A	LK Siegen-Wittgenstein	1.44	0.09	0.00	low
5974	DEA5B	LK Soest	2.65	0.11	0.01	low
5978	DEA5C	LK Unna	3.53	0.12	0.02	low
6411	DE711	SK Darmstadt	9.53	0.22	0.11	elevated
6412	DE712	SK Frankfurt am Main	15.48	0.26	0.23	elevated
6413	DE713	SK Offenbach	2.41	0.29	0.04	low
6414	DE714	SK Wiesbaden	9.73	0.11	0.04	low
6431	DE715	LK Bergstraße	7.84	0.24	0.10	elevated
6432	DE716	LK Darmstadt-Dieburg	8.48	0.21	0.09	low
6433	DE717	LK Groß-Gerau	8.18	0.20	0.09	low
6434	DE718	LK Hochtaunuskreis	9.36	0.10	0.04	low
6435	DE719	LK Main-Kinzig-Kreis	6.00	0.13	0.04	low
6436	DE71A	LK Main-Taunus-Kreis	8.06	0.13	0.05	low
6437	DE71B	LK Odenwaldkreis	6.22	0.18	0.06	low
6438	DE71C	LK Offenbach	7.71	0.25	0.11	elevated
6439	DE71D	LK Rheingau-Taunus-Kreis	6.46	0.08	0.01	low
6440	DE71E	LK Wetteraukreis	6.91	0.16	0.05	low
6531	DE721	LK Gießen	6.40	0.15	0.04	low
6532	DE722	LK Lahn-Dill-Kreis	2.36	0.11	0.01	low
6533	DE723	LK Limburg-Weilburg	5.23	0.10	0.02	low
6534	DE724	LK Marburg-Biedenkopf	6.12	0.11	0.03	low
6535	DE725	LK Vogelsbergkreis	6.56	0.08	0.02	low
6611	DE731	SK Kassel	3.52	0.12	0.02	low
6631	DE732	LK Fulda	5.43	0.06	0.01	low
6632	DE733	LK Hersfeld-Rotenburg	2.48	0.07	0.00	low
6633	DE734	LK Kassel	0.84	0.09	0.00	low
6634	DE735	LK Schwalm-Eder-Kreis	3.31	0.08	0.01	low

Kreis-kennziffer	NUTS-ID	Name	incidence rate	climatic suitability	hazard potential	hazard class
6635	DE736	LK Waldeck-Frankenberg	1.27	0.10	0.00	low
6636	DE737	LK Werra-Meißner-Kreis	5.94	0.08	0.01	low
7111	DEB11	SK Koblenz	5.28	0.15	0.04	low
7131	DEB12	LK Ahrweiler	0.78	0.10	0.00	low
7132	DEB13	LK Altenkirchen	3.88	0.11	0.02	low
7133	DEB14	LK Bad Kreuznach	6.35	0.08	0.01	low
7134	DEB15	LK Birkenfeld	6.19	0.09	0.02	low
7135	DEB16	LK Cochem-Zell	4.85	0.08	0.01	low
7137	DEB17	LK Mayen-Koblenz	2.82	0.11	0.01	low
7138	DEB18	LK Neuwied	4.41	0.11	0.02	low
7140	DEB19	LK Rhein-Hunsrück-Kreis	0.97	0.08	0.00	low
7141	DEB1A	LK Rhein-Lahn-Kreis	2.45	0.09	0.01	low
7143	DEB1B	LK Westerwaldkreis	1.99	0.09	0.01	low
7211	DEB21	SK Trier	6.36	0.16	0.05	low
7231	DEB22	LK Bernkastel-Wittlich	2.68	0.08	0.01	low
7232	DEB23	LK Bitburg-Prüm	1.02	0.09	0.00	low
7233	DEB24	LK Vulkaneifel	0.00	0.09	0.00	low
7235	DEB25	LK Trier-Saarburg	0.68	0.12	0.00	low
7311	DEB31	SK Frankenthal	2.06	0.29	0.03	low
7312	DEB32	SK Kaiserslautern	1.01	0.08	0.00	low
7313	DEB33	SK Landau i.d.Pfalz	8.69	0.20	0.09	low
7314	DEB34	SK Ludwigshafen	10.80	0.35	0.22	elevated
7315	DEB35	SK Mainz	8.90	0.13	0.05	low
7316	DEB36	SK Neustadt a.d.Weinstraße	1.88	0.22	0.02	low
7317	DEB37	SK Pirmasens	0.00	0.09	0.00	low
7318	DEB38	SK Speyer	11.87	0.46	0.34	high
7319	DEB39	SK Worms	4.84	0.21	0.05	low
7320	DEB3A	SK Zweibrücken	2.90	0.09	0.01	low
7331	DEB3B	LK Alzey-Worms	10.14	0.12	0.05	low
7332	DEB3C	LK Bad Dürkheim	12.03	0.15	0.09	low
7333	DEB3D	LK Donnersbergkreis	6.65	0.08	0.01	low
7334	DEB3E	LK Germersheim	7.80	0.47	0.22	elevated
7335	DEB3F	LK Kaiserslautern	2.84	0.08	0.01	low
7336	DEB3G	LK Kusel	2.82	0.08	0.01	low
7337	DEB3H	LK Südliche Weinstraße	9.02	0.22	0.11	elevated
7338	DEB3I	LK Rhein-Pfalz-Kreis	10.45	0.38	0.24	elevated
7339	DEB3J	LK Mainz-Bingen	8.13	0.11	0.04	low
7340	DEB3K	LK Südwestpfalz	7.29	0.10	0.02	low
8111	DE111	SK Stuttgart	8.44	0.11	0.04	low
8115	DE112	LK Böblingen	4.41	0.12	0.02	low
8116	DE113	LK Esslingen	7.38	0.09	0.02	low
8117	DE114	LK Göppingen	5.50	0.07	0.01	low
8118	DE115	LK Ludwigsburg	3.72	0.17	0.03	low
8119	DE116	LK Rems-Murr-Kreis	8.52	0.10	0.03	low
8121	DE117	SK Heilbronn	4.85	0.31	0.09	low
8125	DE118	LK Heilbronn	5.04	0.25	0.07	low
8126	DE119	LK Hohenlohekreis	7.23	0.14	0.04	low
8127	DE11A	LK Schwäbisch Hall	5.18	0.09	0.01	low
8128	DE11B	LK Main-Tauber-Kreis	3.78	0.12	0.02	low

Kreis-kennziffer	NUTS-ID	Name	incidence rate	climatic suitability	hazard potential	hazard class
8135	DE11C	LK Heidenheim	7.60	0.06	0.01	low
8136	DE11D	LK Ostalbkreis	4.81	0.07	0.01	low
8211	DE121	SK Baden-Baden	7.37	0.37	0.16	elevated
8212	DE122	SK Karlsruhe	14.19	0.55	0.49	high
8215	DE123	LK Karlsruhe	10.67	0.44	0.29	elevated
8216	DE124	LK Rastatt	6.55	0.36	0.14	elevated
8221	DE125	SK Heidelberg	15.01	0.28	0.24	elevated
8222	DE126	SK Mannheim	12.80	0.37	0.28	elevated
8225	DE127	LK Neckar-Odenwald-Kreis	4.89	0.19	0.05	low
8226	DE128	LK Rhein-Neckar-Kreis	11.94	0.33	0.23	elevated
8231	DE129	SK Pforzheim	5.67	0.28	0.09	low
8235	DE12A	LK Calw	5.13	0.14	0.03	low
8236	DE12B	LK Enzkreis	4.06	0.26	0.06	low
8237	DE12C	LK Freudenstadt	5.14	0.10	0.02	low
8311	DE131	SK Freiburg i.Breisgau	22.41	0.57	0.81	high
8315	DE132	LK Breisgau-Hochschwarzwald	11.14	0.19	0.11	elevated
8316	DE133	LK Emmendingen	11.64	0.39	0.28	elevated
8317	DE134	LK Ortenaukreis	8.27	0.35	0.17	elevated
8325	DE135	LK Rottweil	6.51	0.11	0.03	low
8326	DE136	LK Schwarzwald-Baar-Kreis	8.09	0.06	0.01	low
8327	DE137	LK Tuttlingen	4.34	0.09	0.01	low
8335	DE138	LK Konstanz	8.50	0.25	0.12	elevated
8336	DE139	LK Lörrach	8.35	0.21	0.09	low
8337	DE13A	LK Waldshut	5.33	0.14	0.03	low
8415	DE141	LK Reutlingen	4.93	0.08	0.01	low
8416	DE142	LK Tübingen	3.56	0.13	0.02	low
8417	DE143	LK Zollernalbkreis	2.13	0.11	0.01	low
8421	DE144	SK Ulm	17.75	0.06	0.01	low
8425	DE145	LK Alb-Donau-Kreis	4.66	0.06	0.01	low
8426	DE146	LK Biberach	8.66	0.08	0.02	low
8435	DE147	LK Bodenseekreis	11.26	0.25	0.15	elevated
8436	DE148	LK Ravensburg	11.36	0.10	0.04	low
8437	DE149	LK Sigmaringen	6.14	0.12	0.03	low
9161	DE211	SK Ingolstadt	14.22	0.07	0.02	low
9162	DE212	SK München	27.66	0.06	0.03	low
9163	DE213	SK Rosenheim	7.98	0.09	0.02	low
9171	DE214	LK Altötting	13.71	0.11	0.06	low
9172	DE215	LK Berchtesgadener Land	3.83	0.09	0.01	low
9173	DE216	LK Bad Tölz-Wolfratshausen	12.73	0.06	0.01	low
9174	DE217	LK Dachau	15.25	0.07	0.02	low
9175	DE218	LK Ebersberg	15.11	0.06	0.02	low
9176	DE219	LK Eichstätt	9.94	0.05	0.01	low
9177	DE21A	LK Erding	9.60	0.06	0.01	low
9178	DE21B	LK Freising	9.67	0.05	0.00	low
9179	DE21C	LK Fürstenfeldbruck	11.99	0.08	0.03	low
9180	DE21D	LK Garmisch-Partenkirchen	6.83	0.06	0.01	low
9181	DE21E	LK Landsberg a.Lech	5.90	0.08	0.01	low
9182	DE21F	LK Miesbach	9.11	0.06	0.01	low
9183	DE21G	LK Mühldorf a.Inn	2.65	0.08	0.01	low

Kreis-kennziffer	NUTS-ID	Name	incidence rate	climatic suitability	hazard potential	hazard class
9184	DE21H	LK München	16.60	0.06	0.02	low
9185	DE21I	LK Neuburg-Schrobenhausen	4.18	0.07	0.01	low
9186	DE21J	LK Pfaffenhofen a.d.Ilm	6.40	0.06	0.00	low
9187	DE21K	LK Rosenheim	12.43	0.08	0.03	low
9188	DE21L	LK Starnberg	4.45	0.08	0.01	low
9189	DE21M	LK Traunstein	6.27	0.09	0.02	low
9190	DE21N	LK Weilheim-Schongau	8.22	0.08	0.02	low
9261	DE221	SK Landshut	15.71	0.05	0.01	low
9262	DE222	SK Passau	9.79	0.15	0.07	low
9263	DE223	SK Straubing	2.12	0.05	0.00	low
9271	DE224	LK Deggendorf	6.80	0.09	0.02	low
9272	DE225	LK Freyung-Grafenau	3.84	0.06	0.00	low
9273	DE226	LK Kelheim	4.17	0.05	0.00	low
9274	DE227	LK Landshut	8.36	0.06	0.01	low
9275	DE228	LK Passau	3.71	0.13	0.02	low
9276	DE229	LK Regen	5.18	0.06	0.00	low
9277	DE22A	LK Rottal-Inn	5.85	0.11	0.02	low
9278	DE22B	LK Straubing-Bogen	2.02	0.05	0.00	low
9279	DE22C	LK Dingolfing-Landau	7.37	0.08	0.02	low
9361	DE231	SK Amberg	2.36	0.05	0.00	low
9362	DE232	SK Regensburg	14.80	0.05	0.01	low
9363	DE233	SK Weiden i.d.OPf.	7.06	0.05	0.00	low
9371	DE234	LK Amberg-Sulzbach	5.82	0.05	0.00	low
9372	DE235	LK Cham	4.73	0.05	0.00	low
9373	DE236	LK Neumarkt i.d.OPf.	3.80	0.05	0.00	low
9374	DE237	LK Neustadt a.d.Waldnaab	2.12	0.05	0.00	low
9375	DE238	LK Regensburg	9.97	0.05	0.00	low
9376	DE239	LK Schwandorf	6.88	0.05	0.00	low
9377	DE23A	LK Tirschenreuth	1.37	0.05	0.00	low
9461	DE241	SK Bamberg	2.64	0.07	0.00	low
9462	DE242	SK Bayreuth	6.84	0.08	0.01	low
9463	DE243	SK Coburg	2.43	0.05	0.00	low
9464	DE244	SK Hof	2.21	0.05	0.00	low
9471	DE245	LK Bamberg	3.42	0.07	0.00	low
9472	DE246	LK Bayreuth	7.70	0.06	0.01	low
9473	DE247	LK Coburg	4.61	0.05	0.00	low
9474	DE248	LK Forchheim	4.34	0.08	0.01	low
9475	DE249	LK Hof	3.13	0.05	0.00	low
9476	DE24A	LK Kronach	4.44	0.06	0.00	low
9477	DE24B	LK Kulmbach	2.78	0.07	0.00	low
9478	DE24C	LK Lichtenfels	7.50	0.06	0.00	low
9479	DE24D	LK Wunsiedel i.Fichtelgebirge	1.37	0.05	0.00	low
9561	DE251	SK Ansbach	4.82	0.06	0.00	low
9562	DE252	SK Erlangen	14.51	0.10	0.05	low
9563	DE253	SK Fürth	10.37	0.10	0.04	low
9564	DE254	SK Nürnberg	8.40	0.10	0.03	low
9565	DE255	SK Schwabach	4.91	0.10	0.02	low
9571	DE256	LK Ansbach	7.14	0.06	0.01	low
9572	DE257	LK Erlangen-Höchstadt	7.43	0.10	0.03	low

Kreis-kennziffer	NUTS-ID	Name	incidence rate	climatic suitability	hazard potential	hazard class
9573	DE258	LK Fürth	9.49	0.10	0.03	low
9574	DE259	LK Nürnberger Land	3.55	0.07	0.01	low
9575	DE25A	LK Neustadt a.d. Aisch-Bad Windsheim	7.05	0.09	0.02	low
9576	DE25B	LK Roth	0.80	0.07	0.00	low
9577	DE25C	LK Weißenburg-Gunzenhausen	5.32	0.06	0.00	low
9661	DE261	SK Aschaffenburg	7.23	0.20	0.08	low
9662	DE262	SK Schweinfurt	3.79	0.09	0.01	low
9663	DE263	SK Würzburg	13.49	0.10	0.05	low
9671	DE264	LK Aschaffenburg	9.22	0.16	0.07	low
9672	DE265	LK Bad Kissingen	4.85	0.07	0.01	low
9673	DE266	LK Rhön-Grabfeld	8.77	0.06	0.01	low
9674	DE267	LK Haßberge	4.74	0.06	0.01	low
9675	DE268	LK Kitzingen	8.91	0.09	0.03	low
9676	DE269	LK Miltenberg	5.45	0.17	0.05	low
9677	DE26A	LK Main-Spessart	7.13	0.11	0.03	low
9678	DE26B	LK Schweinfurt	3.48	0.08	0.01	low
9679	DE26C	LK Würzburg	11.80	0.10	0.04	low
9761	DE271	SK Augsburg	9.67	0.08	0.02	low
9762	DE272	SK Kaufbeuren	4.64	0.06	0.00	low
9763	DE273	SK Kempten	7.40	0.06	0.01	low
9764	DE274	SK Memmingen	2.31	0.07	0.00	low
9771	DE275	LK Aichach-Friedberg	6.85	0.07	0.01	low
9772	DE276	LK Augsburg	5.25	0.07	0.01	low
9773	DE277	LK Dillingen a.d.Donau	3.17	0.08	0.01	low
9774	DE278	LK Günzburg	6.48	0.07	0.01	low
9775	DE279	LK Neu-Ulm	11.11	0.06	0.01	low
9776	DE27A	LK Lindau	17.29	0.11	0.08	low
9777	DE27B	LK Ostallgäu	13.02	0.06	0.01	low
9778	DE27C	LK Unterallgäu	2.13	0.07	0.00	low
9779	DE27D	LK Donau-Ries	6.05	0.06	0.01	low
9780	DE27E	LK Oberallgäu	8.45	0.06	0.01	low
10041	DEC01	LK Stadtverband Saarbrücken	2.73	0.25	0.04	low
10042	DEC02	LK Merzig-Wadern	1.92	0.19	0.02	low
10043	DEC03	LK Neunkirchen	2.99	0.11	0.01	low
10044	DEC04	LK Saarlouis	2.54	0.29	0.04	low
10045	DEC05	LK Saar-Pfalz-Kreis	2.08	0.13	0.01	low
10046	DEC06	LK Sankt Wendel	5.65	0.10	0.02	low
11000	DE300	SK Berlin	14.29	0.08	0.04	low
12051	DE401	SK Brandenburg a.d.Havel	4.19	0.08	0.01	low
12052	DE402	SK Cottbus	1.00	0.08	0.00	low
12053	DE403	SK Frankfurt (Oder)	1.72	0.05	0.00	low
12054	DE404	SK Potsdam	9.31	0.09	0.03	low
12060	DE405	LK Barnim	3.90	0.08	0.01	low
12061	DE406	LK Dahme-Spreewald	4.82	0.08	0.01	low
12062	DE407	LK Elbe-Elster	1.92	0.08	0.00	low
12063	DE408	LK Havelland	5.64	0.08	0.01	low
12064	DE409	LK Märkisch-Oderland	2.09	0.06	0.00	low
12065	DE40A	LK Oberhavel	4.31	0.08	0.01	low

Kreis-kennziffer	NUTS-ID	Name	incidence rate	climatic suitability	hazard potential	hazard class
12066	DE40B	LK Oberspreewald-Lausitz	1.79	0.08	0.00	low
12067	DE40C	LK Oder-Spree	2.80	0.07	0.00	low
12068	DE40D	LK Ostprignitz-Ruppin	3.02	0.07	0.01	low
12069	DE40E	LK Potsdam-Mittelmark	3.77	0.09	0.01	low
12070	DE40F	LK Prignitz	0.00	0.07	0.00	low
12071	DE40G	LK Spree-Neiße	5.14	0.07	0.01	low
12072	DE40H	LK Teltow-Fläming	4.25	0.09	0.01	low
12073	DE40I	LK Uckermark	3.31	0.07	0.01	low
13003	DE803	SK Rostock	5.78	0.06	0.01	low
13004	DE804	SK Schwerin	6.27	0.07	0.01	low
13071	DE80J	LK Mecklenburgische Seenplatte	3.06	0.06	0.00	low
13072	DE80K	LK Rostock	2.80	0.06	0.00	low
13073	DE80L	LK Vorpommern–Rügen	2.22	0.06	0.00	low
13074	DE80M	LK Nordwestmecklenburg	1.91	0.07	0.00	low
13075	DE80N	LK Vorpommern–Greifswald	3.79	0.07	0.01	low
13076	DE80O	LK Ludwigslust–Parchim	1.41	0.07	0.00	low
14511	DED41	SK Chemnitz	3.25	0.05	0.00	low
14521	DED42	LK Erzgebirgskreis	2.32	0.05	0.00	low
14522	DED43	LK Mittelsachsen	0.64	0.06	0.00	low
14523	DED44	LK Vogtlandkreis	6.06	0.05	0.00	low
14524	DED45	LK Zwickau	3.42	0.06	0.00	low
14612	DED21	SK Dresden	6.58	0.07	0.01	low
14625	DED2C	LK Bautzen	2.95	0.07	0.00	low
14626	DED2D	LK Görlitz	0.77	0.06	0.00	low
14627	DED2E	LK Meißen	1.23	0.08	0.00	low
14628	DED2F	LK Sächsische Schweiz-Osterzgebirge	0.81	0.05	0.00	low
14713	DED51	SK Leipzig	8.05	0.08	0.02	low
14729	DED52	LK Leipzig	2.71	0.08	0.01	low
14730	DED53	LK Nordsachsen	2.52	0.08	0.01	low
15001	DEE01	SK Dessau-Roßlau	2.42	0.08	0.01	low
15002	DEE02	SK Halle	3.36	0.08	0.01	low
15003	DEE03	SK Magdeburg	4.62	0.09	0.01	low
15081	DEE04	LK Altmarkkreis Salzwedel	0.00	0.09	0.00	low
15082	DEE05	LK Anhalt-Bitterfeld	1.23	0.08	0.00	low
15083	DEE07	LK Börde	0.58	0.08	0.00	low
15084	DEE08	LK Burgenlandkreis	2.73	0.07	0.00	low
15085	DEE09	LK Harz	1.37	0.07	0.00	low
15086	DEE06	LK Jerichower Land	0.00	0.08	0.00	low
15087	DEE0A	LK Mansfeld-Südharz	2.15	0.07	0.00	low
15088	DEE0B	LK Saalekreis	2.69	0.08	0.01	low
15089	DEE0C	LK Salzlandkreis	2.57	0.08	0.01	low
15090	DEE0D	LK Stendal	2.62	0.09	0.01	low
15091	DEE0E	LK Wittenberg	3.92	0.08	0.01	low
16051	DEG01	SK Erfurt	2.37	0.06	0.00	low
16052	DEG02	SK Gera	4.22	0.06	0.00	low
16053	DEG03	SK Jena	6.35	0.07	0.01	low
16054	DEG04	SK Suhl	5.62	0.05	0.00	low
16055	DEG05	SK Weimar	4.66	0.06	0.00	low

Kreis-kennziffer	NUTS-ID	Name	incidence rate	climatic suitability	hazard potential	hazard class
16056	DEG0N	SK Eisenach	0.00	0.07	0.00	low
16061	DEG06	LK Eichsfeld	0.99	0.08	0.00	low
16062	DEG07	LK Nordhausen	1.18	0.07	0.00	low
16063	DEG0P	LK Wartburgkreis	4.81	0.06	0.01	low
16064	DEG09	LK Unstrut-Hainich-Kreis	3.85	0.07	0.01	low
16065	DEG0A	LK Kyffhäuserkreis	7.82	0.07	0.01	low
16066	DEG0B	LK Schmalkalden-Meiningen	2.43	0.06	0.00	low
16067	DEG0C	LK Gotha	3.69	0.06	0.00	low
16068	DEG0D	LK Sömmerda	4.28	0.07	0.01	low
16069	DEG0E	LK Hildburghausen	3.11	0.05	0.00	low
16070	DEG0F	LK Ilm-Kreis	5.50	0.05	0.00	low
16071	DEG0G	LK Weimarer Land	2.43	0.06	0.00	low
16072	DEG0H	LK Sonneberg	5.31	0.05	0.00	low
16073	DEG0I	LK Saalfeld-Rudolstadt	4.62	0.06	0.00	low
16074	DEG0J	LK Saale-Holzland-Kreis	4.73	0.06	0.01	low
16075	DEG0K	LK Saale-Orla-Kreis	4.86	0.06	0.00	low
16076	DEG0L	LK Greiz	2.01	0.06	0.00	low
16077	DEG0M	LK Altenburger Land	5.46	0.07	0.01	low

Manuscript 3: Extrinsic incubation period of dengue: knowledge, backlog, and applications of temperature dependence

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Background

Dengue is generally believed to be one of the most hazardous vector-borne diseases, with over 40% of the world's population at risk of an infection [1]. While in the past the disease has mainly been observed in the tropical regions, recent studies suggest that, under the pressure of future climate change, new areas as far north as Europe may become endangered. In fact, in 2010 the first European cases of autochthonous dengue since the epidemic outbreak in Greece in the late 1920s [2] were reported from Croatia [3] and France [4]. Recently, Madeira experienced a severe epidemic of dengue fever, with about 2,000 cases within two months [5].

When it comes to determining the risk of dengue occurring in a given region, the extrinsic incubation period (EIP) plays an important role. The EIP is commonly defined as "the interval between the acquisition of an infectious agent by a vector and the vector's ability to transmit the agent to other susceptible vertebrate hosts" [6]. In the case of dengue, after the virus is ingested by a mosquito through a blood meal, some time is required for the virus to replicate, escape the midgut, and spread through the mosquito's body

until it ultimately reaches the salivary glands (SG), from where it can be passed on to another host during the next blood meal.

For dengue, the duration of the pathogen's EIP is known to be temperature-dependent, but very few mechanistic risk models (usually based on the basic reproductive number R_0, i.e., the number of secondary cases produced by one primary case in a completely susceptible population [7]) have taken that into account until now. In fact, most of the models implemented for dengue use fixed values for the duration of the EIP or rather rough estimates of temperature dependence [8].

This may be due to the fact that experimental studies on this topic are rare, and their results may appear to some extent inconsistent or even contradictory. However, the implementation of a realistic, temperature-dependent EIP will greatly improve mechanistic dengue modeling: since EIP appears as an exponent in the equations used for the determination of R_0 and vector capacity [7, 9, 10], even small changes in EIP can have a large impact on the results of mechanistic dengue models that build on the concept of R_0. The practical relevance of this issue has been demonstrated for dengue [9] as well as other vector-borne diseases such as malaria [11] and bluetongue [12].

In addition, correlative models based on environmental factors and vector distributions (also referred to as "climate envelope models" or "environmental niche models") have to be revised and enhanced. Currently, these models usually focus on the spatial distribution of vector species. But if temperatures do not support amplification and establishment of the virus even though the vector is present, risk assessment based solely on vector distributions leads to an overestimation of areas at risk. Combining such models with information on temperature requirements for the virus derived from the EIP can reduce uncertainty [13].

Here, we give a short overview of the few experimental studies that are explicitly addressing the temperature dependence of the EIP of dengue. We analyze the implications of these studies and discuss current uncertainties in

modeling dengue risk in face of climate change. We identify methodological challenges and formulate suggestions for the design of future studies from a spatio-ecological point of view.

What has been done so far?

In order to assess current knowledge about the temperature dependence of the EIP of dengue, we conducted an extensive literature search, using the Thomson Reuters Web of Knowledge research portal (which includes the databases Web of Science, BIOSIS, Current Contents Connect, MEDLINE, and Journal Citation Reports) as well as Google Scholar and Google Books. Search terms were built from all possible combinations of the keywords "dengue," "DENV," "extrinsic," "EIP," "incubation period," and "temperature." Journal articles and books that were found to provide secondary information on the topic were scanned for references to experimental studies, and a forward and reverse literature search was performed for experimental studies.

We found five experimental studies that explicitly addressed the temperature dependence of the EIP of dengue. The first one was carried out by Blanc and Caminopetros in Greece during the winter of 1928–1929 [14]. This was followed by two publications by McLean et al. in the mid-1970s [15, 16] and another article by Watts et al. in 1987 [17]. Rohani et al. revived the topic in 2009 [18]. In addition to these works, we include two further studies in the dataset that examine the duration of the EIP at a single, fixed temperature: Salazar et al. [19] studied the spread of dengue virus within the body of *Aedes aegypti* at 28 °C, and Anderson and Rico-Hesse [20] examined the effect of viral genotype on the vector capacity of *A. aegypti* at 30 °C.

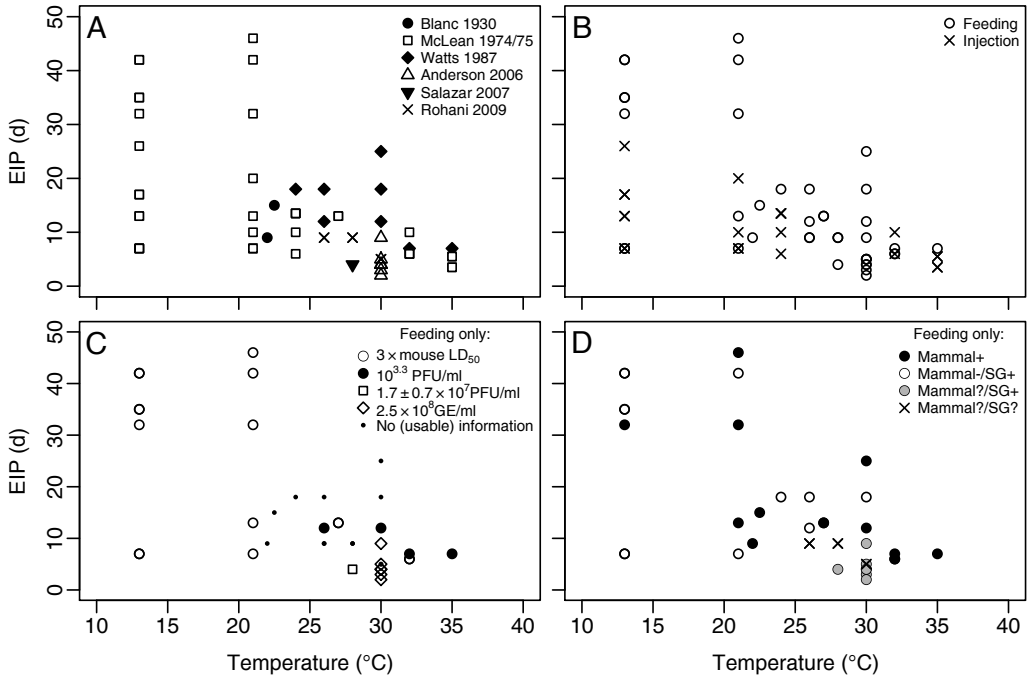

Figure 1. Overview of the available data for the temperature dependence of the EIP of dengue. Each point represents the duration until the first observed transmission or infection of SG at a given temperature in a single experiment. (A) Complete dataset, divided by study. (B) Complete dataset, divided by method used to infect the mosquitoes: results obtained by letting mosquitoes feed on infected mammals or artificial blood meals versus results obtained via intrathoracic injection of virus solution. (C) Data from mosquitoes infected via feeding, divided by the amount of virus ingested by mosquitoes. GE, genome equivalents; LD50, mean lethal dose; PFU, plaque forming units. (D) Data from mosquitoes infected via feeding, divided by method of demonstration of transmission. Black circles: Transmission was demonstrated by allowing infected mosquitoes to feed on mammals. White circles: Tests on mammals yielded negative results, but SG contained virus. Grey circles: Tests on mammals were not done, but SG contained virus. Xs: Neither transmission to mammals nor SG were tested.

All experiments have in common that they examined the EIP of dengue virus type 2 in *A. aegypti*, with the exception of Blanc and Caminopetros, who did not provide information about the serotype examined (retrospective studies suggest dengue virus types 1 and 2 occurred during the Greece epidemic [21]), and Rohani et al., who additionally examined dengue virus type 4. However, the experimental approaches vary considerably in many respects within and

between the studies. An overview of the durations of the EIP as observed by the different studies is given in Figure 1A; a detailed list can be found in Table S1.

Differences start with the study material used: the provenance of the mosquitoes used ranges from recently captured wild animals [14] to colonies that had been held in the laboratory for more than 30 years [18]. Since populations that have been held in the laboratory for a longer time may develop adaptions to the artificial environment, field-relevant mosquitoes are preferred for determining EIP, in order to yield results that reflect natural processes as closely as possible [19]. This is also true for viruses that have been maintained in the laboratory for longer periods [19]. Additionally, it is highly important to cover the whole range of genetic variations that occur in nature, since it has been demonstrated that different genotypes or strains of the dengue virus can show significant differences regarding their EIP [10, 15, 20].

Moreover, differences in experimental techniques for infecting the mosquitoes became obvious: while intrathoracic injection of virus solution provides the opportunity to exactly determine the amount of virus a mosquito receives, it bypasses the midgut infection and escape barriers. This drastically shortens the EIP [15, 22], leading to overestimation in the process of risk assessment. In the case of dengue, this problem affects about 60% of the data points by McLean et al. [15, 16] (Figure 1B). Hence, we strongly suggest the use of more natural and realistic feeding techniques that use viremic vertebrates or artificial blood meals.

Since the duration of the EIP also depends on the amount of virus ingested during the blood meal, ideally the complete range of virus titers observed in vertebrate hosts in nature should be considered. The methods and units used for determining and presenting the amount of virus differ across the experiments, making it difficult to conduct an adequate comparison (see Figure 1C for an overview and Table S1 for the details). While a consistent methodology would surely help to make the results of such experiments more comparable and more accessible for scientists from other fields, in our eyes the

most important issue is to make sure that future experiments resemble nature as closely as possible.

Furthermore, the method used to test the ability of an infected mosquito to transmit the virus should be chosen carefully. Allowing the mosquito to take a second blood meal from uninfected mammals such as mice [15, 16], monkeys [17], or even humans [14], and then monitoring the mammals for dengue symptoms or virus content may seem desirable, since it gives rather clear evidence of transmission. However, because of ethical as well as logistical restraints, in most cases this cannot be considered as an option anymore today. Consequently, other methods have been developed that focus on the detection of virus content in the SG of the mosquito. While it is generally assumed that transmission can occur as soon as the SG are infected, the literature provides some cases where the SG tested positive for virus content but additional transmission tests with mammals gave negative results [15–17]. A possible explanation for this may be the existence of a "salivary gland escape barrier," which has been shown to exist for other viruses [23] but which is considered controversial for dengue [24]. However, new techniques exist that circumvent this potential problem by causing mosquitoes to spill their saliva, which can then be assayed for virus content [22]. Equally, methods that use complete heads or even full bodies to extract virus RNA are not suitable for the assessment of the EIP. The latter method was used by Rohani et al. [18], unfortunately making their data unsuitable for real-life modeling approaches even though the data seem to be consistent with the rest of the dataset. An overview of the implications of this issue for the dataset is presented in Figure 1D; additional details are given in Table S1.

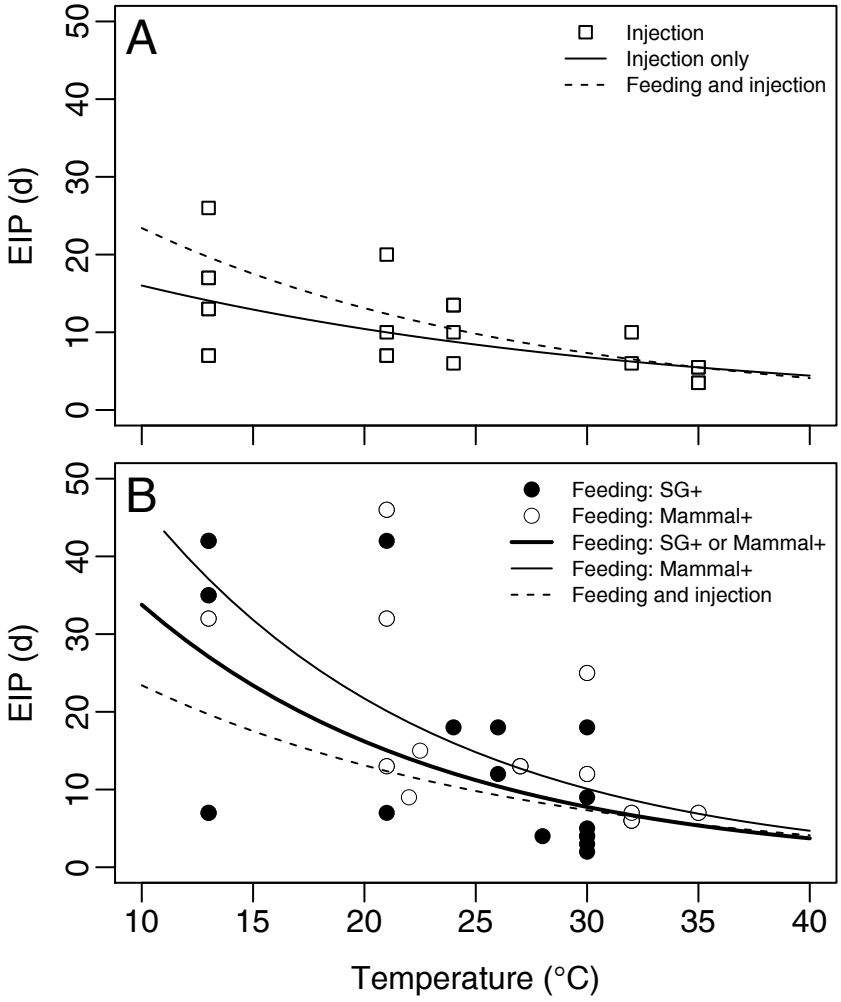

Figure 2. Estimated temperature dependence of the EIP of dengue based on the dataset used. Each point represents the duration until the first observed transmission or infection of SG at a given temperature in a single experiment. Estimation was done via a simple linear model in R 2.14.1 [31], using log-transformed values of the duration of the EIP. (A) Results obtained from experiments with mosquitoes infected via intrathoracic injection; the solid line depicts the linear model for those data (adjusted $R^2 = 0.40$, $p < 0.001$). (B) Results obtained from experiments with mosquitoes infected via feeding. Filled circles: SG tested positive for virus content, but transmission to mammals was either negative or not tested. Unfilled circles: Transmission to mammals was observed. Thick solid line: Linear model for cases where either transmission to mammals was observed or SG tested positive for virus content (adjusted $R^2 = 0.34$, $p < 0.001$). Thin solid line: Linear model for cases where transmission to mammals was observed (adjusted $R^2 = 0.46$, $p < 0.01$) For better comparability, in both panels the dashed line shows the linear model for all data (injection as well as feeding) combined (adjusted $R^2 = 0.32$, $p < 0.00001$).

Careful preprocessing is crucial in order to gain meaningful results from the data that are currently available. First, experimental results that were obtained using intrathoracic injection to infect mosquitoes should be discarded, since their inclusion would lead to underestimation of the EIP and thus overestimation of areas at risk (Figure 2A). Then, data points for which verification of transmission does not exist by either examination of vertebrates bitten during a second blood meal or by examination of the SG should be discarded, too. Whether one wants to include data points for which transmission was verified only via examination of the SG may depend on the context the data are being used in: Figure 2B shows that the inclusion of these points in general leads to a shorter mean EIP, particularly at the lower end of the temperature range. Hence, risk maps based on a dataset that includes those points may overestimate the threat in regions with lower temperatures—which from an ethical point of view would be preferable to the underestimation that would probably result from the exclusion of those data. Additionally, data obtained from experiments at low temperatures (<20 °C) are especially scarce, so that further reduction must be carefully weighed for statistical reasons.

Design of future experiments with respect to interdisciplinary research

Apart from the specific problems that arose in analyzing the experiments that have been done so far, there are some other things that might be worth considering when it comes to planning future works. Because the EIP varies between single mosquitoes, usually a batch of mosquitoes is examined for each time point during the experiment. The EIP can then be estimated as the period of time between the infectious blood meal and the point in time when (1) for the first time at least one mosquito of the batch is able to transmit the virus, (2) a given fraction (typically 50%) of the mosquitoes are transmitting, or (3) all mosquitoes are transmitting. A more advanced approach has been applied by Paaijmans et al. [25] that considers the fact that even after long incubation periods not all mosquitoes of a batch are able to transmit the virus. Here, we

decided to use the time until the first observed occurrence of transmission or infection of the SG for the data shown in Figures 1 and 2 for two reasons. First, this is the most conservative approach, as it utilizes the shortest possible EIP and hence is unlikely to underestimate risk. Second, in some cases batches consisted of only five or fewer mosquitoes [15–17], which is too few to derive statistically meaningful fractions. In order to facilitate the application of advanced statistical methods, this issue should be taken into account during the design of future experiments: in our opinion, batches of 20 to 30 mosquitoes, as used by Salazar et al. [19] and Paaijmans et al. [25], are desirable.

Another important issue to note is that past laboratory studies usually held temperatures constant over the whole experiment. This neglects the fact that in nature diurnal temperature is far from constant. Recent studies imply that diurnal fluctuations in temperature may play a more decisive role for pathogen amplification than previously thought [26, 27]. Including thermal fluctuations in future experiments and comparing the results with those from identical experiments with constant temperatures may prove rewarding.

Furthermore, not only the current main vector of dengue, *A. aegypti*, deserves attention: *A. albopictus* has undergone a vast global spread over the last decades [28] and is being considered as serving as a potential future main vector of dengue in Europe [29]. Until recently, knowledge about the EIP of dengue for *A. albopictus* was scarce and was mentioned only in a side note in the study by McLean et al. stating that "comparable results were obtained with […] *A. albopictus* mosquitoes" [16]. In 2012, Richards et al. compared the vector competence of *A. albopictus* and *A. aegypti* for dengue at different temperatures [30]. Even though the duration of the EIP was not explicitly examined (a fixed incubation period of 14 days was used), this study can be regarded as a step in the right direction, since experiments focusing on *A. albopictus* are urgently needed.

In conclusion, further studies on the EIP of dengue based on experiments with modern methodology and adequately high resolution in time and

temperature may facilitate risk assessment by improving mechanistic as well as correlative modeling approaches. Since the lack of knowledge on the temperature dependence of the EIP seems to be even bigger when it comes to other arthropod-borne viral diseases such as Chikungunya, the identified challenges and suggestions may turn out to be of relevance beyond the example of dengue.

Copyright

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Competing interests

The authors have declared that no competing interests exist.

Supporting information

Table S1. Summary of the data obtained from the literature. This table provides information about the different experimental studies, including study material used and methodological details. The duration until the first observed transmission or infection of SG at a given temperature is given for each study. https://doi.org/10.1371/journal.pntd.0002207.s001 (XLS)

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Appendix: Supporting information

Table S1. Summary of the data obtained from the literature. This table provides information about the different experimental studies, including study material used and methodological details. The duration until the first observed transmission or infection of SG at a given temperature is given for each study. Adopted for print, the original .xls-file can be accessed via https://doi.org/10.1371/journal.pntd.0002207.s001

Study	Mosquito source	Amount of virus ingested by or injected into mosquitoes	Mosquito infection pathway	Feeding: source	Feeding: host/blood source	Dengue type	Dengue genotype	Dengue strain	Temperature (°C)	EIP	salivary glands positive	transmission to mammals	Mammals used for confirming transmission
Blanc 1930	captured in Athens	NA	feeding	infected animal	human	NA	NA	NA	22	9	not tested	yes	human
	raised in the lab								22.5	15			
McLean 1974	lab colony at British Columbia Research Council lab	3 × LD50 (mouse)	feeding	artificial blood meal	sheep	DEN-2	NA	NC-6	32	6	yes	yes	suckling mice
									27	13			
									13	35		no	
								40173	32	6		yes	
									27	13			
									13	35		no	

Study	Mosquito source	Amount of virus ingested by or injected into mosquitoes	Mosquito infection pathway	Feeding: source	Feeding: host/blood source	Dengue type	Dengue genotype	Dengue strain	Temperature (°C)	EIP	salivary glands positive	transmission to mammals	Mammals used for confirming transmission
			intrathoracic injection	NA	NA			193-72	24	13–14		yes	
									13	13		no	
									35	5–6			
								40173	13	25–27		yes	
									24	13–14			
									32	10		no	
									35	3–4			
								NC-6	13	13		yes	
									24	6			
									24	13–14			
									32	6			
								PR-159	13	17		no	

Study	Mosquito source	Amount of virus ingested by or injected into mosquitoes	Mosquito infection pathway	Feeding: source	Feeding: host/blood source	Dengue type	Dengue genotype	Dengue strain	Temperature (°C)	EIP	salivary glands positive	transmission to mammals	Mammals used for confirming transmission
									24	10		yes	
									35	5–6			
									35	3–4		no	
McLean 1975	lab colony at British Columbia Research Council lab	3 × LD_{50} (mouse)	feeding	infected animal	suckling mice	DEN-2	NA	NC-6	13	32	yes	yes	suckling mice
									13	42		no	
									21	46		yes	
									21	32			
								PR-159	13	42		no	
									13	7			
									13	7			
									21	13		yes	

Study	Mosquito source	Amount of virus ingested by or injected into mosquitoes	Mosquito infection pathway	Feeding: source	Feeding: host/blood source	Dengue type	Dengue genotype	Dengue strain	Temperature (°C)	EIP	salivary glands positive	transmission to mammals	Mammals used for confirming transmission
									21	42		no	
									21	7			
			intrathoracic injection	NA	NA				13	17			
									13	7			
									13	7			
									21	10		yes	
									21	7		no	
									21	20		yes	
									21	7		no	
Watts 1987	collected in Bangkok (F2 progeny)	$10^{3.3}$ PFU/ml blood	feeding	infected animal	rhesus monkey	DEN-2	NA	NA	26	12	yes	no	rhesus monkey
									30	12			
									32	7			

Study	Mosquito source	Amount of virus ingested by or injected into mosquitoes	Mosquito infection pathway	Feeding: source	Feeding: host/blood source	Dengue type	Dengue genotype	Dengue strain	Temperature (°C)	EIP	salivary glands positive	transmission to mammals	Mammals used for confirming transmission
									35	7			
		NA							30	25		yes	
									24	18			
									26	18			
									30	18			
Anderson 2006	McAllen (Texas) strain (F4)	2.5×10^8 genome equiva-lents per ml blood	feeding	artificial blood meal	rabbit	DEN-2	Southeast Asian	CO489	30	3	yes	not tested	NA
								K0049		4			
								Mara3		2			
							American	IQT2913		5			
								131		9			
								Ven2		4			

Study	Mosquito source	Amount of virus ingested by or injected into mosquitoes	Mosquito infection pathway	Feeding: source	Feeding: host/blood source	Dengue type	Dengue genotype	Dengue strain	Temperature (°C)	EIP	salivary glands positive	transmission to mammals	Mammals used for confirming transmission
Salazar 2007	new lab colony (F3-F6) established with specimens from Yucatan	$1.7 \pm 0.7 \times 10^7$ PFU/ml	feeding	artificial blood meal	sheep	DEN-2	NA	NA	28	4	yes	not tested	NA
Rohani2009	lab colony(> 30 years old)	100µl virus solution in 1ml blood	feeding	artificial blood meal	human	DEN-2	NA	NA	26	9	not tested	not tested	NA
									28	9			
									30	5			
									26	9			
									28	9			
									30	5			

Manuscript 4: Evaluating the risk for Usutu virus circulation in Europe: comparison of environmental niche models and epidemiological models

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Abstract

Background

Usutu virus (USUV) is a mosquito-borne *flavivirus*, reported in many countries of Africa and Europe, with an increasing spatial distribution and host range. Recent outbreaks leading to regional declines of European common blackbird (*Turdus merula*) populations and a rising number of human cases emphasize the need for increased awareness and spatial risk assessment.

Methods

Modelling approaches in ecology and epidemiology differ substantially in their algorithms, potentially resulting in diverging model outputs. Therefore, we implemented a parallel approach incorporating two commonly applied modelling techniques: (1) Maxent, a correlation-based environmental niche model and (2) a mechanistic epidemiological susceptible-exposed-infected-removed (SEIR) model.

Across Europe, surveillance data of USUV-positive birds from 2003 to 2016 was acquired to train the environmental niche model and to serve as test cases for the SEIR model. The SEIR model is mainly driven by daily mean temperature and calculates the basic reproduction number R_0. The environmental niche model was run with long-term bio-climatic variables derived from the same source in order to estimate climatic suitability.

Results

Large areas across Europe are currently suitable for USUV transmission. Both models show patterns of high risk for USUV in parts of France, in the Pannonian Basin as well as northern Italy. The environmental niche model depicts the current situation better, but with USUV still being in an invasive stage there is a chance for under-estimation of risk. Areas where transmission occurred are mostly predicted correctly by the SEIR model, but it mostly fails to resolve the temporal dynamics of USUV events. High R_0 values predicted by the SEIR model in areas without evidence for real-life transmission suggest that it may tend towards over-estimation of risk.

Conclusions

The results from our parallel-model approach highlight that relying on a single model for assessing vector-borne disease risk may lead to incomplete conclusions. Utilizing different modelling approaches is thus crucial for risk-assessment of under-studied emerging pathogens like USUV.

Background

Vector-borne diseases (VBDs) are of growing importance. Due to global transport, long-distance travel, population growth, environmental and climatic changes, VBDs are emerging all over the world [1–4]. In addition to human-mediated spread, mobile species such as migratory birds are promoting long-distance transport of pathogens [5]. If the local conditions at the introduction sites (e.g. hosts, vectors, and climate) are suitable, the pathogen can establish and evolve quickly, resulting in rapid local spread [6]. Usutu virus (USUV) is an example where both processes resulted in the recent arrival and spread of a zoonotic mosquito-borne virus in Europe [5].

USUV is a *flavivirus* [7] belonging to the Japanese encephalitis virus serocomplex [8]. As a member of the family Flaviviridae, USUV is a single-stranded RNA virus closely related to Murray Valley encephalitis virus, Japanese encephalitis virus, and West Nile virus (WNV) [8]. It was first isolated in 1959 from *Culex neavei* mosquitoes in Swaziland and named after the Usutu river [7]. Its most important vectors are mosquito species of the genus *Culex* [9]. Since the first record, USUV has been reported for several African countries (e.g. Senegal, Central African Republic, Nigeria, Uganda) and detected in mosquitoes, birds, and humans [10]. In Europe USUV has been detected in 15 countries, with increasing spatial distribution and host range [9, 11–15] (Fig. 1). The earliest evidence of USUV in Europe came from a dead common blackbird (*Turdus merula*) found in Italy in 1996, although this case was not identified as such until 2013 [16]. The first USUV epidemic in Europe was a series of dead common blackbirds reported from Austria in 2001 [17]. In the subsequent years, USUV was reported in further European countries. USUV or corresponding antibodies were detected in horses, bats, dogs [11, 18, 19], and at least 58 bird species, with common blackbirds as dominant avian host [14].

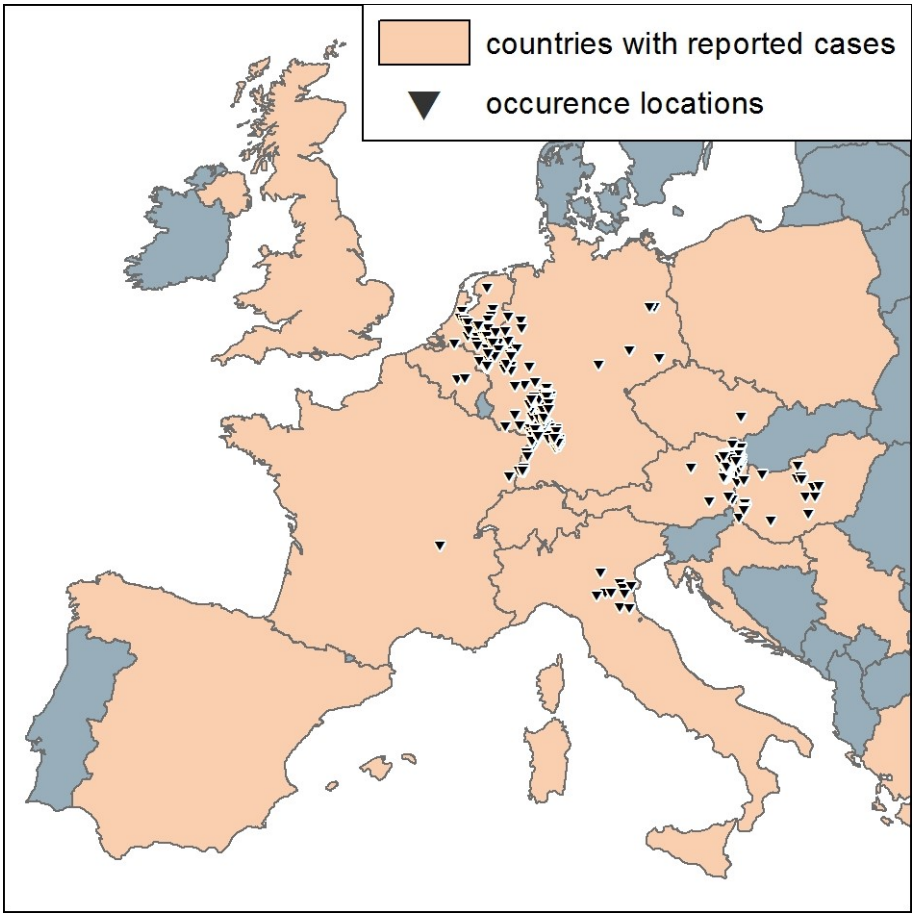

Fig. 1 USUV in Europe. Orange areas: European countries where cases of USUV have been reported, regardless of species and method of confirmation. Triangles: Spatially explicit records of USUV occurrence 2003–2016 before spatial rarefication. These are locations where individual USUV-positive dead birds have been found, confirmed by reverse transcription polymerase chain reaction (RT-PCR).

In 2009, the first human case of USUV infection in Europe was reported in Italy [20], followed by further human cases in Germany [21, 22], Croatia [23], Austria [24], and France [25]. Human cases are commonly characterized by mild symptoms including fever, rash, jaundice, headache, nuchal rigidity, hand tremor and hyperreflexia [20, 23, 26, 27]. However, at least in immunosuppressed patients USUV can cause a neuro-invasive infection [20], and it has recently been suspected to have caused idiopathic facial paralysis [25]. In addition to that, USUV infections were also detected from blood donors and healthy forestry workers in Germany and Italy [21, 22, 28], suggesting that asymptomatic infections can occur among humans. Recent data from Italy

indicate that human USUV infections may not be a sporadic event and can even be more frequent than WNV infections in areas where both viruses co-circulate [9, 29, 30]. Furthermore, due to cross reactions in antibody tests, the number of human USUV cases may be underestimated through confusion with other flaviviruses [26]. As a consequence, the actual distribution of USUV and associated number of cases is likely to be larger than currently known [31].

The transmission cycle with birds as enzootic hosts creates a complex setting related to the risk for human health. First, migratory birds may transport the pathogen over large distances and can cause repeated re-introduction of the virus into a specific region that is not appropriate to maintain an outlasting population of the pathogen [5]. Second, common blackbirds are the predominant host [9, 14]. This species is very common across Europe and has grown accustomed to urban habitats, exhibiting high population densities in human settlements [32]. This means that vectors only need to cover short spatial distances between infected birds and humans—and the widespread mosquito species *Cx. pipiens* is a known bridge vector between mammals, birds and humans [33, 34]. In consequence, USUV is becoming an increasing threat for Europe as a mosquito-borne and zoonotic disease. Measures should be undertaken to improve or even create awareness towards zoonotic VBDs. For this purpose, spatial representations of risk are needed.

Models for vector borne viral diseases can be generated at various spatial and temporal scales [35]. Maps of vector occurrence or disease transmission risk derived from them can be used to direct vector surveillance and control programs as well as to inform public health officials, medicine practitioners and the general public about potential risks. Current approaches can be divided into two basic groups: correlative models (e.g. environmental niche models) and process-based models (e.g. epidemiological models). Both types of models have their own strengths and weaknesses [35]. Correlative environmental niche models, on the one hand, typically utilize species occurrence records and environmental predictor variables to estimate the current and future potential

spatial distribution of a target species [36] or disease [37–42]. They do not require a priori knowledge about the specific effects single variables have, and are typically used on coarser spatio-temporal scales [35]. Process-based epidemiological models, on the other hand, aim to simulate the entire transmission process. Using knowledge gained from laboratory experiments or field observations, they require a deeper understanding of disease dynamics. As all models for VBD have their individual strengths and weaknesses, it is best practice not to rely on a single approach, but draw a conclusion from a consensus of multiple different models [35]. Although both model categories are widely used when modeling VBDs [35], comparisons of different models' outputs are typically made within those categories (e.g. [43]), and a comparison across categories is still missing.

To date only a limited number of USUV models for spatially confined areas exist. Based on an epidemiological model for WNV, Rubel et al. [44] developed a mechanistic susceptible-exposed-infected-removed (SEIR) model for USUV in Vienna (Austria) [44–46], which was later successfully applied to Germany and neighboring countries [47]. This model is mainly driven by daily mean temperature, and to enable the comparison of modeled bird deaths and observed bird deaths, it was originally carried out with interpolated monthly mean temperature values so as to achieve the same temporal resolution as the available bird death data [44]. A different, environmental niche model-based approach was followed by Lühken et al. [31], who adopted boosted regression trees to assess the spatio-temporal risk for USUV in Germany by estimating the risk in each grid cell.

Here we present, for the first time, USUV risk maps covering the entirety of the European mainland. Using two models in parallel, we utilize the mechanistic SEIR model by Rubel et al. [44] as well as a newly developed environmental niche model based on the machine-learning technique Maxent. Instead of using interpolated monthly mean temperature values for a single location, rasterized daily mean temperature was used to run the SEIR model. In order to increase

comparability between the models, the same data source was also applied for the use of Maxent. Spatial risk maps were generated by both models. By using models from these two different groups, we are aiming at (1) estimating the potential risk for USUV transmission under current climate conditions in Europe and (2) investigating the differences between the outputs of two widely-used modelling approaches, which could be a first step towards interdisciplinary model comparison.

Methods

Study area and USUV occurrence records

In this study, we focus on current European occurrence records of USUV in the years of 2003–2016, from the earliest to the latest USUV cases available. The investigation area is limited by the natural coastlines, as well as through the reported USUV locations in Eastern Europe (Fig. 1).

To achieve a good data quality, only locations of USUV-positive birds confirmed by reverse transcription polymerase chain reaction (RT- PCR) were taken into account. This was done because (1) data from USUV-positive mammals or mosquitoes are collected quite unsystematic, i.e. data on USUV-positive birds are most consistent and comparable between the different European countries, and (2) other methods such as antibody analysis may not be able to distinguish USUV from other closely related flaviviruses such as WNV [48]. According to this rule, a total number of 376 USUV records was collected. USUV-positive data in Germany were collected by the German Mosquito Control Association (KABS), the Nature and Biodiversity Conservation Union (NABU), the local veterinary authorities and/or by the local state veterinary laboratories [47, 49–51]. Records for other European countries were derived from the literature (Additional file 1): Geographical coordinates published in the literature were directly entered into the database, precise site descriptions were digitized using Google Earth Pro, and high-quality occurrence maps were geo-referenced using ESRI ArcGIS 10.2.2.

Climate data

Time series of daily mean temperature data, required by the SEIR model, were acquired from the E-OBS dataset version 15.0 [52] on a regular latitude-longitude grid with a spatial resolution of 0.25° (about 20 km). E-OBS provides gridded daily temperature and precipitation data for Europe based on data from weather stations. To compare the results from the SEIR model and the environmental niche model properly, bio-climatic variables, which are required by the environmental niche model, were generated from the E-OBS dataset as well. Therefore, time series of daily minimum, maximum temperature and daily precipitation sums were acquired in addition to daily mean temperature.

Since the occurrence records for USUV cover the years of 2003–2016, these time series were trimmed accordingly. Considering that the spatial coverage of the E-OBS time series varies over time, grid cells with more than 10% missing data were excluded from our analyses. Monthly mean values were derived using the "raster" package [53] for R 3.2.1 [54] and 19 bio-climatic variables were calculated in SAGA-GIS version 2.1.4 [55] for use with the environmental niche model.

Environmental niche model: Maxent

For the environmental niche model, we used Maxent 3.3.3k [56]. Maxent is a powerful machine-learning technique that is widely used [35] to model the potential distribution of species, especially when the occurrence data are sparse [57]. Using occurrence records and environmental predictor variables as input data, Maxent generates maps of environmental suitability for transmission of USUV. Ranging between 0 for the lowest and 1 for the highest suitability, these maps can optionally be converted into presence/absence maps by applying a threshold value.

Maxent models are fitted assuming that all locations in the landscape are equally likely to be sampled. However, when the occurrence records are

collected with different methods, sampling bias is inevitable. Compared to other methods, systematic sampling, also called spatial filtering of biased records [58], has a good performance regardless of species and bias type [58, 59]. It was applied by using the *SDM tool box* [60], an addon for ESRI ArcGIS that provides advanced tools and convenience functions for the Maxent workflow. To determine an appropriate spatial filtering resolution (the minimum distance between any two locations), the following rules were taken into consideration: (1) The spatial filtering process should decrease the bias distribution, but the remaining records should still represent the observed spatial patterns well. (2) There should be enough records left to run Maxent after spatial filtering. Consequently, the spatial filtering resolution was set to 20 km (about 0.25°), and 92 USUV records left after filtering in order to achieve optimum results and to avoid artefacts (Fig. 2).

Selection of the environmental predictors for the model followed a two-step approach (Table 1). First, 8 out of the 19 bio-climatic variables that were deemed unsuitable for the task were excluded due to the following ecological reasons: BIO2 and 3 ("mean diurnal range" and "isothermality") were excluded because while daily fluctuations in temperature are important for the mosquito life cycle and transmission dynamics, the monthly averages available here were considered unsuitable for capturing such short-term fluctuations. BIO12 ("annual precipitation") was excluded because summer and winter precipitation play very different roles in this context and should be considered separately. All variables referring to the wettest/driest quarter or month of the year (BIO8, 9, 13, 14, 16, and 17) were excluded because seasonal precipitation patterns vary largely across Europe. As such, the wettest time of the year can be summer in some regions and winter in others, making this kind of variable unsuitable for larger scale analyses. The remaining eleven variables were further reduced through the built-in Jackknife feature in Maxent with a ten-fold cross-validation run, following the recommendations of Elith et al. [61]. In the end, a combination of five variables was chosen, consisting of annual mean temperature, minimum temperature of coldest month, mean temperature of

coldest quarter, precipitation seasonality, and precipitation of warmest quarter. We used default settings for Maxent (10,000 background locations, 500 iterations), but disabled the use of "threshold" and "hinge" features, that would have led to over-fitting due to an inappropriate amount of model complexity.

Maxent, like many other environmental niche model approaches, generates pseudo-absence ("background") locations to make up for the lack of field records of true absence of the target species. Careful selection of the area from which these background locations are allowed to be drawn from is an important part of model creation, as it can affect model performance and results. According to Barve et al. [62], this should be done by requiring the background locations to be within the area the species could realistically disperse to. We followed a buffer-based method [63] by setting a series of buffer radii from 0.5° to 24° (see Additional file 2), given the grid cell size of 0.25°. It is suggested to take the radius when the model performance stops increasing [63]. In addition to the built-in AUC (area under the receiver operator characteristic curve), true skill statistic (TSS) was also calculated as an indicator of model performance (Additional file 2). A radius of 12° was chosen as suggested, with the final model reaching an AUC of 0.92 and a TSS score of 0.78, both suggesting good model performance. In this model, the minimum temperature of the coldest month had the strongest contribution to the model (58%), followed by precipitation of the warmest quarter (21%) and annual mean temperature (13%). The threshold for distinguishing predicted presence and absence was based on the receiver operator characteristic (ROC), choosing the point along the ROC curve that maximized the sum of sensitivity and specificity. We chose this criterion also known as "maxSSS" because it is objective [64], widely used, performs consistently well with presence-only data [65, 66] and delivers threshold values that are relatively low [66], facilitating the high sensitivity desired in risk assessment studies.

Table 1 Excluded and selected environmental predictor variables for the environmental niche model.

Abbreviation	Variable description
Excluded – Monthly minima and maxima are not suitable to estimate daily fluctuations:	
BIO2	Mean Diurnal Range (Mean of monthly (max temp - min temp))
BIO3	Isothermality (BIO2/BIO7) × 100
Excluded – Summer and winter precipitation are important to distinguish for mosquitoes and disease transmission dynamics:	
BIO12	Annual Precipitation
Excluded – Wettest/driest time of the year can be in different seasons across Europe:	
BIO8	Mean Temperature of Wettest Quarter
BIO9	Mean Temperature of Driest Quarter
BIO13	Precipitation of Wettest Month
BIO14	Precipitation of Driest Month
BIO16	Precipitation of Wettest Quarter
BIO17	Precipitation of Driest Quarter
Excluded by jackknife:	
BIO4	Temperature Seasonality (standard deviation × 100)
BIO5	Max Temperature of Warmest Month
BIO7	Temperature Annual Range (BIO5-BIO6)
BIO10	Mean Temperature of Warmest Quarter
BIO19	Precipitation of Coldest Quarter
Model input:	
BIO1	Annual Mean Temperature
BIO6	Min Temperature of Coldest Month
BIO11	Mean Temperature of Coldest Quarter
BIO15	Precipitation Seasonality (Coefficient of Variation)
BIO18	Precipitation of Warmest Quarter

Epidemiological model: SEIR

The SEIR model used in this study was developed by Rubel et al. [44] for Vienna (Austria) and surrounding areas based on data from different parts of the world. The model simulates the seasonal life cycles and inter-species USUV infections of the main vector and host species, *Cx. pipiens* and *T. merula* respectively. Health states of birds and mosquitoes are classified into nine compartments (larvae state of mosquitoes, health states susceptible/latent infected/infectious of mosquitoes and birds as well as recovered and dead birds, see [44]), and described by ordinary differential equations (see Additional file 3). The basic reproduction number R_0 is then calculated as the dominant eigenvalue of the next-generation matrix as described in [67], resulting in (see Table 2 for model parameters and Additional file 3 for details):

$$R_0 = \sqrt{\left[\frac{\delta_M \gamma_M \beta_M}{(\gamma_M + m_M) m_M} \frac{S_B}{K_B}\right] \left[\frac{\delta_M \gamma_B \beta_B}{(\gamma_B + m_B)(\alpha_B + m_B)} \frac{S_M}{K_B}\right]}$$

The SEIR model is mainly driven by variables responding to temperature. Further drivers are latitude, calendar day, and parameters with constant values [44].

The original SEIR R-code of the model was upgraded to work on a spatial grid rather than a single point location, and daytime length was calculated for each grid cell based on the geographical latitude of its center. Instead of interpolating daily data from monthly mean temperature, the model was run with true daily temperature data from the E-OBS dataset [52]. As an extensive literature review did not yield any new information, all other variables and parameters originally used by Rubel et al. were maintained in this study.

As the SEIR model for USUV was created for and calibrated within a temperate climate, water availability or precipitation were not considered a limiting factor by the developers. However, this assumption is not applicable for the entire study area, as the dry summers of Mediterranean climates can lead to a different, two peaked activity pattern of *Cx. pipiens* mosquitoes [68].

Consequently, the model was applied only to regions with a climate that is classified as cold or temperate with warm to hot summers but no dry season (Cfa, Cfb, Dfa and Dfb in the Köppen-Geiger system [69, 70]) (Fig. 2b).

The basic reproduction number R_0 (the number of secondary cases arising from a single infection in an otherwise uninfected population) of USUV calculated by the SEIR model is a threshold value: if $R_0 > 1$, an outbreak is possible after a single introduction of the pathogen; whereas if $R_0 < 1$, the introduced virus population will die out [67]. The daily R_0 value of each cell within the spatial raster was calculated within the time span of 2003-01-01 to 2016-12-31. From this, the average yearly number of days with $R_0>1$ was calculated for each raster cell and the maxSSS threshold was calculated for direct comparison with the environmental niche model based on the same presence and background locations that were used in the Maxent model. In addition to that, the average daily R_0 value of the main transmission season (June–September) was calculated for each year and raster cell.

Table 2 Variables and parameters in the R_0 equation, following [44]. T = daily mean temperature in °C.

Parameter		Value
Mosquitoes		
mortality rate	m_M	$m_M(T) = 0.00025 \cdot T^2 - 0.0094 \cdot T + 0.10257$
biting rate	κ	$\kappa(T) = \frac{0.344}{1 + 1.231 \cdot e^{-0.184(T-20)}}$
product of biting rate (κ) and transmission possibility from mosquitoes to birds (P_M)	β_M	$\beta_M(T) = P_M \cdot \kappa(T)$ P_M = 1
Percentage of non-hibernating mosquitoes	δ_M	$\delta_M = 1 - \frac{1}{1 + 1775.7 \cdot e^{1.559\,(D-18.177)}}$ $D = 7.639 \cdot arcsin\left(tan(\epsilon) \cdot tan(\varphi) + \frac{0.0146}{cos(\epsilon) \cdot cos(\varphi)}\right) + 12$ $\epsilon = 0.409 \cdot sin\left(\frac{2\pi\,(d - 80)}{365}\right)$ D: daytime length, ϵ: declination, φ: geographic latitude
exposed – infected/infectious rate	γ_M	$\gamma_M(T) = 0.0093 \cdot T - 0.1352, T \geq 15^{\circ}$ $\gamma_M(T) = 0, T < 15^{\circ}$
susceptible mosquito population	S_M	Dynamic value, see Additional File 3
Birds		
mortality rate	m_B	0.0012
removal rate: fraction of infected birds either recovering or dying	α_B	0.182
exposed – infected/infectious rate	γ_B	0.667
product of biting rate (κ) and transmission possibility from birds to mosquitoes (P_B)	β_B	$\beta_B(T) = P_B \kappa(T)$ P_B= 0.125
susceptible black bird population	S_B	Dynamic value, see Additional File 3
environmental capacity	K_B	see Additional File 3

Results

The potential geographic distribution of USUV predicted by both models on the continental European scale are shown in continuous form in Fig. 2, and as a direct comparison based on the maxSSS thresholds (environmental niche model: 0.35 in Maxent's logistic output format, epidemiological model: 40 days of $R_0 > 1$) in Fig. 3. While there are differences between the two models in parts of the study area, 15% of the study area are projected to be suitable by both approaches. The northern Italian outbreak region in and around the Po Valley is identified as a highly suitable area for USUV by both models. The same is true for eastern Austria, the Pannonian Basin and adjoining areas, as well as a narrow strip along the Rhône river in France. Large parts of north-eastern France, the Benelux states and western and northern Germany are predicted to be at least somewhat suitable by both models. On the other hand, environmental niche model and SEIR agree on low risk being present in northern and mountainous regions (such as Sweden, Norway and the British Isles), where relatively low average and minimum temperatures keep the probability of transmission low.

In general, the environmental niche model accurately determines the occurrences of birds found positive with USUV. Compared to the SEIR, it suggests elevated climatic suitability for USUV to the north and west of the Jura Mountains as well as northwards along the Rhine and the North Sea coast until southern Denmark (Fig. 2a). Following the maxSSS threshold, the environmental niche model predicts a total of 17% of the study area to be suitable for transmission (sensitivity: 0.946, specificity: 0.852). 2% of the entire area are considered suitable only by the environmental niche model and not by the SEIR, including most parts of Denmark and adjoining parts of northern Germany, northern Netherlands, southern Belgium and a few areas in northern Britain (Fig. 3).

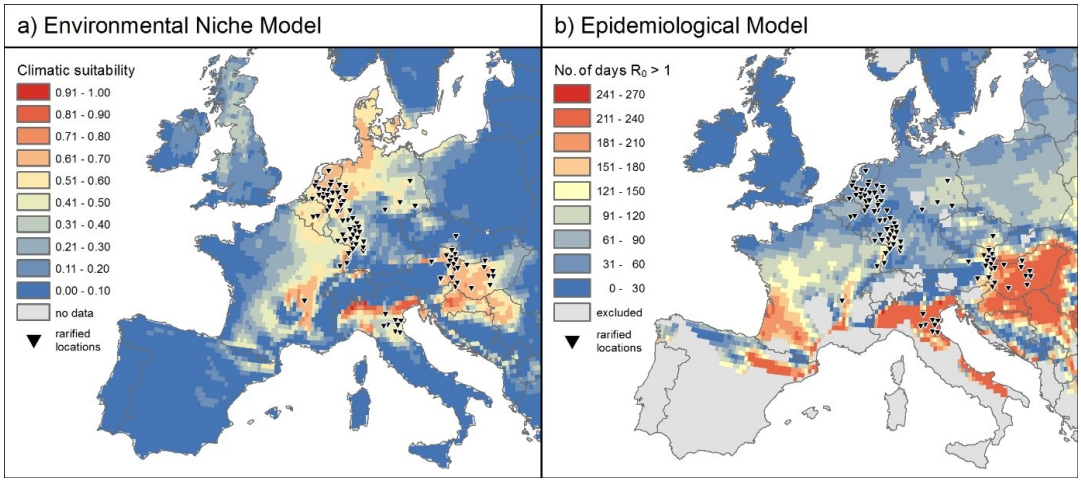

Fig. 2 Potential geographic distribution of USUV in Europe. **a** Climatic suitability estimated by the environmental niche model, and **b** the yearly mean absolute number of days of $R_0 > 1$ simulated by the epidemiological SEIR model. Gray areas in **b** denote regions with a dry season that were not included in the SEIR model. Both models use the same E-OBS climate data for 2003–2016. Locations of recorded cases for the environmental niche model were rarified (in comparison to Fig. 1) to avoid spatial autocorrelation (see "Methods").

In contrast, the average yearly number of days with $R_0 > 1$ derived from the SEIR suggests a high risk for USUV in southwestern France and southeastern Italy, but shows relatively low risk in the northern Germany-Netherlands-Belgium region (Fig. 2b). North of the Pyrenees, the former French regions of Aquitaine and Midi-Pyrénées show a high transmission potential as well. Medium values mainly occur in Poland and northeastern Germany, along the Upper Rhine Valley and in central France. For the outbreak area in the Netherlands and northern Germany, the SEIR in this form suggests relatively low risk of transmission. However, following the maxSSS threshold, most of this region can still be classified as suitable for USUV transmission (Fig. 3). A total of 67% of the whole study area lies above the threshold for this model, resulting in a sensitivity that is slightly higher (0.989) than that of the environmental niche model but a very low specificity (0.274).

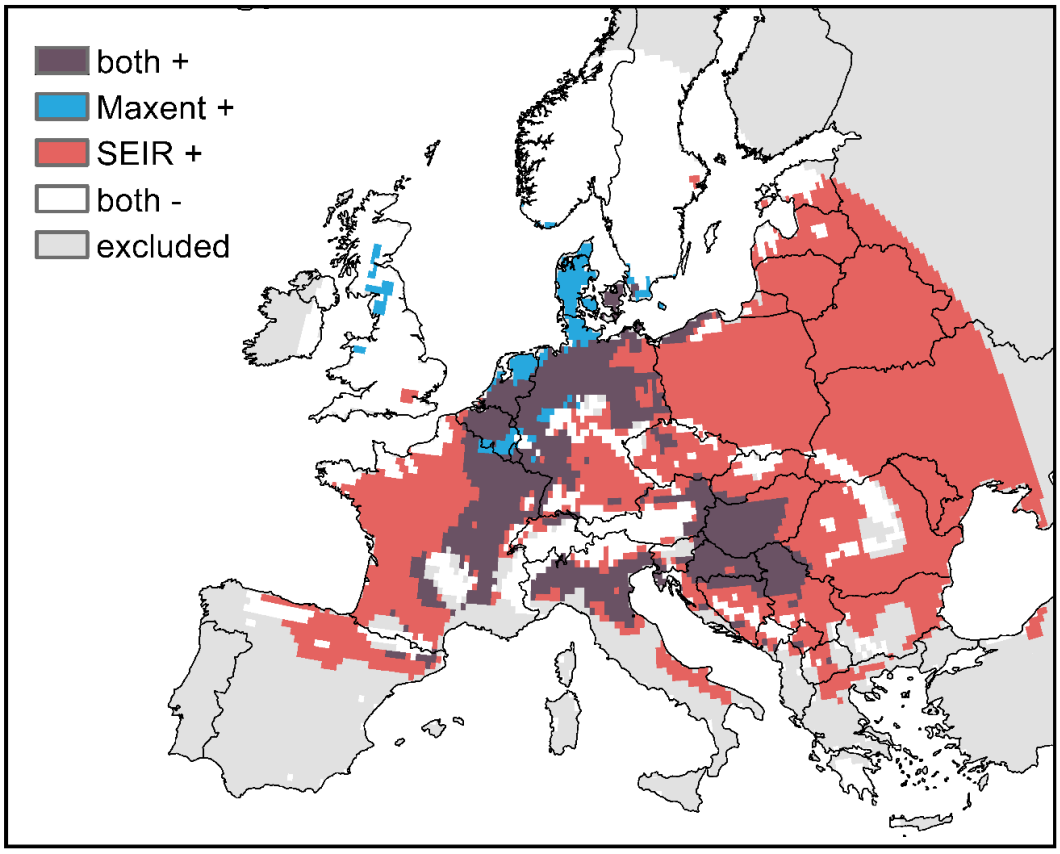

Fig. 3 Areas of agreement and disagreement of both models. Dark purple areas denote regions where both models predict suitable conditions for USUV-transmission based on the maxSSS threshold. In the blue and red areas, only the environmental niche model and SEIR predict suitable conditions, respectively. In white areas none of the models predicts suitable environmental conditions, while gray areas were excluded from further analyses because they are outside the climatic zones the SEIR model was developed for, or outside the buffer applied to the Maxent model.

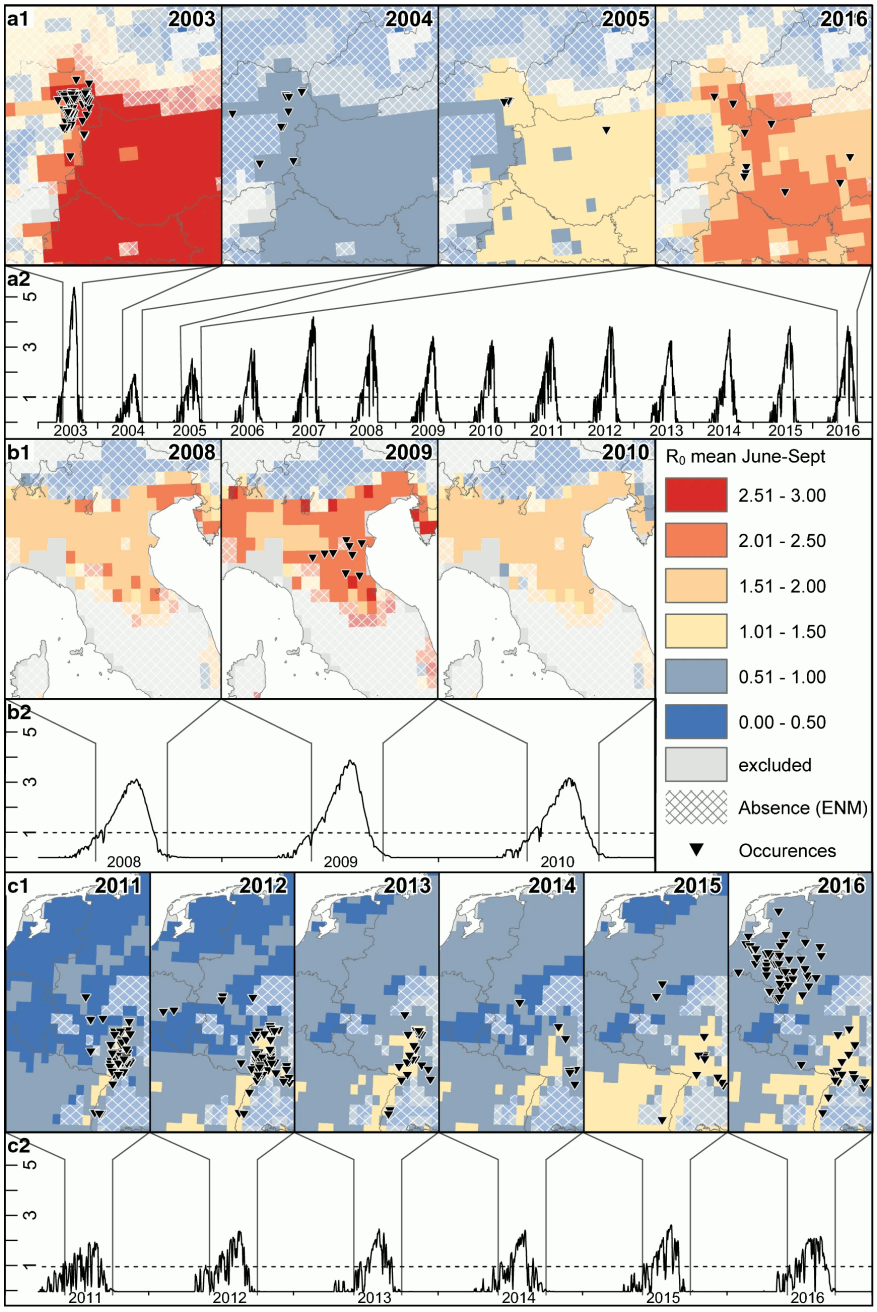

Fig. 4. Temporal patterns of the average R_0 values for three selected regions of Europe. **a** Austria and the Pannonian Basin, **b** northern Italy, and **c** Germany and the Netherlands. (1) Spatial representation of both models for years with USUV events. Color coding in the maps shows the average daily R_0 values throughout June to September for the given years. Gray areas denote climate types with dry seasons, thus the SEIR model was not applied there. Cross-hatching indicates areas where the environmental niche model suggests absence of USUV, based on climate data for the whole time period from 2003 to 2016. (2) Time series curves illustrate the daily R_0 value, averaged over all occurrence records of the respective region for each given year.

Zooming in towards the main areas of observed USUV transmission allows a closer inspection of the models. In the Austrian-Hungarian outbreak area, Maxent predicts climatic suitability values sufficient for USUV transmission at all observed occurrences (Fig. 4 a1). The SEIR model predicts the highest R_0 values for the largest USUV event in 2003 (Fig. 4 a2) and considerably lower values for the following 2 years with less observed cases (Fig. 4 a). Relatively high R_0 values are observed again for the last USUV event in 2016. Interestingly, though, values for the USUV-free years of 2006–2015 are higher than those of 2004/5 (Fig. 4a2).

In Italy, Maxent is able to predict the general outbreak area (Fig. 4 b1). The SEIR model predicts elevated R_0 values for the year of 2009 where USUV occurred, but similarly high values for the USUV-free years before and after (Fig. 4 b2).

In the largest outbreak area in western Germany and the Benelux states, Maxent closely resembles the observed pattern of USUV occurrence (Fig. 4 c1). Compared to the other two regions, the SEIR model in these areas shows much lower average and absolute R_0 values as well as higher temporal variability throughout the transmission season (Fig. 4 c2). Average R_0 values for the transmission season rise above 1 and match the occurrence records well in the Rhine Valley but stay below 1 in the northern parts of the area, i.e. the Netherlands and northwestern Germany.

Discussion

In face of emerging VBDs and rapid spread into new regions with suitable climatic conditions, models that show the current geographic regions at risk are required to allow local health authorities to be prepared. However, modelling approaches can differ substantially in philosophy, structure, and algorithms. Pros and cons of different approaches are evident and, obviously, there is not one single approach to be preferred for every pathogen, area or timespan.

In this study, two fundamentally different models were applied to describe the current emergence of USUV in Europe. This disease exhibits a series of complex interactions between the virus, vectors and host species [9]. Process-based models offer direct links between model outcome and underlying mechanisms, which makes interpretation of the observed spatial patterns relatively straightforward. However, exact knowledge on the parameters of USUV transmission is still scarce. With large numbers of USUV-positive birds reported from distinct geographical hot spots, the application of biogeographical distribution models may be a viable alternative. In order to identify coinciding and deviating model output, we ran the analyses based on the same climate data and following standard processes to detect regions at risk for the transmission of USUV.

The large-scale spatial patterns predicted by the two models (Figs. 2, 3) are quite similar close to the observed USUV events—with the notable exception of northern Germany and the Netherlands. Here, the environmental niche model favors higher latitudes as far north as Denmark, while the epidemiological model suggests good conditions for transmission in southwestern France and northeastern Spain (Fig. 2b) and at least suitable conditions for most parts of Eastern Europe (Fig. 3). Given the observed recent increase in temperatures across Europe and the projected further increase during the upcoming century [IPCC] [71], it can be expected that both models under-estimate future potential for USUV transmission to some degree. If precipitation patterns change dramatically so as to affect mosquito populations, the SEIR model may not be a reliable option any more in some regions. Similarly, both models are not suitable to predict today's potential for USUV transmission in areas that are climatically very different from the study region.

Environmental niche model

As the environmental niche model is strongly driven by existing spatial records, it is not surprising that it reflects the current distribution of USUV records better. However, it has to be kept in mind that there is no consistent

monitoring of USUV across Europe, leading to biases in the occurrence records. For instance, many USUV events were reported in Italy, Austria, Hungary, and Croatia (though no RT-PCR positive birds), but to date no USUV case was reported in their neighbor countries—Slovenia and Slovakia. Due to the same reason, only bird cases were included in our approach, as it is the least biased dataset in Europe, compared to USUV cases from wild mammals (e.g. bats and wild boars) or humans. Furthermore, we restricted our USUV dataset to USUV cases confirmed by RT-PCR counts, as other methods bear the possibility of false positives that would lead to overestimation of risk. Given the high activity of West Nile Virus in the area that could easily be mistaken for USUV in antibody tests, the gain from avoiding false positives should outweigh the loss from potentially excluding some true positives. Even though Maxent is relatively insensitive to sampling bias compared to other environmental niche models [57] and records were spatially rarified in this study, the modelling output would still be inevitably affected, e.g. in Italy, where occurrence records are comparably sparse.

In addition, USUV is still spreading in Europe and likely does not occupy its entire environmental niche yet, which may lead to under-estimation of risk through the environmental niche model in areas that may be climatically suitable, but have not been reached yet (compare e.g. [72]). The quality and accessibility of observed records of occurrence of vectors, hosts and especially pathogens is a major practical obstacle for the development of models of the environmental niche model family. Only a consistent and advanced monitoring system covering a selection of representative areas across Europe could give more accurate and reliable occurrence records to produce risk maps. Consequently, the environmental niche model performance can be improved as more occurrence data with high quality are available and the sampling bias is minimized. Ideally, such a monitoring system is centralized, open access and would not only focus on birds or mosquitoes but also include mammalian hosts such as rodents or bats to cover different types of potentially circulating pathogens. Especially the latter have been suspected to be under-estimated but

important hosts for other viral zoonotic diseases [73]. As USUV outbreaks typically cease with the arrival of winter, hibernating bats could enable overwintering of the virus. However, coordinated efforts are also needed for centralized and open access to the occurrence records resulting from these improved measures [35].

Epidemiological model

As an absence of records does not necessarily indicate an absence of risk, it makes sense to use a mechanistic model to point out regions such as southwestern France, where transmission appears to be possible. The SEIR model captured the USUV events in the Pannonian Basin and Po Valley regions well, though the events in Germany and the Netherlands were not represented correctly. Hence, it must be questioned whether the current knowledge on processes, mechanisms and underlying parameters is sufficient to explain USUV transmission patterns and outbreaks. Although an extensive literature review was conducted with the aim of improving and updating the parameters for the SEIR model, no information supporting the integration of additional processes, drivers or variables was found. Therefore, all the parameters and variables used already in the 2008 study of Rubel et al. [44] were kept unchanged, even though some of them are probably not suitable for the whole study area. For instance, population density as well as birth and mortality rates of common blackbirds are unlikely to be constant across the whole study area. An advanced, open-access monitoring system as discussed above could also be of great use for this.

Furthermore, although precipitation is known to affect mosquito life cycles and disease transmission dynamics [74, 75], the applied SEIR model does not take this into account. The SEIR model for USUV was originally developed and calibrated for temperate climates. It is thus possible that certain ecological factors (e.g. precipitation), which are not limiting in the calibration area but could be limiting elsewhere, are not included in the model. In our study we restrained the extent for the SEIR model by excluding climate types with dry seasons in order to avoid making predictions for regions the model is not

suitable for. Future models should aim to improve the population model components for vectors and hosts, leading to a more universally useful model. In addition, explicit parameters for USUV are not available yet and had to be substituted by data for the related WNV. For instance, no information about the extrinsic incubation period and its relation to ambient temperature is currently available. Data from a single experiment on a single strain of another virus (i.e. West-Nile virus) [76] is far from optimal, as it has been shown that these experiments are subject to large uncertainty for various reasons [77]. This is a common problem, though, since updated and realistic experiments are sorely needed for many VBDs [35]. Future models could account for some of this uncertainty by incorporating stochastic variations instead of relying on fixed values, as it has already been done e.g. for Chikungunya [78].

Another point worth considering is that so far there is no standardized way of converting the daily values of R_0 calculated by the SEIR model for each grid cell into interpretable maps. Obviously, some amount of temporal aggregation needs to be applied in order to gain low dimensional, printable maps. In practice, this ranges from R_0 being displayed as averages for single months (e.g. [79]) up to R_0 values being averaged over 30-year periods (e.g. [80]). Here, we chose to display average R_0 values for single transmission seasons, which apparently failed to predict the 2016 USUV event in Northwest Europe (Fig. 4 c). However, R_0 is a threshold value. Thus, while a value of $R_0>1$ indicates high risk of disease spread, an average $R_0 < 1$ for the same period does not necessarily mean no or even low risk, depending on how the length of that period was chosen and how often the threshold was exceeded. This is a serious drawback of SEIR model results to visualize the spatial-explicit risk of pathogen transmission. Hence, an alternative way of illustrating these models is concentrating on the duration of time where $R_0 > 1$. Here, we chose to count the (average) number of days per year where $R_0 > 1$, but this can also be done on other temporal scales (e.g. months [81]). In our case, this value apparently fails to capture the outbreak area in Germany and the Netherlands (Fig. 2 b). However, a closer look reveals that this again is a lack of knowledge about the

details of the disease that prevents a meaningful interpretation of these maps, i.e., how many days of $R_0 > 1$ are actually needed for an USUV event to occur. When this threshold would be known, the average yearly number of days of $R_0 > 1$ map can be converted to a categorized risk map showing whether there is a risk and how severe it is. Furthermore, it has to be questioned, if higher absolute R_0 values during the transmission season would reduce the number of days of $R_0 > 1$ days required for an USUV outbreak. Only when these primary questions are addressed, a more reasonable risk map can be generated.

Outlook

Further efforts should strive towards the unification of the two streams of modeling. As shown in this study, the ecological niche model reflects spatial distribution better, while the epidemiological model has the advantage of capturing short term variabilities, as it uses daily temperature data. Ecological niche models are run with climate data which typically covers decades, and as a consequence, extreme weather events such as heat waves would not be captured. An integrated model could benefit from both models' advantages. For example, in a hierarchical approach, spatial distribution of risk could first be estimated by an environmental niche model, followed by a zoom into a finer scale for the investigation of temporal risk patterns in high risk areas through an epidemiological model with well-updated parameters and variables. In this case, the finer temporal scale epidemiological model, using daily weather data or even weather forecast data, can work as a live early warning forecast. Instead of projecting where climate is suitable, ecological niche models can also be applied to exclude unsuitable regions. In addition, in an integrated approach, environmental niche models that estimate the abundance of vectors and hosts could be nested in an epidemiological model as well, in order to gain more precise information on the required vector-to-host ratio.

Conclusion

In conclusion, this study highlights the necessity to consider different approaches to detect the current and future areas under risk of VBDs. Environmental niche models and epidemiological models examine rather complementary aspects, especially in terms of short-term weather conditions versus long-term climatic conditions. Environmental niche models are typically built upon long-term climate data and thus can be used to gain a general overview of the areas at risk and estimate potential effects of climate change. Given enough spatially explicit occurrence records are available, these models are particularly useful for a rapid risk assessment of emerging VBDs, while more detailed data about the transmission mechanisms is gathered. Once this data is available, elaborate mechanistic models can offer more fine-grained insights on the progression of outbreaks, with the potential for short-term forecasts based on weather models. At this point, environmental niche models for host or vector populations can provide valuable input data for advanced epidemiological models. Thus, using both approaches complementing each other is key for a comprehensive and effective risk evaluation.

Wide parts of Europe are currently at risk of USUV circulation, and its status of a mostly neglected emerging disease makes estimation of its potential future range difficult. Evidence suggests that USUV event s may be more likely to occur in climatically favored regions within Europe such as the Po Valley in northern Italy [82] and the Rhine Valley [48, 50]. At the same time, these areas have a high human population density and exhibit large urban areas and cities. Remnant wetland habitats along rivers serve as habitats for migratory bird stops resulting in a combined setting with humans being exposed to high risk. The detected spatial patterns can be used to indicate regions where surveillance activities should be focused and intensified.

Additional files

- Additional file 1. Records of USUV-infected bird locations confirmed by RT PCR collected from the literature.
- Additional file 2. Buffer radii versus model performance.
- Additional file 3. Detailed description of the SEIR model.

Authors' contributions

YC, NT, ST, AJ, RL, and CB developed the concept of the study. YC, UZ and RL complied the occurrence records. NT and YC processed the climate data and adapted the SEIR model. YC and NT ran the Maxent models. CB, ST and AJ supervised the modelling process. YC prepared the figures. All authors discussed the preliminary results and figures at various stages of the modelling process. YC and NT wrote the original draft of the manuscript. All authors discussed and revised the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and material

All climate data is publically available from the sources mentioned in the manuscript. Occurrence records for Europe are publicly available from the sources listed in Additional File 1. Occurrence records from Germany were collected within a dead bird surveillance program of the Friedrich-Loeffler-Institut, Greifswald-Insel Riems, Germany and the Bernhard Nocht Institute for

Tropical Medicine, Hamburg, Germany in cooperation with the German Mosquito Control Association (KABS), the Nature and Biodiversity Conservation Union (NABU), the local veterinary authorities and/or by the local state veterinary laboratories. These datasets were used under license for the current study, and so are not publicly available. They are however available from the authors upon reasonable request and with permission of the respective third parties involved.

Consent for publication

Not applicable

Ethics approval and consent to participate

Not appliacable.

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Appendix: Additional files

Additional File 1. Records of USUV-infected bird locations confirmed by PCR collected from the literature.

Countries	Outbreak years	Data type	Reference
Austria	2003–2005	Map	[1]
Hungary	2005–2006	Map	[2]
Italy	2009	Map	[3]
Italy	2009	Map	[4]
Italy	2010	Map	[5]
Austria and Hungary	2010–2016	Coordinates	[6]
Italy	2011	Map	[7]
Germany	2011, 2015	Site description	[8]
Czech Republic	2011–2012	Coordinates	[9]
Germany	2011–2013	Map	[10]
Belgium	2012	Coordinates	[11]
Italy	2012	Site description	[12]
Germany	2013	Coordinates	[13]
Italy	2013	Map	[14]
France	2015	Site description	[15]
Netherlands	2016	Map	[16]

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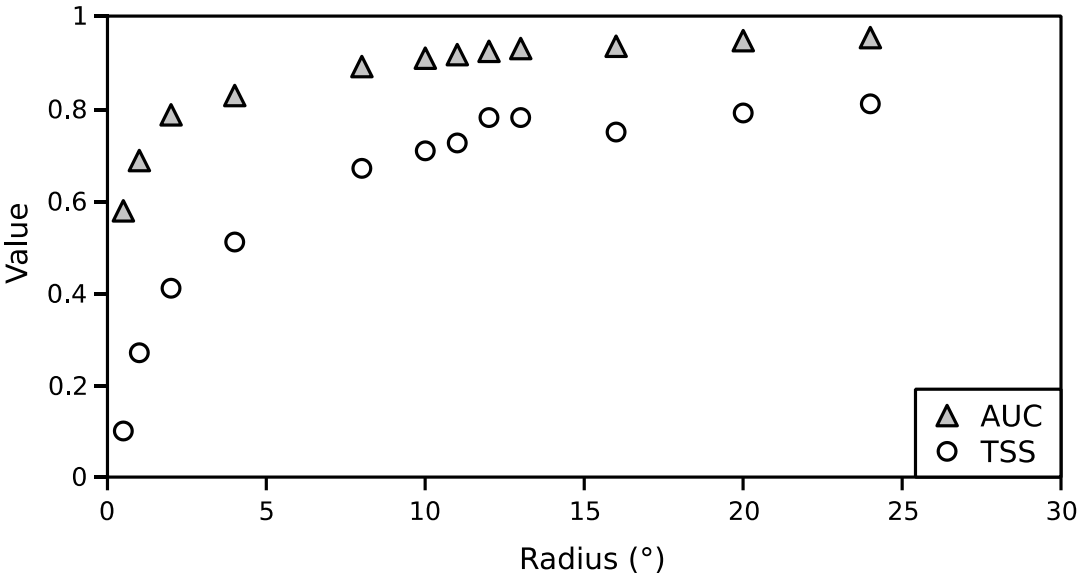
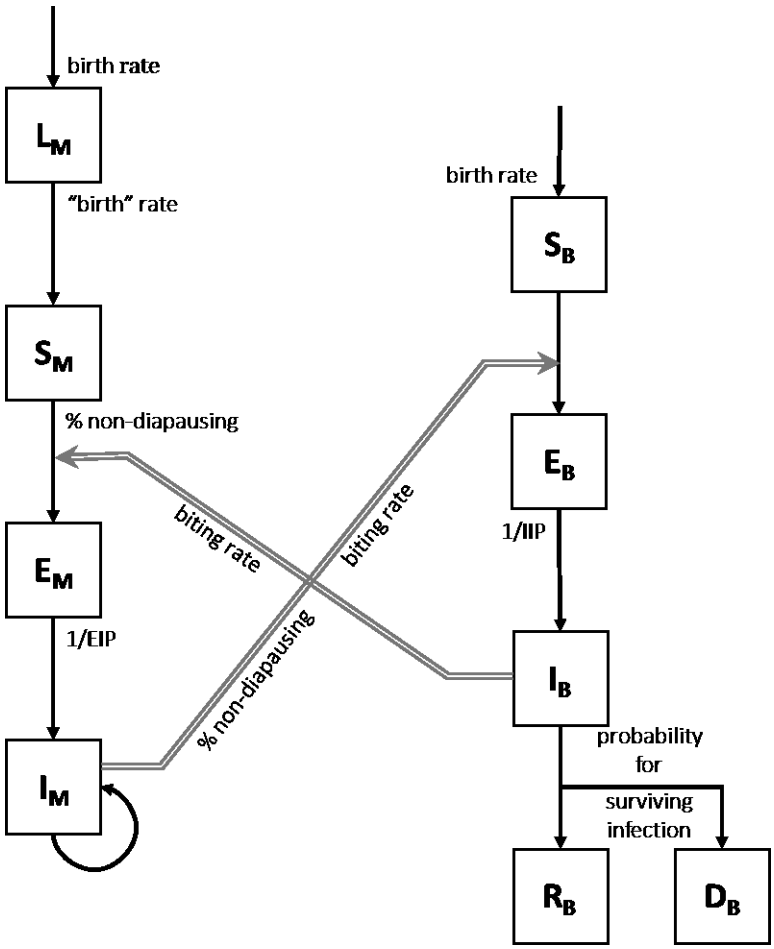
Additional File 2. Buffer radii vs. model performance.



Model performance as measured by AUC and TSS in dependence of the size of the study area. The latter is determined by circular buffer zones of different radii drawn around the occurrence records.

Additional File 3. Detailed description of the SEIR model.

Simplified diagram of the Usutu virus (USUV) epidemiological model:



Each health state of mosquitoes / black birds can be described by Ordinary differential equations (ODEs).

Population growth of black birds:

$$\frac{dN_B}{dt} = r_B N_B = b_B N_B - m_B N_B \qquad (1)$$

N_B is the total number of black birds, r_B is the population growth rate, $b_B$is the birth rate and m_B is the mortality rate (B stands for black birds). Following logistic population growth (density dependent model):

$$\frac{dN_B}{dt} = r_B\left(1 - \frac{N_B}{K_B}\right)N_B \tag{2}$$

As $r_B = b_B - m_B$, the above can be written as:

$$\frac{dN_B}{dt} = \left(b_B - (b_B - m_B)\frac{N_B}{K_B}\right)N_B - m_B N_B \tag{3}$$

K_B stands for the environmental capacity. It can be understood as the maximum number of individuals that can be supported by the environment under ideal conditions.

The population of "larval" mosquitoes (includes all aquatic stages of *Culex* mosquitoes, only females taken into account) also follows logistic population growth:

$$\frac{dL_M}{dt} = (b_L N_M - m_L L_M)\left(1 - \frac{L_M}{K_M}\right) - b_M L_M \tag{4}$$

L_M is the total number of larvae, b_L is the birth rate of larvae, m_L is the mortality rate of larvae, b_M is the "birth rate" of mosquitoes (transformation from larvae to adult mosquitoes). Note here: although also following logistic population growth, mosquito growth is divided to aquatic and terrestrial stages, thus the equation looks different from black birds'.

Total density of terrestrial stages of *Culex* mosquitoes (N_M):

$$\frac{dN_M}{dt} = b_M L_M - m_M N_M \tag{5}$$

Cross-infection between mosquitoes and black birds:

$$\lambda_B = \beta_B \frac{I_B}{K_B} = \kappa P_B \frac{I_B}{K_B} \tag{6}$$

$$\lambda_M = \beta_M \frac{I_M}{K_B} = \kappa P_M \frac{I_M}{K_B} \tag{7}$$

λ_B denotes the possible fraction of cross-transmission from birds to mosquitoes, and λ_M vice versa. β_B is the product of biting rate (κ) and transmission possibility from birds to mosquitoes(P_B), and β_M vice versa. Transmission possibility from mosquitoes to birds is P_M.

Then the different *health states of birds* can be described by following ODEs:

1. The susceptible black bird population (S_B)

$$\frac{dS_B}{dt} = \left(b_B - (b_B - m_B)\frac{N_B}{K_B}\right)N_B - m_B N_B - \delta_M \lambda_M S_B \qquad (8)$$

It can be understood as:

(current total number of susceptible black birds) = (current total number birds) – (natural death of birds) – (birds moving to the next health state)

Here "natural death of birds" means deaths not due to Usutu virus (USUV) infection.

2. The exposed black bird population (E_B)

$$\frac{dE_B}{dt} = \delta_M \lambda_M S_B - m_B E_B - \gamma_B E_B \qquad (9)$$

δ_M : Percentage of non-hibernating mosquitoes

γ_B : The exposed – infected/infectious rate of birds

From this equation:

(current total number of exposed black birds) = (birds coming into this health state from the previous stage) − (natural death of birds) − (birds moving to the next health state)

3. The infected black bird population (I_B)

$$\frac{dI_B}{dt} = \gamma_B E_B - m_B I_B - \alpha_B I_B \qquad (10)$$

α_B: The removal rate, removed from the previous health state, either get recovered (immunized) or dead.

4. The black bird deaths (D_B) due to USUV infection

$$\frac{dD_B}{dt} = \nu_B \alpha_B I_B \tag{11}$$

ν_B: the percentage of bird deaths due to USUV infection

5. The recovered black bird population (R_B)

$$\frac{dR_B}{dt} = (1 - \nu_B)\alpha_B I_B - m_B R_B \tag{12}$$

And

$$N_B = S_B + E_B + I_B + R_B \tag{13}$$

Note: In this model both horizontal and vertical virus transmission in birds are not taken into account, so the transmission is limited to through mosquitoes' blood meal.

Similarly, the different *health states of mosquitoes* are described as following:

6. The larval population of *Culex* mosquitoes:

$$\frac{dL_M}{dt} = (b_L N_M - m_L L_M)\left(1 - \frac{L_M}{K_M}\right) - b_M L_M \tag{14}$$

7. The susceptible mosquito population:

$$\frac{dS_M}{dt} = b_M L_M - m_M S_M - \delta_M \lambda_B S_M \tag{15}$$

From this equation, similar to bird equations:

(current total number of susceptible mosquitoes) = (mosquitoes entering this health state from the previous stage) – (natural death of mosquitoes) – (mosquitoes moving to the next health state).

8. The exposed mosquito population:

$$\frac{dE_M}{dt} = \delta_M \lambda_B S_M - m_M E_M - \gamma_M E_M \quad (16)$$

γ_M: The exposed – infected/infectious rate of mosquitoes

9. The infected mosquito population:

$$\frac{dI_M}{dt} = \gamma_M E_M - m_M I_M \quad (17)$$

And

$$N_M = S_M + E_M + I_M \quad (18)$$

Note: Infectious mosquitoes remain in the infectious state and will not get recovered.

In addition, δ_M is determined by the latitude and the calendar day of the year.

$$\delta_M = 1 - \frac{1}{1 + 1775.7\exp[1.559(D - 18.177)]} \quad (19)$$

where D denotes "Daytime length", and

$$D = 7.639 arcsin\left[tan(\epsilon)tan(\varphi) + \frac{0.0146}{cos(\epsilon)cos(\varphi)}\right] + 12 \quad (20)$$

$$\epsilon = 0.409 sin\left(\frac{2\pi(d - 80)}{365}\right) \quad (21)$$

φ: The geographic latitude

d: The calendar day

The final equation for R_0:

$$R_0 = \sqrt{\left[\frac{\delta_M \gamma_M \beta_M}{(\gamma_M + m_M) m_M} \frac{S_B}{K_B}\right]\left[\frac{\delta_M \gamma_B \beta_B}{(\gamma_B + m_B)(\alpha_B + m_B)} \frac{S_M}{K_B}\right]} \qquad (22)$$

Additional Table 1: Parameters for the R_0 equation.

	parameter	value
population growth rate	r_B	$r_B = b_B - m_B$
birth rate	b_B	$b_B(d) = 0.125 \frac{(x/\beta)^{\alpha-1}\exp(-x/\beta)}{\beta\Gamma(\alpha)}$ $x = 0.1(d - 105)$, d is transformed Julian calendar day α=1.52, β=1.93, $\Gamma(\alpha)$=0.887
mortality rate	m_B	0.0012
birth rate of larvae	b_L	$b_L(T) = 2.325\kappa(T)$ T :Daily Mean Temperature
mortality rate of larvae	m_L	$m_L(T) = 0.0025T^2 - 0.094T + 1.0257$
"birth rate" of mosquitoes (transformation from larvae to adult mosquitoes).	b_M	$b_M(T) = 0.1b_L$
mortality rate of mosquitoes	m_M	$m_M(T) = 0.1m_L$
possible fraction of cross-transmission from birds to mosquitoes	λ_B	$\lambda_B(T) = \beta_B(T)\frac{I_B}{K_B} = \kappa(T)P_B\frac{I_B}{K_B}$
product of biting rate (κ) and transmission possibility from birds to mosquitoes(P_B)	β_B	$\beta_B(T) = \kappa(T)P_B$ P_B=0.125
biting rate	κ	$\kappa(T) = \frac{0.344}{1 + 1.231\exp(-0.184(T - 20))}$
possible fraction of cross-transmission from mosquitoes to birds	λ_M	$\lambda_M(T) = \beta_M(T)\frac{I_M}{K_B} = \kappa(T)P_M\frac{I_M}{K_B}$
product of biting rate (κ) and transmission possibility from	β_M	$\beta_M(T) = P_M\kappa(T)$

	parameter	value
mosquitoes to birds (P_M)		
Percentage of non-hibernating mosquitoes	δ_M	$\delta_M = 1 - \frac{1}{1 + 1775.7\exp[1.559(D - 18.177)]}$ $D = 7.639 arcsin\left[tan(\epsilon)tan(\varphi) + \frac{0.0146}{cos(\epsilon)cos(\varphi)}\right] + 12$ $\epsilon = 0.409 sin\left(\frac{2\pi(d - 80)}{365}\right)$
exposed – infected/infectious rate of birds	γ_B	0.667
removal rate, removed from the previous health state, either get recovered (immunized) or dead	α_B	0.182
the percentage of bird deaths due to USUV infection	ν_B	0.3
The exposed – infected/infectious rate of mosquitoes	γ_M	$\gamma_M(T) = 0.0093T - 0.1352, T \geq 15^{\circ}$ $\gamma_M(T) = 0,\ T < 15^{\circ}$

* Note that highlighted parameters are also documented in Table 2 in the main text.

Manuscript 5: Mosquito-borne diseases: Advances in Modelling Climate-Change impacts

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Abstract

Vector-borne diseases are on the rise globally. As the consequences of climate change are becoming evident, climate-based models of disease risk are of growing importance. Here, we review the current state-of-the-art in both mechanistic and correlative disease modelling, data driving these models, the vectors and diseases covered, and climate models applied to assess future risk. We find that modelling techniques have advanced considerably, especially in terms of using ensembles of climate models and scenarios. Effects of extreme events, precipitation regimes, and seasonality on diseases are still poorly studied. Thorough validation of models is still a challenge and is complicated by a lack of field and laboratory data. On a larger scale, the main challenges today lie in cross-disciplinary and cross-sectoral transfer of data and methods.

Highlights

- The use of ensembles of different climate models for future projections, as well as multiple different mechanistic or correlative disease models per study, is increasing.
- Communicating uncertainties related to disease models, different climate models, and emission and population pathways to end users is becoming a common thing to do.
- Most models tend to project an increased risk for vector-borne disease (VBD) transmission at high latitudes and elevations during the upcoming century.
- While mechanistic models typically cover the whole chain of infection by default, most environmental niche models (ENMs) still focus on vector distributions alone; they are increasingly applied to whole disease systems as well.

Spatio-temporal models of vector-borne diseases under climate change: An overview.

Modelling spatial patterns and temporal trends in vector-borne diseases (**VBDs**, see Glossary) has been done through a diversity of approaches. This field of research is very active and shows a rapid methodological development with regard to the inclusion of various drivers of diseases.

Models applied in this field are commonly divided into two groups. First, 'correlative' models predict a species' geographic distribution or support the understanding of why populations persist at a certain place. Thereby, both vector and pathogen occurrences can be used as response parameter. For this, various approaches ranging from simple regression to advanced machine learning techniques are employed [1].

Secondly, 'mechanistic' or process-based models make explicit assumptions about the biological [2] and environmental mechanisms that drive species'

distributions or infection dynamics. In epidemiology, these models are mainly derived from the Ross–MacDonald model (compare e.g., [3]). These models are based on a system of differential equations depicting each infectious stage for vectors and/or hosts. Important epidemiological parameters such as vector biting rates, vector development and mortality rates, and the **extrinsic incubation period (EIP)** largely depend on rainfall and temperature. The empirical relationship between climate and these epidemiological parameters is derived from laboratory and, less frequently, field experiments.

The individual strengths and weaknesses, as well as the underlying paradigms, of these two approaches have led to heated discourse (compare [4] and [5]). However, both approaches exhibit specific qualities [2, 6], and some authors explore promising hybrid approaches (e.g., [7–9]).

Model approaches for VBD risk assessment need to consider both positive and negative aspects of altered climatic conditions across different spatial and temporal scales. Global warming may shift climatically suitable regions for vector establishment and disease transmission to higher latitudes and higher elevations. Conversely, it may limit transmission of VBD in the warmest places, where temperature thresholds for vector or pathogen survival may be exceeded [10, 11].

Expectations for long-term climatic trends are mostly robust, particularly as far as average conditions in air temperature are concerned. Projections on future development of medium-term variability [manifested in climatic phenomena such as the North Atlantic Oscillation (NAO) or the El Niño Southern Oscillation (ENSO)] are very uncertain [12]. This is a challenge, because interannual and even multidecadal climatic fluctuations are affecting VBD transmission in some parts of the world [13]. Furthermore, long-term climatic trends affect the probability of extreme temperature and rainfall events, making them less rare in occurrence and more elusive [14]. Even though heat or cold waves, drought, or flooding are important for disease emergence,

vector abundance and pathogen transmission dynamics, such events can hardly be predicted [15].

In this article, we review recent advances in modelling the impacts of climate change (Box 1) on VBD, providing an overview of the literature published since 2014. We discuss primarily mosquito-borne diseases that are monitored by the European Centre for Disease Prevention and Control (ECDC), focusing on the applied models as well as on the data driving them.

Correlative models

Environmental niche models (ENMs), and their spatial application as **species distribution models (SDMs)**, have become an integral tool in the fields of biogeography, ecology, and conservation biology. Different modelling tools and algorithms with individual strengths and weaknesses exist, but the general concept remains the same (Figure 1). First, locations of a target species are collected in the field or derived from existing data. Some modelling tools require knowledge of locations where target species are truly absent, but as this is difficult to acquire for various reasons [1], pseudo-absence or background data are commonly generated instead [16]. The difficulty of finding high-quality presence/absence data of vectors or pathogens is an important limitation for correlative niche models. Spatial data representing environmental parameters relevant to the species in question (such as climate, land use, soil type etc.) are acquired, usually in the form of continuous grids covering the study area.

Box 1. Climate change in Europe

During the 20th century, most of Europe experienced an increase in annual surface air temperature of about 0.8 °C, mostly with a stronger warming in winter than in summer. At the same time, some parts of southern Europe have dried by as much as 20% while precipitation increased by 10–40% over northern Europe [114]. Warm night and daytime temperature extremes increased, cold temperature extremes decreased, and many regions are faced more frequently with heavy-rain days [115]. Expectations for the future vary by region and season. While temperatures are generally expected to increase across the continent, this will be more pronounced in the summer in southern Europe (Figure IA) and in the winter in northern and eastern Europe (Figure IB). Projections for changes in precipitation are subject to relatively high uncertainties. The general trends, however, are reduced rainfall in the south and increased precipitation in the north. At intermediate latitudes, there are opposing effects in the different seasons, with dryer summers and wetter winters (Figure IC, D).

These climatic changes have an impact on vectors' habitats. Winter warming may promote overwintering of vectors. Increased precipitation could lead to increased habitat availability due to increased soil moisture, humidity, and availability of natural ponds. Extreme flooding can lead to the destruction of vectors' habitats through flushing of stagnant water bodies, but at the same time it can create new breeding grounds when the water recedes [116]. Lower summer rainfall in the Mediterranean could make suitable breeding sites scarce – or have the opposite effect if it leads to more open containers being used for water supply and irrigation.

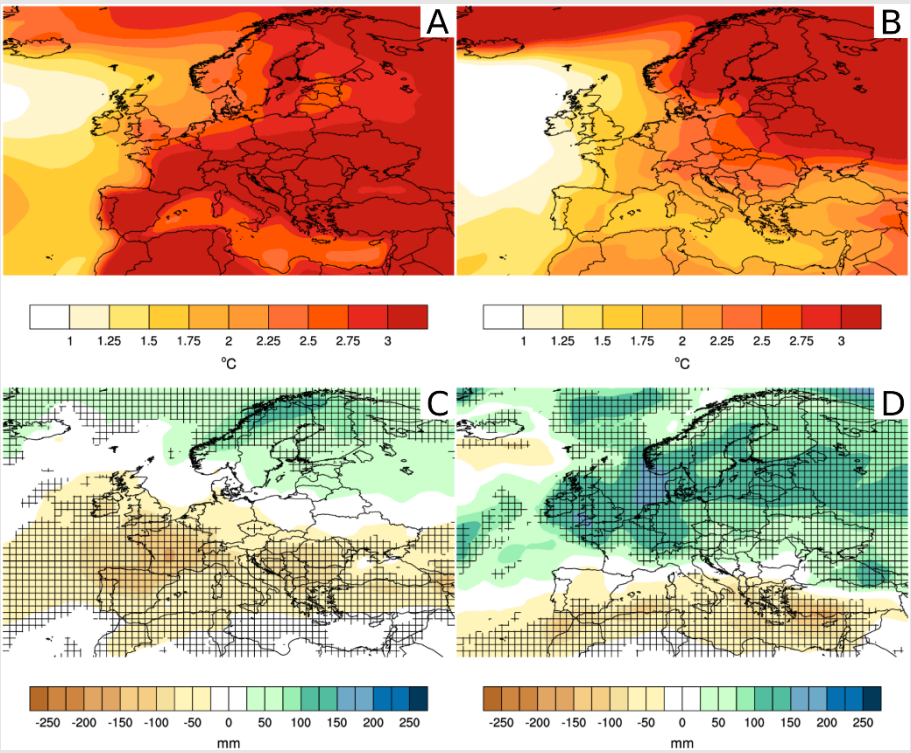

Figure I. Climate Change in Europe. Simulated differences in temperature (A, B) and rainfall (C, D) between the 2065–2085 period and the 1961–1999 reference period under the RCP 4.5 scenario based on 16 global climate models (GCMs). A, C: Boreal summer (June–August), B, D: Boreal winter (December–February). Cross hatching indicates areas of high uncertainty due to low agreement of the different GCMs.

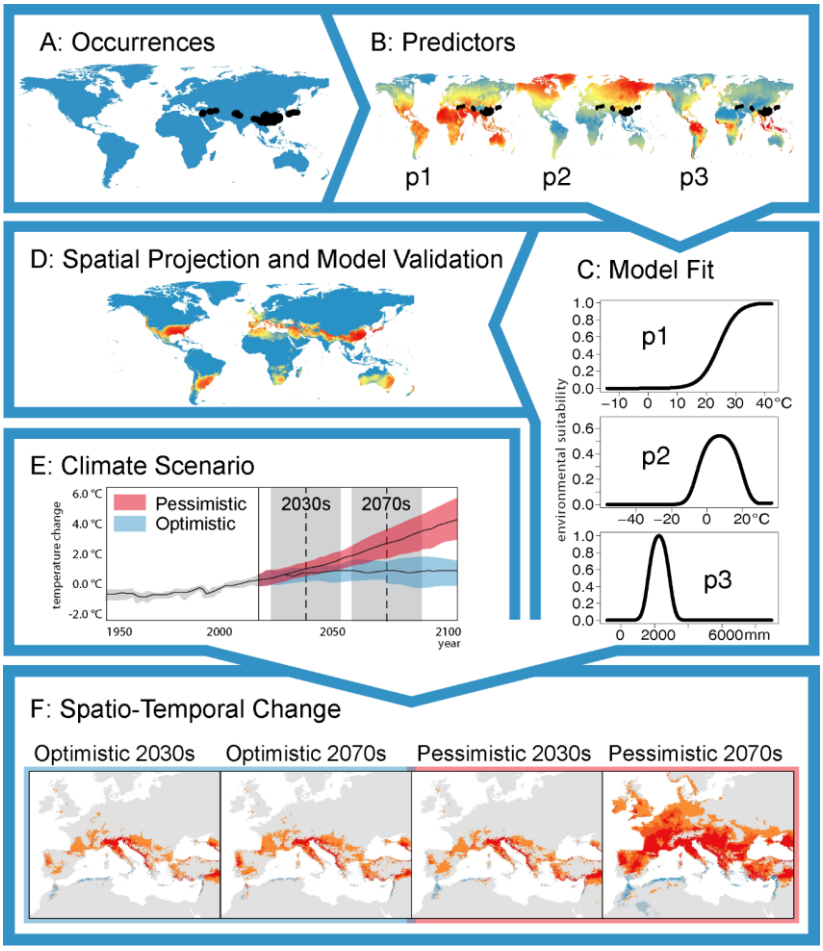

Figure 1. Characteristic workflow of an environmental niche model (ENM). (A) Occurrence records for the vector, host, or disease in question are acquired. (B) A set of predictor variables selected (here exemplarily: p1= summer temperature in °C, p2 = winter temperature in °C, p3 = annual precipitation in mm). (C) Based on these factors, the best fit model that describes the probability of occurrence of the species in (multivariate) dependence to its environmental conditions is developed (here simplified: environmental suitability in dependence of p1–3). Ideally, several different algorithms are utilized. (D) A spatial projection of the model is made based on the predictor variables. (E) A set of future climate change scenarios and relevant time frames is chosen. Shown here is the observed past and expected future average temperature change over time for an optimistic (blue) and a pessimistic (red) climate change scenario. Color shadings around the black lines show an estimate of the uncertainties. (F) Using data from global or regional climate models, further projections for the selected scenarios and time frames (grey vertical bars in panel E) are made. Ideally, different climate models are used to drive the ENM.

In the second step, a multivariate regression model is created. From an ecological perspective, loosely following the Hutchinsonian niche concept [17], this can be seen as constructing a virtual space representing all possible combinations of values of the chosen environmental parameters. From the location of the presence (and, when available, absence) records within this environmental space, the environmental niche of the target species is constructed using methods ranging from simple multiple linear regression models to advanced machine-learning techniques. This model of the species' preferred environmental conditions is then projected back into geographical space, producing a map depicting how suitable the environmental conditions are for the species in each grid cell of the study area. Since functional features, such as dispersal barriers, cannot be directly included in this kind of model, environmental suitability cannot be easily translated into probability of occurrence. Instead, it should be perceived as an indicator for a particular species' ability to survive at a given location if some individuals were to reach this place. On smaller spatial scales, it may be feasible to conduct extensive field collections of species that allow for an estimate of abundance rather than just simple presence or absence. Based on these data, species abundance models can be created in a very similar fashion (e.g., [18]).

In a third step, the prepared model can be used to identify the species' potential to become established in other parts of the world by using the same set of environmental predictors but for a different region as a reference for the projection. Similarly, projections over time can be made by using environmental data that follow historical emissions for the past or emission scenarios for the future [such as **global climate models (GCM)** or **regional climate models (RCM)**, Box 2].

In epidemiology, ENMs are commonly used to map the potential distribution of vector species (Table 1). For simple disease systems, this alone can give a reasonably good estimate of regions that could be affected by pathogen transmission [1], although abundance models should be preferred whenever

possible due to the more differentiated picture they provide. For more complex systems, such as those consisting of multiple different hosts, reservoirs and/or vectors, focusing on a single target species is often insufficient, as different species are likely to have different environmental requirements and competence to transmit diseases. In this particular case, the potential distributions of the different species involved can be modelled as separate components. The expected geographical ranges of these species can then be overlaid in order to derive areas of elevated risk of transmission [19]. For diseases where the involved species, their contribution to disease transmission, or their spatial distribution are unknown, the development of an ENM based on observed occurrence of the disease can be helpful [1]. In a way, this approach considers a pathogen and its transmission range as a species and its established populations. Regarding ectotherm arthropod vectors, this approach has the advantage of being able to additionally account for thermal impacts on the pathogen itself, such as the temperature-dependence of the EIP observed for several viral diseases [20].

While free and open-source software packages (like dismo[i] or biomod2[ii] for R; see https://www.r-project.org) make the development of ENMs relatively easy from a technical point of view, there are several aspects that need to be considered carefully in order to gain meaningful results [1, 21]. These include, for instance, sampling bias in the occurrence records [22], the regions where pseudo-absence locations are drawn from [23], potential niche-shifts of invasive species [24], and the choice of meaningful environmental predictors [25, 26].

Thorough out-of-sample validation of a model is crucial; and there are numerous evaluation methods available for different kinds of ENM. While these evaluation methods have been reviewed elsewhere [27], it seems worth pointing out that the **area under the curve (AUC)** of the **receiver operating characteristic (ROC)**, one of the most widely applied evaluation metrics, has been criticized for being potentially misleading (e.g., [28]).

Box 2. Climate models and scenarios

General circulation models (GCMs), also called global climate models, are used to simulate the earth's climate at large spatial scales and estimate its long-term future development. They usually consist of several coupled components such as the atmosphere, ocean dynamics, sea ice, and vegetation. International efforts in climate modelling are coordinated through the Coupled Model Intercomparison Project (CMIP, http://pcmdi-cmip.llnl.gov), and GCM output data are made available through the various data nodes of the Earth System Grid Federation (ESGF, https://esgf.llnl.gov). Since running GCM simulations is computationally expensive, some finer-scale processes, such as convection, have to be heavily parameterized in global-scale models. However, regional climate models (RCMs) driven by a GCM can be used to make up for this on smaller spatial scales. The Coordinated Regional Downscaling Experiment (CORDEX, http://www.cordex.org) provides a common framework for such initiatives.

The Intergovernmental Panel on Climate Change (IPCC) provides the scientific basis to assess climate change, suggest adaptation and mitigation strategies, and highlight impacts and future risks for decision-makers. The IPCC assessments are compiled by hundreds of leading and volunteering scientists, they undergo multiple rounds of review to ensure objectivity, and underlie negotiations at the Conferences of the Parties (COP) of the United Nations Framework Convention on Climate Change (UNFCCC). In the latest assessment, the Fifth Assessment Report in 2013, new climate-change scenarios, so-called representative concentration pathways (RCPs), were developed. They describe a wide range of possible magnitudes of climate change by specifying concentrations and corresponding emissions. Although not directly based on socioeconomic storylines like the former IPCC Special Report on Emissions Scenarios

(SRES), they are additionally based on short-lived gases and land-use changes [117]. The start-point for all four RCP scenarios is 2006, with a baseline historical period from 1986 to 2005. These RCP*x* scenarios lead to a defined additional radiative forcing by 2100 (increase by *x* W/m^2), which can also be expressed as an increase in the global mean surface temperatures for 2081–2100. This increase for the different RCPs is expected to range between 0.3°C and 1.7°C (RCP2.6), 1.1°C and 2.6°C (RCP4.5), 1.4°C and 3.1°C (RCP6.0), 2.6°C and 4.8°C (RCP8.5) [118]. Both global and regional climate models rely on these pathways for future projections of climate change.

Table 1: Recent studies using environmental niche models to assess vector-borne disease risk under climate change.

Vector/pathogen modelled	ENM	Climate model[a] / scenario[b] / future time period[c]	Environmental variables	Country, region	Main findings	Refs
Aedes aegypti	MaxLike	NA[d] / RCP 4.5, RCP 8.5 / current, 2020s, 2080s	T[e], p[f]	Veracruz, Mexico	Data from the edges of the vector's distribution is valuable for monitoring changes in distribution understanding links between anthropogenic drivers and climate change	[97]
	Climate envelope	GCM: CCCma-CGCM2, CSIRO-MK2, NIES99, UKMO-HadCM3 / A2a, B2b / 2020s	t, p	Global	macroclimate is the main driver of the species range limits anthropogenic influence can help the species to survive in otherwise unsuitable climate	[98]
	Maxent	NA / A2a / 2050s	t, p	Brazil	the vector's range in Brazil will decrease in the future, but will spread further south	[99]
	Maxent	GCM: NA / NA (CMIP5) / 2020s, 2050s	t, p	Tanzania	risk for dengue is currently concentrated in the coastal areas large-scale spread is projected for 2050s	[100]
Aedes aegypti, Aedes africanus, Aedes albopictus	Biomod2 ensemble model	GCM: HadGEM2-ES / RCP8.5/ 2050s	t, p, NDVI[g]	Global	Zika's distribution may be far more constrained than dengue Zika is unlikely to become cosmopolitan in temperate regions	[80]
Aedes aegypti, Aedes albopictus	Maxent	6 GCM / B1, A1B, A2/ 2050s	t, p	Global	complex global rearrangements of potential distributional areas under climate change digitization and sharing of existing distributional data for vectors needs to be a priority	[101]
Aedes albopictus	GARP	GCM: MPI-ESM-LR / RCP 4.5/ 2050s, 2070s	t, p	Mexico, US, Italy, Brazil, Asia	ENM fit on occurrence data from different regions transfer to Mexico well	[102]

	Maxent	RCM: COSMO-CLM / A1B / 2020s, 2050s, 2080s	t, p, cargo movement	Europe	combining ENM with measures of cargo movement can help to identify hot spots for potential areas of introduction availability of transport data in Europe needs to be improved	[103]
	Maxent	GCM: CSIRO-Mk3.6.0 / RCP 2.6, 4.5, 6.0, 8.5 / 2030s, 2050s, 2070s	t, p	Germany	establishment in Germany is possible northward range expansion under climate change	[104]
Anopheles arabiensis	LOBAG-O	GCM: Hadley CM 3 / A1B, A2A, B2A / 2050s	t, p	Africa	the suitable range for the vector in Africa will be strongly reduced under climate change	[105]
Anopheles darlingi, Anopheles nuneztovari	Maxent	GCM: GISS-E2-R, HadGEM2-AO / RCP 2.6 /2050s, 2070s	t, p, topo[h], soil moisture, pop[i], lcov[j]	South America	vectors are projected to experience range expansion under climate change	[43]
Anopheles spp.	Maxent, BRT	GCM: GISS-E2-R, HadGEM2-ES / RCP 8.5/ 2070s	t, p, topo, terrestrial biomes	South America	current main vector will experience reduced habitat suitability under climate change other species of the genus show significant potential for expansion	[44]
Anopheles, *An. dirus,* *An. minimus,* *An. lesteri,* *An. sinensis*	Maxent	GCM: BCC-CSM1-1, CCCma_CanESM2, CSIRO-Mk3.6.0 / RCP 2.6, 4.5, 8.5 / 2030s, 2050s	t, p, lcov	China	the different vector species' ranges will react differently to climate change an over-all net increase in the population exposed to the vectors is expected	[46]
Culicoides imicola, *C. insignis,* *C. variipennis,* *C. sonorensis,* *C. occidentalis,* *C. brevitarsis*	Maxent	62 GCM / RCP 2.6, 4.5, 6.0, 8.5 / 2050s	t, p	Global	potential distribution is projected to broaden under climate change, especially in central Africa, United States and western Russia	[106]
Culicoides imicola	CLIMEX	GCM: CSIRO-MK3.0, Miroc-h / A1B, A2 / 1975, 2030s, 2070s	t, p, rh[k], irrigation	Global	vector's potential distribution under climate change is projected to expand northward in the northern hemisphere potential distribution may contract in Africa	[41]

Culicoides sonorensis	Maxent	GCM: CanESM2 / RCP 2.6, 4.5, 8.5/ 2030s, 2050s	t, p, topo, lcov, VPD[l]	North America	the current northern range limit of the vector is expected to shift northward under climate change	[42]
Lutzomyia evansi, Lutzomyia longipalpis	Maxent	GCM: CSIRO / A2, B2/ 2020s, 2050s, 2080s	t, p, topo	Colombia	the range of the vectors is projected to decrease in size under climate change	[45]
Lutzomyia intermedia, Lutzomyia neivai	GLM, MaxEnt, RF, SVM, GARP	GCM: HadGEM2-ES / RCP 4.5, 8.5 / 2050s	t, p	South America	the different vector species show a different response to climate change "Ecological niche models should be species specific, carefully selected and combined in an ensemble approach."	[81]
Lutzomyia flaviscutellata	6 SDM	17 GCM / RCP 4.5, 8.5 / 2050s	t, p	(Northern) South America	the suitable area for the vector is projected to expand towards higher latitudes and altitudes under climate change	[82]
Lutzomyia major, Lutzomyia tropica	biomod2 ensemble model	GCM: MPI-ESM-LR / RCP 4.5 / 2050s	t, p	Libya	coastal regions of Libya show higher risk because of more suitable climate risk of cutaneous leishmaniasis is projected to increase under climate change	[107]
Chikungunya	Maxent	5 GCM / RCP 4.5, 8.5 / 2030s, 2050s, 2070s	t, p, pop	Global	transmission potential is projected to increase across the globe under climate change some parts of India may see a relative decrease in transmission	[20]

[a] Names of the climate models being used (RCM or GCM, see Glossary and Box 1), unless their number exceeds 5.
[b] Climate change scenario: typically RCPs and/or scenarios following SREP, see Glossary.
[c] 2030s etc. = marks the center of the 30-year time period covered, stands for 2021–2040 or 2020–2039 depending on data source.
[d] NA = information not available.
[e] t = temperature.
[f] p = precipitation.
[g] NDVI = normalized difference vegetation index.
[h] topo = topography (elevation, altitude, slope, aspect ratio).
[i] pop = human population density.
[j] lcov = land cover, land use.
[k] rh = relative humidity.
[l] VPD = vapour pressure deficit.

Among the techniques available, Maxent [29] has been by far the most popular choice for studies of climate change impact on vector-borne diseases over the past few years (Table 1). This is somewhat surprising as there are several other established methods available [such as Bioclim, Boosted Regression Trees (BRT), Random Forest (RF), Generalized Linear Models (GLM), Generalized Additive Models (GAM), or Genetic Algorithm for Rule-set Production (GARP)] and from the numerous studies comparing their performances (e.g., [30–32]), no preferential method has emerged so far. Consequently, there is a new trend towards using an ensemble of different ENMs to make up for the uncertainties inherent to the individual algorithms [31, 33].

Most ENM-type models applied in disease modelling focus on vector distributions (Table 1). Among these, the most studied vector genus is *Aedes* (competent mosquito vector for diseases such as dengue, chikungunya, or Zika) followed by *Anopheles* (malaria mosquito vectors) and *Lutzomyia* (sand flies, vectors of leishmaniasis). While several ENM-type models for complete disease systems have been published recently [7, 34–36], only a few of them feature future projections under climate-change scenarios [20]. The projected future changes in vector ranges vary among species and regions. However, there is a general trend of range expansion towards higher latitudes and altitudes, while some of the regions that are most affected by VBD today may benefit from a decline in environmental suitability under climate change (Table 1).

ENM-type models are commonly applied across all spatial scales. When it comes to future risk mapping, however, they are mostly used on larger global to continental scales (Table 1). Consequently, most studies use global rather than regional climate models. Almost half of the studies in Table 1 incorporate data from more than one climate model. This is good practice, as this leads to better estimates of uncertainty in final model output [37].

Regarding the predictors being used, most models rely mainly on various metrics applied to temperature and precipitation (and combinations thereof,

such as ‘precipitation of the warmest month’), both of which have been identified as important drivers of VBD transmission [38]. Some models additionally use other input parameters that may influence host or vector distribution, such as measures of air moisture [39–42], soil moisture [43], topography [42–45] or land cover/land use [42, 43, 46]. Socioeconomic factors, such as human population density or vulnerability indicators can be included as well (e.g., [7]), but continuous future projections of these are often not available and they are subject to large uncertainties.

One main advantage of ENMs compared to mechanistic approaches is the non-necessity of detailed knowledge about the complex interplay between environment, vectors, hosts, and pathogens [1]. This makes them a practical tool for understudied, that is, ‘neglected’ VBD. However, this comes at the price of accuracy, and consequently ENMs are most useful on medium to large spatial scales. If at least some of the environment-dependent mechanisms are known, those can be used to refine the results [47]. And finally, estimates of distributions or abundances of host and vector species derived from ENMs can also serve as input data for mechanistic models [9].

Mechanistic models

Mechanistic models are built on biophysical relationships between environmental factors vectors, pathogens and hosts (Figure 2). These relationships are generally derived from laboratory- or field-based studies (see also section ‘Adaption and Evolution’). Different mechanistic approaches can be applied. The most common methodology is derived from the standard Ross–MacDonald model [3] or its generalization. A set of differential equations define the different compartmental stages of vectors and hosts (susceptible, exposed, infectious, and recovered for **SEIR** models, or susceptible, infectious, and recovered for **SIR** models). This set of equations can be directly utilized to model the population size in each compartment, based on their relationship to climatic factors [48]. The steady state solution of this system of differential

equations also yields the basic reproduction number, R_0. R_0 is commonly employed in epidemiology to estimate the propensity of an outbreak to expand ($R_0 > 1$) or to shrink ($R_0 < 1$) in a fully susceptible population. Mathematical formulations of R_0 are available for several VBDs. They depend on the number of vectors and hosts considered in the model; see, for example, [49] for a one-host–one-vector formulation of R_0 for malaria, [50] for a two-hosts–one-vector formulation of R_0 for African trypanosomiases, or [51] for a one-host–two-vectors formulation of R_0 for Zika. Other empirical mechanistic models are based on environmental risk factors, such as fuzzy logic models to simulate the risk of malaria [52], or empirical rule-based models, to assess the risk of helminth infections in ruminants based on soil moisture availability and temperature conditions [53].

Mechanistic models can be utilized to model the risk of VBDs backwards (using past environmental data) or forwards (using demographic, economic, and climate-change scenarios) in time. They are generally driven by daily or monthly climate data to simulate the burden of a particular VBD. Their complexity varies; some models include additional effects of population density, surface hydrology [54], and herd immunity factors [55].

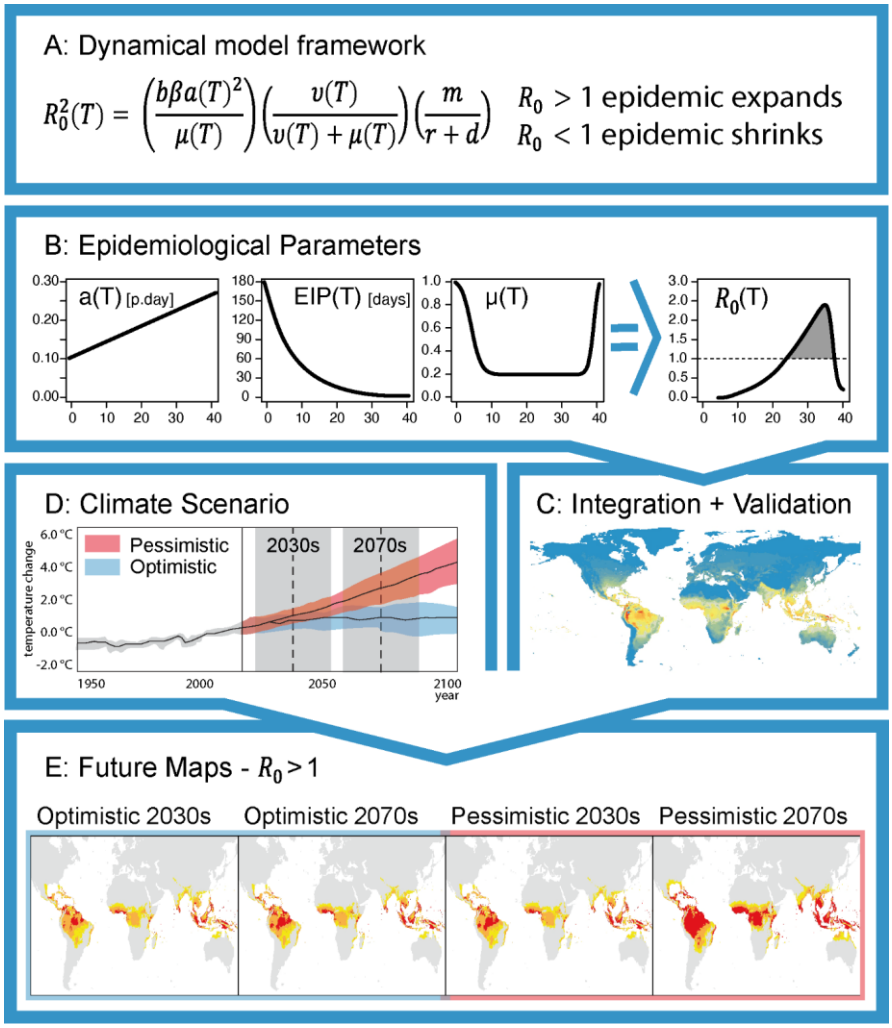

Figure 2. Typical workflow of a mechanistic disease model derived from the Ross–MacDonald framework [R_0(T) model]. (A): Dynamical model framework. T = temperature (°C); b = vector-host transmission probability; β = host-vector transmission probability; m = vector-to-host ratio; r= recovery rate; d = infectious recovery rate; a(T) = vector biting rate per day; EIP(T) = 1/υ(T) = extrinsic incubation period in days; μ(T) = vector mortality rate. (B): Epidemiological parameters derived from laboratory experiments or field data are fed into the model to gain an estimate of R_0(T). (C): A risk map is derived from the model. (D): A set of future climate-change scenarios and relevant time frames is chosen. Shown here is the observed and expected future average temperature increase over time for an optimistic (blue) and a pessimistic (red) climate change scenario. Color shadings around the black lines show an estimate of the uncertainties. (E): Using data from global or regional climate models, further projections for the selected scenarios and time frames (grey vertical bars in panel E) are made. Ideally, different climate models are used to drive the model.

In terms of methodology, the first necessary step (which is common to all modelling approaches) is model validation. For this purpose, mechanistic models are run for the past, and the output is compared to observed VBD burden indicators in space and time. This can be a daunting task as this step depends on the quality and spatiotemporal coverage of observed disease burden information (prevalence, incidence, number of confirmed cases etc.). Different skill scores (like AUC, correlations, or reliability diagrams) are employed to estimate the model capability in reproducing past observed outbreaks and mean seasonality of a VBD. The mechanistic model is then projected forward in space and time, using calibrated climate model data outputs and population scenarios, to estimate future human populations at risk (see [56, 57] for malaria).

Another significant progress lies in the study of historical VBD outbreaks and their relationship with climate variability. An R_0 model showed optimal climatic conditions when an outbreak of bluetongue occurred in northern Europe in 2006 [58]. A similar modelling framework highlighted optimal environmental conditions for mosquito borne transmission risk of Zika virus over South America in 2015, when the largest outbreak occurred [51]. These findings are consistent with former results by Patz *et al.* [59], who showed the capability of a mechanistic model to reproduce past dengue outbreaks over Nicaragua, Honduras, and Thailand. Another advantage of mechanistic models lies in their integration with operational seasonal climate forecasting systems to anticipate the risk posed by a particular VBD for the upcoming season [60–62].

Table 2. Recent studies using mechanistic models to assess vector-borne disease risk under climate change.

Vector/pathogen modelled	Model type	Climate model[a] / scenario[b] / future time period[c]	Environmental variables	Country, region	Main findings	Refs
Aedes albopictus	Mapping indicators of climatic constraints	10 RCM / RCP 4.5, 8.5 / 2020s, 2050s	T[d], p[e]	North America	northward range expansion predicted under climate change additional field studies and surveillance needed to better identify relevant environmental factors	[70]
	Multi-model approach: climatic suitability, seasonal activity	RCM: EBU-POM / A2 /2010s, 2080s	t, p, photoperiod	Serbia	most of Serbia is projected to become significantly more suitable for the vector under climate change	[68]
	Fuzzy logic	GCM: EMAC, CMIP5 multi-model ensemble / A2, RCP 8.5 / 2050s	t, p, rh[f]	Global	environmental conditions in the tropics are projected to become less suitable under climate change, while suitability increases in other regions	[69]
Aedes aegypti	CLIMEX	GCM: CSIRO-Mk3, MIROC-H / A1B, A2 / 2030s, 2070s	t, p, rh	Global	environmental conditions in the tropics are projected to become less suitable under climate change, while suitability increases in other regions	[39]
Anopheles gambiae, Anopheles arabiensis	CLIMEX	0.1 and 2.0 °C increase by 2100; increased precipitation seasonality	t, p, rh	Africa	climate change effects on vector distribution are projected to be strongest in eastern and southern Africa	[40]
Avian malaria	Epidemiological model	RCM: HRCM / A1b, RCP 4.5, 8.5 / 2010–2100 (continuous)	t, p	Hawaii	abundance and diversity of Hawaiian bird populations are projected to decrease under	[108, 109]

Vector/pathogen modelled	Model type	Climate model[a] / scenario[b] / future time period[c]	Environmental variables	Country, region	Main findings	Refs
					climate change due to higher potential for avian malaria current conservation strategies are insufficient	
Chikungunya	R_0	RCM: CRCM5 / RCP 4.5, 8.5 / 2020s, 2050s	t, p	Canada	the current risk for chikungunya in Canada is low small parts of southern coastal British Colombia are projected to become progressively suitable under climate change	[71]
Dengue	Ross–MacDonald (relative vectorial capacity)	5 GCM / RCP 8.5 / 2080s	t, DTR[g]	Global	there is a strong connection between epidemic potential and diurnal temperature range large increases in epidemic potential are projected under climate change	[72]
	CIMSiM, DENSiM	+1 °C	t, virus importation rate	Malaysia	moderate increases in temperature do not necessarily lead to greater incidence	[110]
	GAM and uncertainty	RCM: COSMO-CLM / A1b / 2020s, 2050s, 2080s	t, p, rh, pop[h], urbanisation, GDP per capita and population size	Europe	climate change is likely to contribute to increased dengue risk	[73]
	CIMSiM, DENSiM	GCM: ECHAM5 / A2, B1 / 2050s	t	Australia	depending on which climate scenario is used, dengue risk may be projected to increase or decrease	[74, 75]
Dirofilariasis	GIS-based	NA[i] (Russian Committee of Hydrometeorology) / NA / 2030	t	Former USSR	an increase of potential transmission area and population exposure is projected under climate change	[111]

Vector/pathogen modelled	Model type	Climate model[a] / scenario[b] / future time period[c]	Environmental variables	Country, region	Main findings	Refs
Malaria	Five malaria models: LMM_RO, MIASMA, MARA, VECTRI, UMEA	5 GCM / RCP 2.6, 4.5, 6.0, 8.5 / 2030s, 2050s, 2080s	t, p, socioeconomics	Global	an overall global net increase in climate suitability and population at risk is projected under climate change. Future risk increases in tropical altitude regions	[57]
	R_0	GCM: HadCM3 / A1B / 2020s, 2050s, 2080s	t, NDVI[j], pop	Africa	a modest increase in the overall area suitable for malaria transmission is projected under climate change, with a net decrease in the most suitable area	[63]
	Malaria Ecology Index	16 GCM / A1B / 2080s	t, p	Global	a strong increase in malaria R_0 is projected under climate change	[112]
	VECTRI	GCM: CanESM2, MPI-ESM-LR, IPSL-CM5A-LR, MIROC-ESM / RCP 2.6, 8.5 / 2030–2099	t, p, pop, lcov[k]	Africa	land use change effects on climate are projected to be of minor importance for malaria	[64]
	VECTRI, LMM	5 GCM, 18 RCM / RCP 2.6, 4.5, 6.0, 8.5 / 2020s, 2050s, 2080s	t, p, pop	Eastern Africa	malaria transmission is projected to move to higher altitudes under climate change	[65]
	Epidemiological model: lifetime transmission potential	8 GCM / A2 / 2050s	t	Kenya	downscaling of coarse-scale GCM output can improve epidemiological models	[113]
Rift Valley Fever	LRVF	GCM: GFDL ESM 2M / RCP 4.5, 8.5 / 2011–2050, 2051–2099	t, p	Eastern Africa	there is a high risk for further spread of RVF under climate change	[66]
West-Nile Fever	DyMSiM	GCM: NCCSM / A2, B1 / 2050s, 2090s	t, p	US	vector activity is projected to lengthen under climate change	[67]

[a] Names of the climate models being used (RCM or GCM, see Glossary and Box 1), unless their number exceeds 5.
[b] Climate change scenario: typically RCPs and/or scenarios following SREP, see Glossary.
[c] 2030s etc. = marks the center of the 30-year time period covered, stands for 2021–2040 or 2020–2039 depending on data source.
[d] t = temperature.
[e] p = precipitation.
[f] rh = relative humidity.
[g] DTR = diurnal temperature range.
[h] pop = human population density.
[i] NA = information not available.
[j] NDVI = normalized difference vegetation index.
[k] lcov = landcover, landuse.

Most mechanistic models tend to project an increase in VBD transmission risk to higher latitudes and elevation in the future (Table 2). However, marked differences are shown in the literature, depending on the considered VBD, the studied region, the selected GCM and emission scenario, and the employed disease and vector model. Future risk of malaria transmission is generally expected to increase in the tropical highlands, particularly in eastern Africa where the local population will be highly susceptible to infection [57, 63–65]. Conversely, malaria transmission risk is likely to decrease over the warmer plains of western Africa [57] and at the fringes of its current distribution across the Sahel. Rift Valley fever might also be on the rise in eastern Africa in future [66]. The West Nile virus transmission season in the USA might lengthen, leading to increased disease burden [67]. Important mosquito vectors such as *Aedes albopictus* and *Aedes aegypti,* which are competent to transmit dengue, Zika, and chikungunya, are expected to spread further north in Europe [39, 68, 69] and North America [70], while their future range might contract over the tropics due to extreme temperature conditions [39, 68–70]. The diseases they transmit, like chikungunya and dengue are likely to follow similar trends [71–75].

Mechanistic models can be useful; however, there is still room for improvement. Because they require dynamic drivers available in both space and time, they often lack important parameters, such as socioeconomic and vulnerability indicators, land-use change factors, host immunity parameters, population movement, and indicators of disease-control measures in place. This caveat is a critical point, in particular when considering the progress made in malaria control over the African continent during the past decades, in a warmer climatic background [76].

Challenges in modelling vector-borne diseases under climate change

Using climate data in VBD modelling

The usage of both ENM and mechanistic models has proven to be useful in anticipating the spread of invasive vector species. One of the best examples is the Asian tiger mosquito, *Ae. albopictus*, one of the most invasive species worldwide. Several modelling studies, based solely on environmental factors, anticipated the spread of *Ae. albopictus* in many European countries, years before that species was introduced[iii] [77, 78].

Future projections of disease models need to be carried out for an ensemble of calibrated global (GCM) or regional (RCM) climate models (Box 1), because of the different sensitivities of these climate models to global warming. GCMs are often favoured over RCMs even for national-scale models. This might be related to the output from GCMs being readily available in preprocessed formats from data portals such as worldclim.com or ccafs-climate.org. Output from RCMs is usually free to use for scientific purposes as well, but often requires additional processing before it can be easily utilized by the impact modelling community. Simulating the impact of extreme weather events on the VBD burden remains difficult, in particular when using climate-change scenarios. However, sensitivity experiments could be designed to test the sensitivity of VBD models to idealized temperature and rainfall distributions.

The climate model outputs used to drive the model, such as rainfall and temperature, have to be statistically calibrated ('bias correction') with respect to observed climate [79]. This is an important necessary step because VBDs are sensitive to critical climatic thresholds – for example, *Plasmodium falciparum* transmission by *Anopheles* mosquitoes starts when the temperature exceeds 18°C [61]. Impact simulations have to be driven by an up-to-date ensemble of emission scenarios (**representative concentration pathways, RCPs**), consistent with the guidelines of the **Intergovernmental Panel on Climate**

Change (IPCC), in order to provide decision makers with a range of best- and worst-case scenarios. The impact of initial conditions used to perform the long-term climate change scenarios also needs to be investigated to provide additional uncertainty estimates. Ideally, uncertainties related to the disease models, the different climate models, and the various emission and population pathways have to be communicated to end users [77], and this is a difficult task. Overall, the usage of different climate models and emission scenarios in various future risk assessments of VBD has greatly improved over the past 10 years for Europe and the world (Tables 1 and 2), thanks to significant funding efforts from national and European research councils.

Model approaches and their comparability

The parallel or joint use of multiple disease models within the same study in order to gain more reliable results is increasingly common (Tables 1 and 2; [44, 57, 65, 80–82]). However, there still appears to be a gap between the mechanistic and correlative modelling communities, with studies utilizing both approaches being rare exceptions. This may reflect differences in the underlying paradigms leading to scepticism towards the unknown, but also with differences in model outputs (e.g., R_0 vs. 'suitability') that make direct comparisons difficult. The Coupled Model Intercomparison Project (CMIP) has done an excellent job in setting standards for climate models and thus granting comparability of models created by researchers across the globe. A similar project for VBD modelling could potentially work in a similar manner by defining standard output variables for all disease models. Such a large intercomparison of impact models was pioneered by the ISI-MIP project [83] but it should be further encouraged and funded in the near future to include a larger ensemble of disease and vector models.

Cross-sectoral comparison of climate change impacts

Changing long-term trends, extreme weather events, and climate variability have various direct and indirect impacts which will increasingly interact. For

instance, there are negative consequences of climate change on biodiversity [84], which, in turn, is closely related to ecosystem functioning and services [85]. A loss of biodiversity and ecological complexity is likely to have consequences for the stability and resilience of ecosystems. For example, a loss of native predators or reduced competition through native mosquitoes may facilitate establishment of invasive vector species such as *Ae. albopictus*. As human society depends on these traits in many sectors (e.g., health, food production, and economy), these negative feedback loops can hardly be ignored. Biodiversity and ecosystem functioning are also buffering the impacts of climate change and particularly of climatic extremes [86]. Additionally, climate change may have an influence on poverty [87] and can hamper food security [88], which can further increase the population's vulnerability to VBDs.

Clearly, there is a need for multisectorial risk assessments, including the links between climate change impacts on agriculture and food production, water resources, biodiversity and ecosystem services, and health.

Health and vector data availability

One of the greatest challenges in VBD modelling, regardless of the type of model being used, is undoubtedly the acquisition of the required input data. Much can be learned from the climate-modelling community, which is well organized and publicly shares their data on the centralized repository of the Earth System Grid Foundation (ESGF, https://esgf.llnl.gov). Such a repository, that is jointly used by all scientists across the globe for occurrence records of arthropod vector species, is currently still missing. A promising attempt in this direction is the VectorMap platform offered by the Walter Reed Biosystematics Unit of the Smithsonian Institution (http://vectormap.si.edu), where entomologists can share their field records with the scientific community. For Europe, the VectorNet project hosted by the European Centre for Disease Prevention and Control and the European Food Safety Authority[iv] follows a similar approach, but only publishes maps at a 'regional' level without

providing scalar coordinates. Another interesting approach is followed by the German 'Mückenatlas' citizen science project (https://www.mueckenatlas.de). Here, the general population is asked to catch and send in mosquitoes (along with information on time of capture and location) which will be identified by experts and entered into a database (not publically accessible yet). For important mosquito vectors, publicly available global occurrence data sets exist (e.g., *Ae. aegypti* and *Ae. albopictus* [89]), but they currently do not offer the possibility for real-time updates of newly found records. While these examples are a step in the right direction, what is ultimately needed is a unified, publicly accessible global database for vector-occurrence records. The Global Biodiversity Information Facility (http://www.gbif.org) already provides such necessary infrastructure; it is now up to the VBD community to realize and optimize its potential.

In theory, for human- or livestock-related cases of VBD it should be relatively easy to compile anonymized, georeferenced global databases. The data for this exist, at least for notifiable diseases that are recorded by the national health agencies, but are difficult to access. Current global systems, such as ProMED-mail, HealthMap, or WHO's Global Outbreak Alert and Response Network (GOARN), mainly communicate current cases and outbreaks, rather than providing an accessible, structured archive of laboratory-confirmed cases. The Global Health Data Exchange (http://ghdx.healthdata.org) has the potential to fill this niche if spatiotemporal resolution of the data can be improved. The Malaria Atlas Project is an example of good practice: globally observed malaria prevalence data and ENM model outputs can easily be accessed and downloaded from the related web site (http://www.map.ox.ac.uk). At the European level, the Expert Groups of Health Information (EGHI) and Health System Performance Assessment (HSPA) are currently working on improving the health data information structure. However, this is a difficult task as there are many parties involved [90]. Of course, observed health data can suffer from a variety of problems related to the consistency of disease surveillance systems

(over/under-reporting issues), the quality and modus operandi of public health systems in a given country and region, or the accuracy of diagnostic tests to confirm clinical cases. Still, it can be gathered in a much more systematic and comprehensive way than any kind of vector-occurrence data.

Adaptation and evolution – a stony path

Another critical point is evolution and adaptation. Important model parameters such as biting rate, EIP, or mortality rate, are very often derived from old published studies (see e.g., [91, 92] for the EIP of dengue). Vectors and pathogens have changed over recent decades, and there is a significant need to improve and update what K. Lafferty calls 'thermal response curves of VBD' [93]. There is huge potential for vectors to mutate and adapt to new environmental conditions; and a vector's adaptation can greatly vary in space and time. New mosquito infection experiments that are conducted in the laboratory are needed and should be performed at various temperature and humidity conditions, using different strains of pathogen and fresh vectors collected from different populations [94]. Because vectors rarely experience laboratory conditions, these experiments should further be complemented by field studies [95] to also better estimate vector mortality, the relationship between local rainfall and carrying capacity, and vector-to-host ratios and to track the evolution of vector behaviour in the field. Overall, interdisciplinary approaches, involving health specialists, field entomologists, biologists, mathematicians, and climate scientists, are and will be key to improving VBD models in the future.

Climate services – the connecting bridge

Climate services translate climate data and information into customised tools, products and information to support decision-makers to make informed decisions when addressing existing or emerging risks. Although various good examples for the implantation of climate data in VBD risk assessment already exist, the lack of transfer of knowledge outside the scientific realm often

prevents practical applications of the gained insights. Bridging this gap between science and the public sector is essential for developing solutions to climate change [96]. One example is the 'Healthy Futures' project, that aims to communicate several aspects of high-impact VBDs in eastern Africa through an interactive online atlas (http://www.healthyfutures.eu).

Concluding remarks and future perspectives

Great progress has been made in understanding the possible impacts of climate change on VBDs by means of correlative, mechanistic, and hybrid models. The increasingly common use of ensemble models is an important step towards better reliability and assessment of uncertainties. However, mechanistic and correlative models are still mostly used separately. It is now time for researchers from different backgrounds to join their forces to bring VBD research and modelling to the next level.

Although methodological approaches and climate change input data have improved, open questions remain (see Outstanding Questions). Cross-sectoral comparison of climate change impacts is in its infancy and needs to be assessed by multisectorial risk assessments at the agriculture, water resources, and health nexus. The development of climate service tools based on mechanistic and ecological niche models is needed to guide decision-making processes. There is a need for perturbed parameter experiments for mechanistic models and large multivariate statistics for ENMs to describe models' uncertainties. Model outputs have to be validated with respect to observed health data. The impact of climate modes of variability on VBD burden in Europe, for example, North Atlantic Oscillation and Atlantic Multi-Decadal Oscillation, has not been investigated and tested in detail yet. Mosquitoes and pathogens have also evolved: there is a need for new field- and laboratory-based studies in closer cooperation with modellers to improve model parameter setting. Further integration of remotely sensed data will also support the development of operational forecasting systems and early-warning systems.

In conclusion, after many decades, during which VBDs hardly played a role in Europe, awareness is rising. It is important in times of climate change and globalization to build up appropriate competences and bring together existing knowledge in research in close cooperation with policy, practitioners, public health, and the population concerned, to develop tools and measures that can identify, anticipate, assess, and mitigate risks at an early stage. Of great importance is knowledge already gained in more affected areas of the world to develop concepts and models which can be adapted for temperate regions under changing climatic conditions. That is what Jürg Utzinger, in a recent presentation at the 'Impact of Environmental Change on Infectious Diseases' conference in May 2017, in Trieste, called the 'need for reverse innovation'.

Outstanding questions

- How can the comparability between different modelling approaches be increased?
- How can mechanistic and correlative (ENM-type) models be coupled with each other?
- How can extreme events, precipitation regimes, and seasonality be depicted more accurately in models?
- How can entomological data of vector distributions and anonymized human clinical data be shared more effectively across the globe?
- What is the next step towards cross-sectoral studies of climate change impacts to further investigate the links between the biodiversity–food–water– health nexus?

Glossary

Area under the curve (AUC): the area under the ROC curve (see below) is commonly used for assessing a model's performance in distinguishing between (in this context) presence or absence of a species. An AUC of 1 is considered a

"perfect" model, while a value of 0.5 indicates that the model is not better than a random guess.

Environmental niche model (ENM): a model that estimates the ecological niche (or aspects thereof) of a species based on the environmental conditions at locations where the species is known to exist. It can be used to examine species-environment relationships or as a species distribution model (SDM) in order to predict (changes in) species occurrences in space and time.

Extrinsic incubation period (EIP): the time that needs to pass after a vector's infectious blood meal before it can transmit the pathogen on to another host.

Global Climate Models or General Circulation Models (GCM): models that are used to simulate the earth's climate on a large scale (See Box 2 for details).

Intergovernmental Panel on Climate Change (IPCC): the IPCC defines itself as the "international body for assessing the science related to climate change". Its Assessment Reports aim to make the state-of-the-art in climate research accessible for policy makers and provide the scientific basis for the UN Climate Conferences.

Receiver operating characteristic (ROC): the ROC curve is used when a continuous model output (e.g., probability of presence of a species) is translated into binary information (e.g., presence/absence of the species). It illustrates how the ratio of true vs. false positives varies with different thresholds for the distinction between positive and negative.

Regional Climate Models (RCM): models that can be seen as refinements of GCMs that are able to better reflect local conditions on smaller spatial scales (see Box 2 for details).

Representative Concentration Pathways (RCPs): RCPs succeed the older SRES scenarios (see below).

SEIR/SIR: susceptible, exposed, infectious and recovered are the stages of an infection an individual can typically go through. They make up the different compartments of a typical mechanistic disease model.

Special Report on Emissions Scenarios (SRES): this report, published by the IPCC, introduced a range of scenarios for how emissions of greenhouse gases may change in the future, depending on how mankind reacts to the challenges of climate change. These scenarios have been the basis for IPCC assessment reports, policy making, and climate modelling, but by now have been superseded by the representative concentration pathways (RCPs).

Species distribution model (SDM): SDMs are used to estimate the geographical distribution of a species (or other taxonomic rank). They are often, but not always, based on an environmental niche model (ENM).

Vector-borne diseases (VBDs): illnesses in humans or other vertebrates that are mainly transmitted by other animals – often bloodsucking insects like mosquitoes.

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Resources

[i]https://cran.r-project.org/package=dismo

[ii]https://cran.r-project.org/package=biomod2

[iii]https://ecdc.europa.eu/en/publications-data/development-aedes-albopictus-risk-maps

[iv]https://ecdc.europa.eu/en/disease-vectors/surveillance-and-disease-data

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Appendix

List of abbreviations and acronyms

CDC: Centers for Disease Control and Prevention (US)

CMIP5: Coupled Model Intercomparison Project Phase 5

COVID-19: Coronavirus disease 2019

CHIKV: Chikungunya virus

DDT: Dichlorodiphenyltrichloroethane

DENV: Dengue virus

DNA: Deoxyribonucleic acid

ECDC: European Centre for Disease Prevention and Control

EIP: Extrinsic incubation period

ENM: Ecological/Environmental niche model

EM: Epidemiological model

GCM: Global Climate Model

IPCC: Intergovernmental Panel on Climate Change

MBVD: Mosquito-borne viral disease

RCM: Regional climate model

RCP: Representative concentration pathway

RNA: Ribonucleic acid

RVF: Rift Valley Fever

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

SDM: Species distribution model

USUV: Usutu virus

VBD: Vector-borne disease

WHO: World Health Organization

WNV: West Nile Virus

Glossary

Arbovirus: Short for arthropod borne virus: A collective term for viruses that are transmitted between vertebrate hosts through bloodsucking arthropods.

Autochthonous transmission: Transmission occurred at the place where a case was discovered, rather than a traveler being diagnosed with a disease that was contracted somewhere else.

Biological transmission: Multiplication or cyclic development of the pathogen needs to take place in the vector's body after the bloodmeal before further transmission can take place. Different from mechanical transmission, where the vector is only needed for carrying the pathogen from one host to another without further interaction between vector and pathogen.

Brackish water: Water with intermediate salinity. It typically occurs in coastal regions, where freshwater mixes with sea water.

Communicable disease: An infectious disease that can be transmitted from one organism to another. Not to be confused with the legal term "notifiable disease".

Contagious disease: A communicable disease that can be transmitted directly among hosts (without involvement of a vector species), though direct contact, bodily fluids, respiratory droplets, etc.

Coupled Model Intercomparison Project: An international cooperation project for improving the comparability between different climate models.

Diapause: A type of dormancy often emplayed by insects and other arthropods, that allows them to better endure phases of adverse environmental conditions such as frost or dought.

Dichlorodiphenyltrichloroethane (DDT): a powerful insecticide that has been banned from agricultural use globally for environmental reasons but is still sometimes used for vector control.

Extrinsic incubation period: The time that is needed for a mosquito to become infective after taking a blood meal from an infected host.

Encephalitis: A potentially life-threatening inflammation of the brain, typically due to a viral infection.

Endemic: A disease that is commonly found in a specific place is "endemic" there. Not to be confused with the concept of endemism in biogeographic contexts.

Epidemic: A disease event with a strong increase in the number of cases that goes clearly beyond what would normally be expected for a specific region (Porta, 2014).

Epizootic: The equivalent of an epidemic for non-human animals.

Host: The organism(s) in which an infectious agent occurs. For MBVD, this term usually refers to the vertebrates involved in the regular transmission cycle.

Dead-end host: A host that does not normally transmit the infectios agent further.

Reservoir host: An organism in which and infectious agent normally occurs and replicates. Often used for animals that are the main host of disease that can also affect humans.

Infection: An infectious agent entering an organism, followed by replication and/or development of the agent.

Infectious agent: Collective term for viruses, bacteria and other – often non-eukaryotic – microscopic elements that can cause a disease in an organism (Janeway et al., 2001; Porta, 2014).

Infectious disease: Any disease that is caused by an infectious agent. Often used as a synonym for "communicable disease", as most infectious diseases are indeed communicable. Tetanus is an example for a non-communicable infectious disease.

Kimakonde: Language spoken by the Makonde ethnic group in the region of today's Tanzania where the 1952/53 chikungunya outbreak took place.

Meningitis: A potentially life-threatening inflammation of the meninges (the membranes protecting brain and spinal cord), often caused by viruses.

Meningoencephalitis: An inflammation of both brain (encephalitis) and meninges (meningitis), often caused by viruses.

Mosquito: Common name for *Culicidae,* a family of blood-sucking insects within the order of *Diptera* (flies).

Notifiable disease: Any disease that must, by law, be reported to governmental authorities.

Outbreak: An epidemic that is spatially limited to a small area, such as a town or village (Porta, 2014).

Pandemic: A very large scale epidemic that takes place in multiple countries (Porta, 2014).

Pathogen: In its broadest sense, anything that can cause a disease. This includes infectious agents such as bacteria or viruses as well as non-biological substances, factors and processes.

Paris Green: Copper Acetoarsenite, a highly toxic substance formerly used as a pesticide.

ProMED-Mail: A global network for rapid reporting of outbreaks and newly emerging diseases.

Propagative transmission: After being ingested by an arthropod vector during a bloodmeal, the pathogen has to replicate in the vector's body before it can be transmitted further.

Pyrethrum: A natural insecticide made from *Tanacetum* flowers.

Representative concentration pathway: A series of scenarios for potential future developments oif climate change, part of the IPCC's 5th assessment report.

Serotype: A sub-group of viruses or microorganisms that can be distinguished based on their antigens.

Transmission: The process by which an infectious agent is passed on from one person or animal to another.

Vector: An organism that is able to transmit an infectious agent from one host to another, typically without having symptoms of a disease itself. For MBVD, this term refers to the mosquitoes involved in the transmission cycle.

Vector competence: The ability of a mosquito to transmit a pathogen. This is mostly governed by intrinsic factors, especially immunological and physical barriers different mosquito species possess and that different viruses may or may not be able to overcome (Kramer & Ciota, 2015). Vector competence is an important component of vectorial capacity.

Vectorial capacity: The ability of a mosquito to serve as a disease vector. In addition to vector competence, this includes factors like blood feeding rates, vector-to-host ratio and the probability of surviving the extrinsic incubation period (Kramer & Ciota, 2015).

Viremia, viremic: The condition of viral particles being present in an organism's bloodstream.

Virus: A type of microscopic infectious agent that consists of genetic material (either DNA or RNA) surrounded by protein coat. Whether or not viruses should be considered life-forms is controversial, as they do replicate and evolve but have no metabolism on their own.

Zoonosis, zoonotic disease: An infectious disease that can be naturally transmitted from vertebrate animals to humans (Porta, 2014). Many mosquito-borne viral diseases fall under this definition. Chikungunya, for example, also occurs in non-human primates.

List of publications and manuscripts not included in this thesis

Published

Fischer, D; Thomas, S M; Suk, JE; Sudre, B; Hess, A; **Tjaden, NB**; Beierkuhnlein, C; Semenza, JC: Climate change effects on Chikungunya transmission in Europe: Geospatial analysis of vector's climatic suitability and virus' temperature requirements, *International Journal of Health Geographics*, **12**, 51 (2013), DOI: 10.1186/1476-072X-12-51.

Thomas, S M; **Tjaden, NB**; van den Bos, S; Beierkuhnlein, C: Implementing Cargo Movement into Climate Based Risk Assessment of Vector-Borne Diseases, *International Journal of Environmental Research and Public Health*, **11**(3), 3360-3374 (2014), DOI: 10.3390/ijerph110303360.

Fischer, D; Thomas, S M; Neteler, M; **Tjaden, NB**; Beierkuhnlein, C: Climatic suitability of Aedes albopictus in Europe referring to climate change projections: Comparison of mechanistic and correlative niche modelling approaches, *Eurosurveillance*, **19**(6/4) (2014).

Vetter, V; **Tjaden, NB**; Jaeschke, A; Buhk, C; Wahl, V; Wasowicz, P; Jentsch, A: Invasion of a Legume Ecosystem Engineer in a Cold Biome Alters Plant Biodiversity, *Frontiers in Plant Science*, **9**(715), 1-12 (2018), DOI: 10.3389/fpls.2018.00715.

Andriamifidy, RF; **Tjaden, NB**; Beierkuhnlein, C; Thomas, SM: Do we know how 1 mosquito disease vectors will respond to climate change?, *Emerging Topics in Life Sciences*, **3**(2), 115-132 (2019), DOI: 10.1042/ETLS20180125.

Submitted

Cheng, Y; **Tjaden, NB**; Jaeschke, A; Thomas, SM; Beierkuhnlein, C: Centroid data in Ecological Niche Modelling: Effects on Model Performance in Context with Grain Size, submitted to *Global Ecology and Biogeography*

Cheng, Y; **Tjaden, NB**; Jaeschke, A; Thomas, SM; Beierkuhnlein, C: Deriving risk maps from epidemiological models of vector borne diseases: state-of-the-art and suggestions for best practice, submitted to *Epidemics*

In preparation

Tjaden, NB; Cheng, Y; Beierkuhnlein, C; Thomas, SM: Chikungunya beyond the tropics: Where and when do we expect disease transmission in Europe?

Other academic activities

In the following, I would like to list some of my academic activities that are directly or indirectly related to my thesis.

Conferences

Parts of this thesis were presented by myself at various conferences:

Invited Talk: "Ökologische Artverbreitungsmodelle in der Bekämpfung von Arbovirosen", Seminar on arboviral diseases at the AKNZ of the Federal Office of Civil Protection and Disaster Assistance, Ahrweiler, April 15-17th, 2019.

Talk: "Chikungunya in Germany: Where and when could it happen?", National Symposium on Zoonoses Research, Berlin, Oct. 17-19th, 2018.

Talk: "Climate Change will expand the global potential for Chikungunya in the 21st century", Impact of Environmental Change on Infectious Diseases (IECD), Trieste, May 17-19th, 2017.

Poster: "Modelling Mosquito-Borne Diseases in a Changing Climate: Current State-of-the-Art and Challenges in Cross-Disciplinary Research", National Symposium on Zoonoses Research, Berlin, Oct. 17-19th, 2018.

Poster: "Using the Temperature-Dependence of the Extrinsic Incubation Period for Spatio-Temporal Risk Assessment: A case study for Dengue in Europe", National Symposium on Zoonoses Research, Berlin, Oct. 13-14th, 2016.

Poster: "Defining Risk Zones for Chikungunya Fever in Europe: A Biogeographical Approach", IBS 2015 - 7th International Conference of the International Biogeography Society, University of Bayreuth, Jan 8-12th, 2015.

Poster: "The ZOONOSIS RISKTOOL: Modelling Framework", Joint Conference - German Symposium on Zoonoses Research and 7th International Conference on Emerging Zoonoses, Berlin, Oct. 16-17th, 2014.

Poster: "The Pilot Project "Zoonose RISKTOOL": General Concept and First Results", Junior Scientist Zoonoses Meeting 2014, Hannover, June 2-3rd, 2014.

Teaching

- Taught "Introduction to R", a course for 1st semester M.Sc. *Global Change Ecology* and others, covering the basics of the statistical programming language R.
- Taught "Statistical modelling with R", a course for 1st semester M.Sc. *Global Change Ecology* and others, covering statistical tests (e.g. ANOVA) and statistical models from simple linear regression models to more advances GLMER.
- Co-taught "Foundations of Biogeograpical Modelling", a course for M.Sc. *Global Change Ecology* and others, covering the basics of handling spatial data in R, species distribution modelling, home range estimations, etc.
- Co-taught "R-spatial workshop" (in German), an internal workshop with the faculty and PhD-Students of the Department of Geography, introducing GIS applications of R.
- Co-taught "Methoden zur Vegetationskartierung" (in German), a field course for students of *Physical Geography* and similar programs, covering the basics of vegetation mapping in different environments

Reviewer activcities

I have peer-reviewed manuscripts for:

- Ticks and Tick-borne Diseases
- Epidemiology and Infection
- PLoS Medicine
- PLoS One
- Asian Pacific Journal of Tropical Medicine

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Declarations

(Eidesstattliche) Versicherungen und Erklärungen

Hiermit erkläre ich, dass keine Tatsachen vorliegen, die mich nach den gesetzlichen Bestimmungen über die Führung akademischer Grade zur Führung eines Doktorgrades unwürdig erscheinen lassen.

Hiermit erkläre ich mich damit einverstanden, dass die elektronische Fassung meiner Dissertation unter Wahrung meiner Urheberrechte und des Datenschutzes einer gesonderten Überprüfung hinsichtlich der eigenständigen Anfertigung der Dissertation unterzogen werden kann.

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Hiermit erkläre ich, dass ich keine Hilfe von gewerblichen Promotionsberatern bzw. -vermittlern in Anspruch genommen habe und auch künftig nicht nehmen werde.

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