

# Dengue and chikungunya: modelling the expansion of mosquito-borne viruses into naïve populations

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## SUMMARY

With the recent global spread of a number of mosquito-borne viruses, there is an urgent need to understand the factors that contribute to the ability of viruses to expand into naïve populations. Using dengue and chikungunya viruses as case studies, we detail the necessary components of the expansion process: presence of the mosquito vector; introduction of the virus; and suitable conditions for local transmission. For each component we review the existing modelling approaches that have been used to understand recent emergence events or to assess the risk of future expansions. We identify gaps in our knowledge that are related to each of the distinct aspects of the human-mosquito transmission cycle: mosquito ecology; human-mosquito contact; mosquito-virus interactions; and human-virus interactions. Bridging these gaps poses challenges to both modellers and empiricists, but only through further integration of models and data will we improve our ability to better understand, and ultimately control, several infectious diseases that exert a significant burden on human health.

Key words: emerging infectious disease, Arbovirus, *Ae. Aegypti*, *Ae. albopictus*.

## INTRODUCTION

The last 50 years have seen an expansion in the geographical range of several mosquito-borne viruses, such as dengue, West Nile, Japanese encephalitis and most recently, chikungunya and Zika viruses (Gubler, 1998b; Mackenzie *et al.* 2004; Rezza, 2014; Rodriguez-Morales, 2015). The factors implicated in this are many, including increased connectivity of human populations, expansion of mosquito populations beyond their native ranges, urbanization, climate change and lack of, or ineffective, mosquito control (Gubler, 1998b; Jones *et al.* 2008; Parham *et al.* 2015). Yet, despite our broad understanding of the processes underlying virus expansion, what determines specific patterns of spread is less well characterized and much of what we currently understand relies on theory and data from transmission in endemic areas. Most recently, the emergence of chikungunya in the Western Hemisphere has highlighted the importance of improving our understanding of how viruses are introduced into new environments, and whether they are likely to emerge and establish beyond their current ranges (Nasci, 2014; Weaver and Lecuit, 2015).

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Chikungunya belongs to the genus *Alphavirus* and is primarily vectored by two mosquito species: *Aedes aegypti* and *Aedes albopictus*. It was first identified in Tanzania in 1952, and until recently, human cases had been largely restricted to parts of sub-Saharan Africa, Southeast Asia and the Indian subcontinent (Weaver and Lecuit, 2015). Chikungunya comprises three distinct lineages and several sub-lineages, which appear to have had differential ability in expanding from, and establishing in, various parts of the world (Weaver and Lecuit, 2015). In the last decade, chikungunya has expanded its range considerably, including outbreaks in tropical and subtropical regions of the Caribbean and Central America, attributed to the Asian lineage (Leparc-Goffart *et al.* 2014), as well as seasonal incursions into more temperate regions in Southern Europe, attributed to the Indian Ocean lineage (Rezza *et al.* 2007; Grandadam *et al.* 2011).

The expansion and persistence of chikungunya beyond its historical distribution are, in part, dependent on the expansion of suitable ecological niches of the vectors. However, this alone is not sufficient for expansion, because dengue, a taxonomically-distinct but ecologically-related arbovirus, has persisted in many of these areas for decades (Gubler, 1998a). The difference in the timing and magnitude of the emergence of these viruses underscores the need to improve our understanding of the factors

that create the specific conditions affecting the likelihood of emergence.

Dengue, a member of the *Flavivirus* genus, is a complex of four antigenically-related serotypes (dengue 1–4), vectored by the same mosquito species as chikungunya. Endemic/epidemic dengue virus is thought to have first emerged from sylvatic dengue strains approximately 1000 years ago, in Africa or Asia, and was first associated with human epidemic transmission in the late 18th and early 19th centuries (Vasilakis and Weaver, 2008). By the mid-20th century, dengue was probably widespread in the tropics and subtropics, although high intensity transmission was relatively confined to Southeast Asia. In the 1970s, dengue began to re-emerge in South America, following the collapse of the *Ae. aegypti* eradication program (Gubler, 1998a, b). In the last several decades, all four serotypes have spread throughout the tropical and subtropical parts of the world, and today are endemic to most of Asia, Central and South America, the Caribbean and parts of Africa (Gubler, 1998a; Messina *et al.* 2014). Globally, it is estimated that over 50% of the world's population is at risk of dengue infection (Brady *et al.* 2012) and that 390 million cases of dengue occur each year (Bhatt *et al.* 2013).

As chikungunya and dengue continue to expand both at the margins of existing transmission locales as well as through discrete, longer-range introductions, mathematical and statistical modelling offer unique tools, which enable analysis of recent emergence events, and risk assessment and prediction of future emergence events. While there have been a number of recent papers reviewing mathematical models of mosquito-borne pathogens, these have largely been aimed at understanding disease transmission in endemic settings (Andraud *et al.* 2012; Reiner *et al.* 2013; Perkins *et al.* 2014). Here, we review existing contributions of modelling to understand the expansion of mosquito-borne viruses into naïve populations. We use the term naïve to refer to populations that are immunologically naïve to the virus under consideration, or at least to populations in which pre-existing immunity does not play a significant role in determining the likelihood of local transmission. We choose to focus on the case studies of chikungunya and dengue because they are transmitted by the same mosquito vectors, and modelling frameworks that have been developed for one virus can often be adapted for the other. In addition, by taking a comparative approach we can explore how differences between the viruses impact their ability to emerge in novel populations. In the first part, we identify the necessary factors for expansion of mosquito-borne viruses, discussing the relevant components of the process and contrasting the different modelling approaches. In the second part, we identify gaps in our understanding that lead to

challenges and opportunities for future modelling and empirical studies.

#### FRAMEWORK AND MODELLING APPROACHES

The expansion of mosquito-borne human viruses into naïve populations requires three distinct but related components: (1) the presence of a suitable mosquito vector; (2) the introduction of the virus from an external source; and (3) the ecological and epidemiological conditions permissive to local transmission. Changes in any one of these components, either short-term, such as seasonal fluctuations in adult mosquito populations, or over longer time scales, such as climate-driven changes in mosquito habitat, can lead to changes in the potential for virus expansion.

#### *Mosquito distributions*

The distributions of the primary *Aedes* vectors of chikungunya and dengue have changed significantly over the past century, due to both long-distance translocations and expansions along the margins of their native ranges (Tabachnick, 1991; Benedict *et al.* 2007; Medlock *et al.* 2012; Carvalho *et al.* 2014). Historically, *Ae. aegypti*, an anthropophilic mosquito, was endemic primarily to urban areas in tropical and subtropical regions but the species has been expanding farther into the Northern Hemisphere in recent years (Kraemer *et al.* 2015). This expansion is likely seasonal, but can support self-limited transmission, as was observed during a dengue outbreak in Key West, Florida in 2009–2010 (Radke *et al.* 2012). Overall, it has been shown that the range of *Ae. aegypti* is largely limited by yearly minimum low temperatures, below which its eggs are nonviable (Fischer *et al.* 2011b). As climate change alters the length of warming periods, the geographical range of *Ae. aegypti* egg viability is likely expanding, however the impact of warming on *Ae. aegypti* populations is not yet well understood. In a recent modelling study, Williams *et al.* (2014) demonstrate that *Ae. aegypti* abundance could increase or decrease depending on the rate of warming as well as the magnitude of temperature increase.

*Aedes albopictus*, while also found in tropical and subtropical regions, can tolerate lower temperatures than *Ae. aegypti* (Waldock *et al.* 2013). The eggs of *Ae. albopictus* can undergo diapause, providing a means of over-wintering in otherwise hostile environments. In particular, *Ae. albopictus* populations are now found throughout parts of Europe, particularly southern Europe, where the species was implicated in local transmission of dengue in Croatia in 2010 (Gjenero-Margan *et al.* 2011) and in France in 2013 (Marchand *et al.* 2013), local transmission of chikungunya in France in 2010 and 2014

(Grandadam *et al.* 2011; Delisle *et al.* 2015), as well as an outbreak of chikungunya in Italy in 2007 (Rezza *et al.* 2007). *Aedes albopictus* is also found across much of Eastern North America as far north as New York, where one locally acquired dengue case was reported in 2013 (CDC ArboNET, 2015), but this northern distribution is thought to be limited to summer months (Rochlin *et al.* 2013). Although *Ae. albopictus* can be found in close association with human domiciles, this species often dwells in suburban and peri-urban areas (Hawley, 1988) because it feeds on a broader range of vertebrate hosts (Rai, 1991; Faraji *et al.* 2014).

Changes in mosquito distributions can be caused indirectly by human activities, such as urbanization, water source alterations or movement of man-made containers that serve as mosquito breeding habitat. For example, *Ae. aegypti* was once found along the majority of the Australian coast and a large portion of Queensland and New South Wales (Russell *et al.* 2009). Today, *Ae. aegypti* populations are only found throughout Queensland, primarily in the northeast region of the state. This shift in distribution is attributed to changes in water infrastructure and technological advances, which resulted in the removal of suitable habitat (Russell *et al.* 2009). Mosquito distributions are also affected by direct human interventions, such as nuisance or targeted mosquito control efforts. These human-driven perturbations can impact the abundance and range of disease vectors over much shorter time scales. For instance, intensive control measures targeting *Ae. aegypti* and *Ae. albopictus* populations were conducted in Central and South America (especially Brazil) throughout the 1960s and into the 1970s with the goal of eliminating yellow fever. Following a sharp decline in disease burden, and with the advent of an efficacious yellow fever vaccine, these efforts were discontinued (Gubler, 1998b). As vector control measures waned, *Ae. aegypti* populations experienced a resurgence, and this species is now firmly established in the very areas from which it had been eradicated (Gubler, 1998a).

#### Modelling mosquito distributions

While mosquito biogeography defines the spatial limits of mosquito-borne pathogen expansion, our knowledge of the actual distribution of *Aedes* species is coarse, at best. There have been two major modelling approaches to characterizing the potential range of *Ae. aegypti* and *Ae. albopictus*: mechanistic and correlative (Fischer *et al.* 2014). Mechanistic or process-based studies quantify how aspects of mosquito life history are affected by climatic variables, usually with laboratory- or field-determined empirical relationships, and combine this with meteorological data to assess the suitability of particular regions to support *Ae. aegypti* and *Ae.*

*albopictus* populations. Most studies focus exclusively on temperature, and whether its effects on traits such as egg diapause and adult survival permit persistence (Nawrocki and Hawley, 1987; Kobayashi *et al.* 2002; Medlock *et al.* 2006; Takumi *et al.* 2009; Caminade *et al.* 2012). For example, a recent study by Brady *et al.* (2014) produced a model of the absolute limits of temperature on dengue transmission, taking into account daily and seasonal variation in temperature and its effect on both mosquito survival and viral replication within the mosquito. However, while temperature is perhaps the most crucial climatic variable for mosquito life history, it is certainly not the only one.

The correlative approach is species distribution (or ecological niche) modelling, which combines observational data about a species (usually occurrence data at known locations) with environmental (but potentially any relevant spatial) data to derive statistical models that can be used to predict a species' geographic distribution (Elith and Leathwick, 2009). A large body of work has been devoted to assess the current and future distribution of *Ae. aegypti* and *Ae. albopictus*, predominantly correlating mosquito presence data with climatic variables, often using climate predictions to project mosquito distributions into the future (Campbell *et al.* 2015). Due to its recent rapid expansion there has been an emphasis on *Ae. albopictus*, both globally (Benedict *et al.* 2007; Proestos *et al.* 2015), and regionally in Europe (Fischer *et al.* 2011a; Neteler *et al.* 2011) and the USA (Rochlin *et al.* 2013; Ogden *et al.* 2014), but a few studies have focused on *Ae. aegypti* (Cardoso-Leite *et al.* 2014; Khormi and Kumar, 2014). A recent study by Kraemer *et al.* (2015) used a temperature suitability mask adapted from Brady *et al.* (2014) to filter out regions based on the thermal limits of the species and combined this with a suite of climatic and land-cover variables to predict the global distribution of *Ae. albopictus* and *Ae. aegypti* at high spatial resolution. Temperatures, followed by precipitation and vegetation indices were the best predictors in their model. The distribution of both vectors largely agreed with what is known from surveillance data, although *Ae. albopictus* was predicted to occur more widely in China, Africa and parts of Europe than is currently reported.

While the correlative approach can take advantage of large spatial and temporal climatic datasets, the use of this approach is currently limited. For instance, most of these studies are based on long-term average data that do not predict fine-scale changes in mosquito distributions, although time-specific ecological niche modelling has been utilized to predict dynamic *Ae. aegypti* distributions in Mexico (Peterson *et al.* 2005). In addition, few studies address the introduction and dispersal of mosquito species, for example, via cargo movement

(Thomas *et al.* 2014). Furthermore, although meteorological variables such as temperature and precipitation play major roles in defining mosquito distributions, there are a number of ecological (such as competition) and anthropogenic factors that are known to have significant effects. Finally, local adaptation to micro-climates (Roche *et al.* 2015) can result in mosquitoes occurring in places that would not be predicted by modelling at large spatial scales.

#### *Introduction of the virus*

While necessary for the expansion of arboviruses, the presence of the vectors alone is not sufficient to predict emergence risk. For urban-centric transmission systems like dengue and chikungunya, the introduction of virus into novel susceptible populations is driven by human movement (Gubler, 1998b; Tatem *et al.* 2012; Bhatt *et al.* 2013). *Aedes aegypti*, in particular, moves very short distances (up to 120 m), so even at a local scale human movement patterns likely define the spread of infection within a city (Stoddard *et al.* 2009, 2013). However, one recent study recognized that within the flight range of *Ae. Aegypti* the role of the mosquito in spreading dengue has been underestimated (Thomas *et al.* 2015). As with many other human pathogens, long-distance introductions have largely coincided with an increase in global air travel and connectivity (Gubler, 1998b; Tatem *et al.* 2012).

Recent local transmission of chikungunya in Italy and France are thought to be linked to ongoing transmission of chikungunya in India (Rezza *et al.* 2007; Grandadam *et al.* 2011) and Cameroon (Delisle *et al.* 2015). The 2014 chikungunya outbreak in the Western Hemisphere began following the arrival of an infectious person from the Philippines in Saint Martin, an *Ae. aegypti*-abundant island in the Caribbean. Since then, over 1 million cases have been reported in the Caribbean and Latin America (Johansson, 2015). Importation of dengue by travellers returning, or visiting, from endemic areas (rather than the transport of infectious mosquitoes) is also believed to be responsible for initiating recent outbreaks in Queensland (Naish *et al.* 2014b), Texas (Murray *et al.* 2013; CDC ArboNET, 2015), Hawaii (Effler *et al.* 2005; Johnston *et al.* 2016) and Florida (Rey, 2014; CDC ArboNET, 2015).

Complicating the ability to understand the mechanisms of virus introduction in novel populations, and subsequently identify expansion, initial importations of the virus often go undetected. In particular, the majority of dengue infections are sub-clinical or asymptomatic (Bhatt *et al.* 2013). These patients are much less likely to self-quarantine than symptomatic patients, particularly in naïve regions, in which the virus may not be suspected. This increases the probability of contact with susceptible vectors and contributes to the emergence potential of

the virus. Although the clinical presentation rate of chikungunya is believed to be much higher than dengue (>75%) (Thiberville *et al.* 2013), one recent study from the Philippines suggests this might be an overestimate (Yoon *et al.* 2015). Furthermore, variability in surveillance systems and clinical services at the country level often leads to bias in the reporting of virus expansion and in the application of modelling studies. In particular, global interest in the spread of chikungunya increased considerably following the outbreak on La Réunion (LR), a setting in which there is well developed epidemiological surveillance and the virus has the potential to exert a significant impact on a wealthy nation, France. It is possible that outbreaks occur without detection or with greater underreporting in locations with less developed public health systems (Cash and Narasimhan, 2000).

#### *Modelling introduction of the virus*

A number of studies have focused on the risk of importation into specific locations that have either previously experienced sporadic local cases or where it is known that the mosquito vector is present. For example, the importation of dengue and chikungunya into Europe (Seyler *et al.* 2009), dengue into Italy (Quam *et al.* 2015) and chikungunya into the Americas (Johansson *et al.* 2014). Although almost all of these studies have focused on air travel, during the 2014 chikungunya outbreak in the Caribbean, air traffic volume was not a good predictor of the spread of chikungunya to new islands (Cauchemez *et al.* 2014). Instead a simple model of distance better characterized the spread suggesting that marine transport might have played an important role at a more regional level. Furthermore, human mobility patterns along road networks were important to explain the regional spread of chikungunya on the island of LR (Moulay and Pigne, 2013).

In other work, researchers have modelled mosquito distributions in tandem with human movement. In particular, Tatem *et al.* (2012) combined geospatial data and air traffic information to predict risks of vector-borne disease importation and establishment and have developed an online tool for visualizing these risks to aid in planning mitigation strategies (Huang *et al.* 2012). Similar approaches have been used by Gardner and Sarkar (2013), who coupled species distribution modelling to a model of the airline travel network to quantify the relative risk of dengue importation and establishment posed by each airport based on the likely presence of dengue-infected travellers.

#### *Conditions for autochthonous transmission*

Even in the presence of a suitable vector and with frequently imported human cases, local transmission

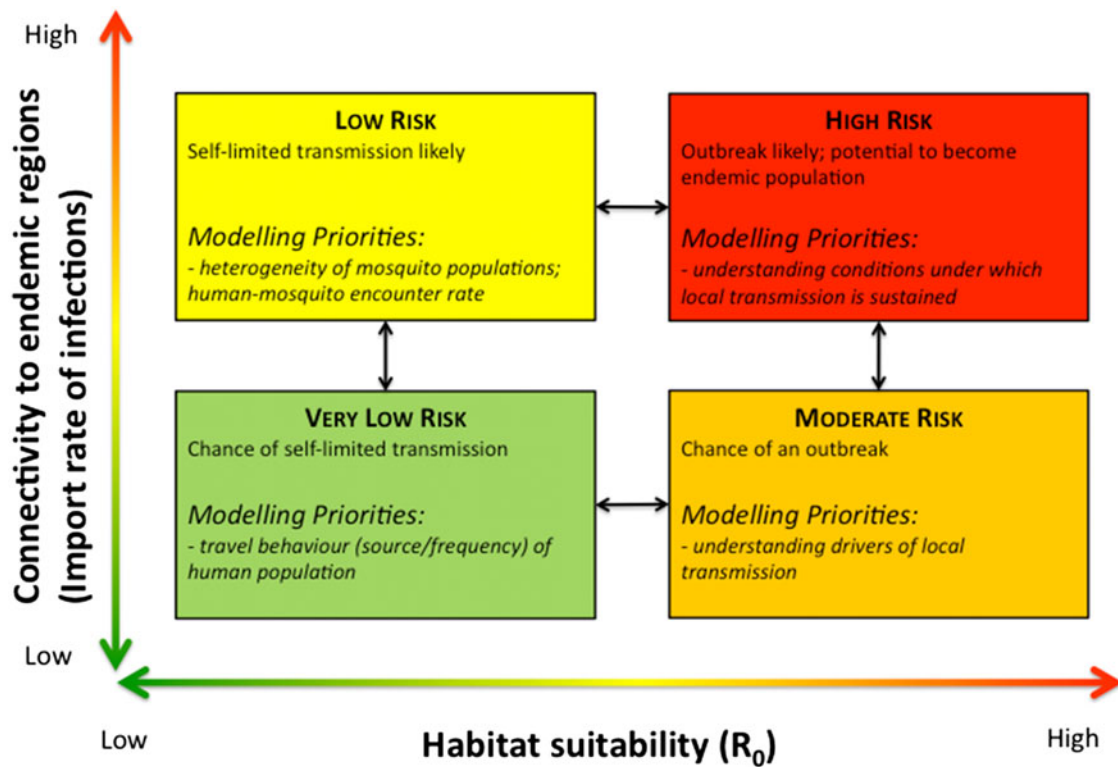


Fig. 1. Classification of naïve populations: risk for virus expansion and modelling priorities. Naïve populations can be categorized as either suitable or unsuitable habitat for the virus, which may change over time under the influence of environmental factors or the specific viral strain introduced (horizontal axis). Expansion into suitable habitats is limited by the frequency of introduction of the virus from source populations (vertical axis). Unsuitable habitats cannot support sustained transmission but short chains of self-limited transmission are possible. Modelling priorities broadly depend on the type of population under consideration: those at the lower risk levels are defined by the components most sensitive to change, affecting whether the populations are likely to move to a higher risk level.

cannot occur without the necessary ecological and epidemiological conditions. The sufficiency of these conditions can help categorize mosquito-borne transmission according to its ecological and epidemiological context (Smith *et al.* 2014). Specifically, Macdonald (1952) proposed two primary categories of transmission, stable and unstable, which, while stemming from malaria research, are relevant to all mosquito-borne pathogens.

From the perspective of the virus, we can distinguish between two distinct scenarios based on ‘habitat’ quality: (1) suitable habitat (stable conditions for transmission); (2) unsuitable habitat (unstable conditions for transmission). A suitable habitat is defined as an environment that has all the necessary conditions to support persistence of the virus; thus there is a non-zero probability of producing an outbreak. The rate-limiting step for emergence success in a suitable habitat is the introduction of the virus from an external source. In addition, following successful virus establishment, a suitable habitat has the potential to serve as a source of virus. An unsuitable habitat will have insufficient conditions at some stage of the emergence process. For example, while an introduction could lead to a short chain of transmission, large-scale outbreaks

are not possible. In unsuitable habitats, emergence failure could be due to inadequate mosquito abundance, insufficient contact between human and mosquito populations, or a lack of sustained environmental conditions to support continued transmission.

Although habitats can be classified as suitable or unsuitable, this classification is dynamic. Unsuitable habitats may become suitable either permanently, due to long-term climate change, or transiently, due to seasonal climatic variation, the latter of which is often indicated by epidemic behaviour. Likewise, suitable habitats may be rendered temporarily unsuitable due to extreme weather events or permanently unsuitable due to human actions (e.g. land use changes). Assuming the virus is initially introduced into an immunologically susceptible human population, then a basic reproductive number of one ( $R_0 = 1$ ) defines the threshold between habitat types. In Fig. 1, we summarize how habitat quality and frequency of virus introductions from source populations can interact to produce different levels of risk in naïve populations. In particular, populations may move from one risk group to another depending on, for example, seasonal changes in local mosquito populations (affecting

habitat quality), or seasonal changes in travel behaviour (affecting import rates). The modelling priorities at the lower risk levels are defined by the components most sensitive to change, which determine whether populations are likely to move to higher risk levels.

#### *Modelling autochthonous transmission*

Models that aid in categorizing the ecological context are thus essential for understanding the potential for autochthonous transmission. This is often decoupled from the importation step (except for Johansson *et al.* (2014)) partly because modelling of local transmission is often in response to the detection of an introduction. In this context, models have been used in a variety of ways, both to (a) understand the key drivers of transmission, as well as to (b) assess the future risk of transmission.

(a) *Understanding the drivers of autochthonous transmission in naïve populations:* A substantial part of the modelling of dengue and chikungunya in emergence settings has involved analysing outbreaks in real-time or after the event. Characterizing local transmission by the human-to-human reproduction number,  $R$  (the average number of secondary cases generated by a primary case), is often the first step in assessing the potential intensity of transmission and providing guidance for mitigation efforts. Methods developed for directly-transmitted pathogens have been adapted and applied to the 2005–2006 chikungunya outbreaks on LR as well as the 2014 outbreaks in the Caribbean. An empirical approach that requires an estimate of the distribution of the generation (or serial) interval of the pathogen (Fine, 2003; Wallinga and Teunis, 2004) and incidence data from the early part of the epidemic curve was used in both settings. For the outbreak on LR, Boëlle *et al.* (2008) estimated an initial  $R$  of 3.7, with a possible range 2–11, and Cauchemez *et al.* (2014) (using the exponential growth method of Wallinga and Lipsitch (2007)) found that the initial  $R$  for the islands of Saint Martin, Martinique and Guadeloupe was in the range 2–4.

While incidence data are often available in close to real-time, the window of time chosen can lead to variability in the estimates of  $R$  (Cauchemez *et al.* 2014). Further complicating this for dengue, and to a lesser degree for chikungunya, is the high percentage of subclinical and asymptomatic cases, as previously discussed. Low rates of clinical presentation lead to lower frequencies of reported cases, which in turn impact the ability to obtain accurate estimates of case numbers.

In addition, estimating the generation interval of the pathogen (the time distribution between symptoms in a primary case and that of its secondary cases) encompasses all aspects of the transmission process and requires the specification of time from

infectiousness to symptoms in the human host, time from infectiousness in the human host to a mosquito bite infecting the vector, time from infection to symptoms in the human host, and time between infection of the mosquito and a subsequent bite infecting a human host (Boëlle *et al.* 2008). Similar issues arise when fitting mechanistic models using variations of the Susceptible Exposed Infectious Recovered (*SEIR*) framework to the entire epidemic curve, because assumptions about these distributions are implicit in model structure and parameterization. Comparable estimates of  $R$  (in the range 3–4) were found using this approach for the outbreak on LR (Bacaër, 2007; Yakob and Clements, 2013). However, Dumont *et al.* (2008) parameterized a mechanistic transmission model with independent data for different cities on the island in 2005 and 2006, and found substantial variation in estimates of  $R$ . This variation was largely driven by differences in mosquito populations and a change in the extrinsic incubation period (EIP), highlighting that between-city and between-year differences were important to explain chikungunya incidence in space and time.

These analyses confirm that such locations were suitable habitat for the pathogen and that once introduced, chikungunya was able to invade. Retrospective analyses aimed at understanding the factors responsible for why locations were suitable habitat can help inform future surveillance and mitigation programs. For the Caribbean outbreak of chikungunya, Perkins *et al.* (2015) adapted the time series susceptible infectious recovered (TSIR) formalism used for directly-transmitted diseases to investigate whether the effects of environmental drivers could explain outbreak dynamics at the country level. Even at this coarse spatial resolution for both climate and incidence data, they revealed that climate-driven seasonality in transmission (specifically, mean temperature and precipitation) could explain variation in between-country dynamics. At the other extreme of spatial scales, modelling mosquito habitats as small as containers, a simulation-based framework for dengue, DENSiM (Focks *et al.* 1995), was successfully applied retrospectively to outbreaks in northern Australia (Bannister-Tyrrell *et al.* 2013). Their analysis demonstrated that inter-annual weather variation was one of the key determinants of whether an outbreak occurred in Cairns from 1991 to 2009. While this model is also able to make predictions about the impacts of specific vector control measures and the impacts of future climate, it requires detailed meteorological, entomological and demographic data as inputs, which limits its use to areas with extensive entomological surveillance. An alternative spatially-explicit, individual-based model that was calibrated on the 2003 Cairns dengue outbreak does not require the same entomological inputs but is still calibrated against mosquito trap data (Karl *et al.* 2014). Their

study supports the hypothesis that despite warmer temperatures and increased human mobility, a shorter virus strain-specific EIP largely explains the explosive outbreak in Cairns in 2008–2009 (Ritchie *et al.* 2013).

(b) *Assessing future risk of autochthonous transmission:* An alternative role for models is to extrapolate beyond what has been observed and understand the transmission potential in regions where  $R$  is not always above one, and not necessarily limited by a lack of virus importations. Some studies aim to quantify the potential for future transmission by explicitly modelling aspects of the transmission process. Most of these models, directly (or indirectly), link weather variables such as temperature to mosquito, and sometimes virus, population dynamics. Following the chikungunya outbreak in Italy, Poletti *et al.* (2011) coupled a stage-structured model of temperature-driven *Ae. albopictus* population dynamics to an epidemic model using the *SEIR* framework and demonstrated that variability in the probability of observing a major outbreak after the introduction of an index case was due to variation in the vector-host ratio. A similar approach was taken by Ruiz-Moreno *et al.* (2012), who predicted windows of risk for different regions of the USA, largely determined by the effects of regional temperature profiles on mosquito abundance, and Lourenço and Recker (2014), who analysed the 2012 dengue outbreak on Madeira. In addition, Johansson *et al.* (2014) incorporated temperature-driven estimates of mosquito life-history and the EIP into a branching process model to predict the probability of local transmission of chikungunya in new locations in the Americas. Overall 8 out of the 10 locations that were predicted to be the most likely locations for introduced chikungunya transmission in the first 4 months of the outbreak reported local cases within this time frame (Johansson *et al.* 2014).

In these and other studies, process-based models have been used to explore the sensitivity of poorly understood parameters. The most sensitive parameters are usually those associated with the mosquito part of the transmission cycle (Manore *et al.* 2014), in particular those pertaining to vector-host contact (Christofferson *et al.* 2014b), such as the vector-host ratio (Poletti *et al.* 2011) and the proportion of bloodmeals on human hosts (Ruiz-Moreno *et al.* 2012). The duration of human infectiousness is also a sensitive parameter and for the index case, the timing of introduction relative to the duration of infectiousness is crucial for determining the likelihood of autochthonous transmission (Christofferson *et al.* 2014b). Unfortunately, many of the most sensitive parameters are subject to uncertainty and thus building this uncertainty into model predictions is essential for assessing risk (Johansson *et al.* 2014).

In addition to these process-based models, there is a body of work on correlative models that use

statistical associations between historical prevalence data and climatic or environmental data to predict the future risk of dengue transmission (Racloz *et al.* 2012; Louis *et al.* 2014). Some of these studies are aimed at producing early warning systems for areas where dengue has occurred previously but not continuously. For example, Descloux *et al.* (2012) developed a statistical model relating climate, *Ae. aegypti* and dengue as an early warning system for New Caledonia. There was also intense interest in mapping the risk of dengue during the 2014 Brazil World Cup (Lowe *et al.* 2014). Most recently, a study assessing the risk of chikungunya transmission in Argentina emphasizes that it is only a matter of time before cases of chikungunya are reported in this region (Carbajo and Vezzani, 2015). An alternative approach uses the same methodology employed in mosquito distribution modelling, often to identify risk of transmission in regions where dengue has not yet been reported (Machado-Machado, 2012).

With many of these approaches assuming mechanistic or correlative associations between climatic variables and dengue/chikungunya transmission, it is natural to consider how long-term climate change might impact future emergence. Indeed, Naish *et al.* (2014a) reviewed the quantitative modelling approaches that have been used to assess the potential impact of climate change on future dengue transmission. Most of these studies couple current climate change projections with climate-based models that associate *Aedes* mosquito distributions and/or virus occurrence with climatic variables, such as temperature and humidity. For example, Fischer *et al.* (2013) investigated the impacts of climate change scenarios in Europe on chikungunya in *Ae. albopictus*, predicting the highest risk in France, Northern Italy and East-Central Europe by the end of this century. In a different study, Bouzid *et al.* (2014) combined climatic variables and socio-economic factors in statistical models built using contemporary dengue occurrence data from Mexico, then applied the model to climate change scenarios in Europe and predicted the highest risk of dengue in areas clustered around the Mediterranean and Adriatic coasts.

#### CHALLENGES AND OPPORTUNITIES

It is apparent that a significant amount of research has focused on the necessary conditions for mosquito-borne virus emergence: the presence of mosquito populations and the importation of the virus. However, studies looking at the sufficient conditions for emergence are fewer, and often in reaction to the detection of novel introductions and outbreaks. While our understanding of transmission in endemic regions has improved, there are certain gaps in our understanding that deserve more

attention within the context of emergence. In this section, we identify the major gaps for each subcomponent of the transmission cycle: (i) mosquito ecology; (ii) human–mosquito contact; (iii) mosquito–virus interactions; and (iv) human–virus interactions. We discuss how these challenges ultimately present opportunities for future modelling and empirical work.

(i) *Finer description of mosquito populations at a local scale*: Predicting local chains of transmission is complicated by the lack of characterization of mosquito populations at the relevant scales. We know that the spatial distributions of *Ae. aegypti* and *Ae. albopictus* are highly dynamic, even within relatively small urban areas (e.g. in Madagascar (Raharimalala *et al.* 2012), and in Florida (Leisnham *et al.* 2014)). While many models are able to successfully predict the geographical extent of mosquito species distributions, and even changes in these distributions due to long-term trends from climate change, these predictions are often over large spatial scales. Predictions about transmission at local scales are dependent on accurate projections of mosquito population sizes, which have yet to be fully understood.

Mosquito abundance is affected by a combination of environmental (Chaves *et al.* 2014), ecological and anthroponotic variables; and often complicated by the nonlinear interaction of these factors (Chaves *et al.* 2012). Mechanistic models that build such interrelations into descriptions of mosquito dynamics have rarely been applied and tested in emergence settings. A number of models have been developed for *Aedes* population dynamics that describe mosquito abundance as a direct function of food resources (Romeo Aznar *et al.* 2015), rainfall and temperature (Tran *et al.* 2013), or a suite of eco-physiological processes (Padmanabha *et al.* 2012a). And others have used mathematical models to explore the effects of different environmental factors on mosquito dispersal (Dufourd and Dumont, 2013). Although these methods have rarely been calibrated to address the relevant scale of transmission at local levels, there are opportunities to do so by capitalizing on the wealth of climatic and remote sensing data that is routinely collected at finer temporal and spatial scales (Tran and Raffy, 2006).

Additionally, models require further input from laboratory experiments characterizing the relationship between, for example, temperature and mosquito life history traits (Yang *et al.* 2009), as well as validation from targeted mosquito surveillance in the field. Mosquito surveillance in the USA, for example, is targeted for an ecologically distinct genus (*Culex* spp.), and there is no similarly broad program available for *Aedes* species. Entomological studies aimed at estimating abundance are often reliant on crude metrics such as the Breteau Index or the Container Index, which have been shown to

reflect actual population distributions poorly and disease incidence even worse (Bowman *et al.* 2014). In the absence of reliable mosquito abundance data, mechanistic models of disease transmission could be validated by comparing model output with alternative sources of data, such as derived statistical relationships (and their corresponding uncertainty) between weather variables and disease incidence at a local scale in endemic settings.

(ii) *Better characterization of human–mosquito encounters*: In otherwise permissive environments, such as along margins of high intensity transmission foci, reduced contact between humans and mosquitoes is often the mitigating factor in preventing disease outbreaks. Yet, we have still to fully characterize how contact varies between the populations, among individual humans and mosquitoes, and over time. A significant component of human–mosquito contact is influenced by the preferences of each vector. *Ae. aegypti* is endophilic and endophagic (i.e. preferring to rest and feed indoors), whereas *Ae. albopictus* is exophilic and exophagic (i.e. preferring to rest and feed outdoors) (Schoof, 1967; Scott *et al.* 2000; Delatte *et al.* 2010). This disparity leads to different interactions between humans and the two vectors.

*Aedes aegypti* has a strong preference for feeding on humans. This implies that given a large enough population of humans relative to mosquitoes (humans are not a limiting resource), the human biting rate (the number of bites per human per unit time) can be estimated simply by measuring the number of bites on humans. Although theoretically straightforward, this is practically difficult and estimates rely on indirect landing rates (Casas Martínez *et al.* 2013; Tangena *et al.* 2015). *Aedes albopictus* also prefers to feed on humans, but is less selective than *Ae. aegypti* and will feed upon a broader range of vertebrate hosts. Blood meal analyses have been performed in the field for both species (Savage *et al.* 1993; Ponlawat and Harrington, 2005; Valerio *et al.* 2010), but with the lack of good population estimates for alternative hosts, extrapolation of the proportion of mosquito bites on humans is also difficult.

Additionally, the risk (and frequency) of being bitten by mosquitoes depends on mosquito behaviour and certain anthropological factors. In general, daily behaviour of *Ae. aegypti* and *Ae. albopictus* and differences in behaviour as a function of environmental and climatic variables are not well characterized. For instance, one study by Dieng *et al.* (2010) showed that *Ae. albopictus*, usually a peri-domestic day-biting mosquito, exhibits a tendency to live and breed indoors and bite more frequently at night on the island of Penang. The relative epidemiological impact of this change in behaviour is not yet clear. Factors associated with the human population, and human behaviour in particular,



could also lead to differential impacts on the spread of dengue and chikungunya. These factors include age (surface area), occupation, social habits, recreational activities (affecting time spent outdoors), or socio-economic status (affecting housing infrastructure such as window screens and air conditioning, density of and distance to breeding containers). Several studies have linked risk of dengue infection to socio-economic status (Waterman *et al.* 1985; Reiter *et al.* 2003; Brunkard *et al.* 2007), and the recent dengue outbreak in Martin County, Florida (Teets *et al.* 2014) was contained to two older neighbourhoods that either lacked mosquito-avoiding infrastructure or where residents traditionally spent part of the evening outdoors.

While models of mosquito-borne disease have been developed to include heterogeneity in human–mosquito contact (Smith *et al.* 2004), including host-seeking behaviour (Cummins *et al.* 2012) and realistic feeding patterns (Rock *et al.* 2015), few studies have considered their importance in emergence settings (Manore *et al.* 2014). Moreover, although modelling frameworks that incorporate socio-economic factors have been applied to vector-borne diseases (e.g. Werneck *et al.* (2007)), these factors are largely ignored in transmission models and should be a priority for future research. In particular, models that can account for contact heterogeneity in terms of individual human behaviour, such as agent-based models (Padmanabha *et al.* 2012b; Chao *et al.* 2013; Dommar *et al.* 2014; Manore *et al.* 2015), do not always make a direct link to the risk factors discussed above, and remain underused for understanding the potential for mosquito-borne virus expansion.

(iii) *Recognition of the role of diversity in mosquito–virus interactions*: An increasing amount of evidence supports the notion that individual viral strains have differential efficiency within mosquito populations and that, likewise, across geographically distinct mosquito populations (of the same species) the same virus strain may have altered fitness. This interaction of mosquito and virus has the potential to define differences in the ability of a virus to emerge in ecologically similar areas. For example, chikungunya strains of the Asian lineage have been displaced by the Indian Ocean lineage, specifically the LR sub-lineage. This LR sub-lineage emerged in 2006, when the strains present on LR island adapted to the local *Ae. albopictus* population, increasing the competence of this species to equal that of the usual vector *Ae. aegypti* (Tsetsarkin *et al.* 2007). Furthermore, the emergence of dengue 3 in Cairns, Australia was, in part, attributed to the increased vector competence of a particular invading strain relative to previous strains (Ritchie *et al.* 2013). Previous modelling work has considered how changes in viral strains have affected vector competence through manipulation of the average

EIP (Dumont *et al.* 2008; Manore *et al.* 2014). However, modelling studies can overestimate the impact of changes in viral strains by misinterpreting the variety of ways in which vector competence data is reported. For example, studies often report the earliest time to a disseminated infection (Dubrulle *et al.* 2009), but this does not necessarily translate into the average EIP, which is frequently used in models.

In addition, these viral strain–dependent interactions are modified by extrinsic factors such as temperature, though the modification of specific strains due to extrinsic factors is understudied. Predictions about the potential for virus expansion should be informed by studies speaking to the variability of viral strain phenotype in mosquito vectors and its impact on transmission. Such studies include both empirical work in the laboratory to determine the spectrum of vector competence and EIPs (and how these might differ depending on the combination of vector species and viral strain), as well as theoretical work to determine the most appropriate parameterization of models with these data (Christofferson *et al.* 2014a). Moreover, models can be used to investigate the sensitivity of the transmission cycle to changes in vector competence, and to identify locations, where even small changes might lead to large impacts on transmission potential.

(iv) *Incorporation of heterogeneity in human–virus interactions*: Recent studies have shown that human viremia curves differ among dengue serotypes, which directly translates into infectivity to mosquitoes (Carrington and Simmons, 2014; Whitehorn *et al.* 2015). Further, the changes in viremia over the course of an individual's infectious period affect the transmissibility of that infection to naïve vectors. However, limited data exist comparing clinical against sub-clinical cases, and the relationship regarding meaningful differences in viremia and disease presentation remains poorly understood (Tang *et al.* 2010; Stramer *et al.* 2012; de la Cruz-Hernández *et al.* 2013). Data concerning chikungunya viremia in humans are even more limited, though available data suggest it is likely to be highly variable (Appassakij *et al.* 2013; Chusri *et al.* 2014). For both viruses, little is known about the time to onset of symptoms/fever relative to the onset of infectiousness, which is relevant for accurate estimates of the generation interval of the virus.

In emergence settings, it is important to consider how temporal heterogeneity in viremia within an individual human affects model predictions. For example, Christofferson *et al.* (2014b) showed that if the contact rate between human and mosquito populations is high, then even periods of very low human infectiousness can contribute to the probability of an outbreak. However, if contact rates are low, then the window of human infectiousness is effectively truncated and imported human cases are

unlikely to lead to local transmission. Further work is needed to integrate models of local transmission with the dynamics of imported cases, including the timing of travel relative to exposure.

## CONCLUSIONS

The emergence of a mosquito-borne virus in a naïve population is a complex process that requires the presence of a suitable mosquito vector, the introduction of the virus and conditions amenable to transmission of the virus. As we have discussed here, models have made progress toward developing a better understanding of the processes driving disease emergence by focusing independently on these three components, but our ability to fully understand and predict expansion into naïve populations is still lacking.

We have outlined a number of challenges to modelling the emergence of mosquito-borne viruses that are necessary to address as the field moves forward. To respond to these challenges will require collaboration among modellers and empiricists on surveys, experiments and models across a spectrum of complexity and scales. For example, large-scale surveys of human activity patterns are important to understand how humans influence movement of the virus throughout and between populations; experiments are needed to test factors contributing to heterogeneity in vector competence, human viremia and mosquito population dynamics; and data-driven, mechanistic models are critical to understand micro-scale contributions to transmission and to predict emergence potential at the population level.

This study has focused primarily on the emergence of mosquito-borne viruses in naïve populations; however, much of what has been discussed is applicable to the many regions of the world that lie on the margins of becoming endemic to dengue and chikungunya. For example, regions such as northern Vietnam experience yearly dengue epidemics, but are regarded as sink populations for the virus which is reintroduced each year from human population centres in southern Vietnam (Rabaa *et al.* 2013). In these regions, small changes in subcomponents of the transmission process can have large consequences on long-term virus persistence, highlighting the broader importance of understanding the sensitivity of these disease systems to environmental, evolutionary and anthropogenic changes.

Although the work surveyed here is with respect to the mosquito-borne viruses of dengue and chikungunya, the primary vectors of these two viruses are also the major vectors of yellow fever virus, as well as two newly emerging viruses: Zika and Mayaro (Auguste *et al.* 2015; Buathong *et al.* 2015; Campos *et al.* 2015). In addition, many of the gaps in understanding and modelling apply to other mosquito-borne pathogens such as Japanese encephalitis

virus, West Nile Virus and malaria. Further integration of models and data to understand the basic mechanisms behind emergence of mosquito-borne pathogens will benefit our understanding of, and ultimately our ability to better control, a number of diseases that have significant impacts on human health.

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