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Temperature-dependent variation in the extrinsic incubation period elevates the risk of vector-borne disease emergence

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ABSTRACT

Identifying ecological drivers of disease transmission is central to understanding disease risks. For vector-borne diseases, temperature is a major determinant of transmission because vital parameters determining the fitness of parasites and vectors are highly temperature-sensitive, including the extrinsic incubation period required for parasites to develop within the vector. Temperature also underlies dramatic differences in the individual-level variation in the extrinsic incubation period, yet the influence of this variation in disease transmission is largely unexplored. We incorporate empirical estimates of dengue virus extrinsic incubation period and its variation across a range of temperatures into a stochastic model to examine the consequences for disease emergence. We find that such variation impacts the probability of disease emergence because exceptionally rapid, but empirically observed incubation — typically ignored by modelling only the average — increases the chance of disease emergence even at the limits of the temperature range for dengue transmission. We show that variation in the extrinsic incubation period causes the greatest proportional increase in the risk of disease emergence at cooler temperatures where the mean incubation period is long, and associated variation is large. Thus, ignoring EIP variation will likely lead to underestimation of the risk of vector-borne disease emergence in temperate climates.

1. Introduction

Temperature is a key climatic feature driving the risk of vector-borne diseases, impacting the vital performance of arthropod vector species (Dell et al., 2011) as well as the development of parasites within those vectors (Paaijmans et al., 2011; Liu et al., 2017). Many traits of vectors and parasites exhibit unimodal thermal performance curves, with the peak performance observed at some intermediate temperature (Mordecai et al., 2013). Mathematical models taking into account these relationships have predicted that the estimates of disease risks are highly temperature-sensitive (Mordecai et al., 2013, 2017b; Johnson et al., 2015), and their predictions have been instrumental in understanding the expanding threat of vector-borne diseases in the context of climate change.

A growing body of experimental studies documents the time-course of pathogen incubation and maturation in arthropod vectors, showing considerable variation in the time it takes for a vector to become infectious following exposure, known as the extrinsic incubation period (EIP) (e.g., West Nile virus (Reisen et al., 2006; Johansson et al., 2010); malaria (Paaijmans et al., 2011); bluetongue virus (Carpenter et al., 2011); dengue (Carrington et al., 2013; Chan and Johansson, 2012)). The process of extrinsic incubation involves a journey through several vector tissues and organs. For example, in dengue virus, the mosquito stage of the virus's lifecycle starts when the mosquito ingests a blood meal from an infectious host. After the virus spreads and multiplies in the midgut, viral particles migrate to various tissues before reaching the salivary gland, from where the virus can be transmitted, and the vector thus becomes infectious (Guzman et al., 2016). For many vector-borne parasites, the timing of incubation is crucial for their success because the average adult lifespan of a female mosquito is comparable to the average EIP. Empirical data for dengue show that the timing is particularly tight at both temperature extremes, where the expected EIP is the same or longer than the expected lifespan (Fig. 1a). Under these conditions, the odds are stacked against a “typical” parasite in a “typical” vector (i.e., infection with the expected EIP duration) to successfully complete incubation before the vector dies due to extrinsic causes. The probability of successfully completing incubation, and the vector becoming infectious to the next vertebrate host, diminishes exponentially with every passing moment after infecting a mosquito because the vector is expected to suffer extrinsic mortality due to, for

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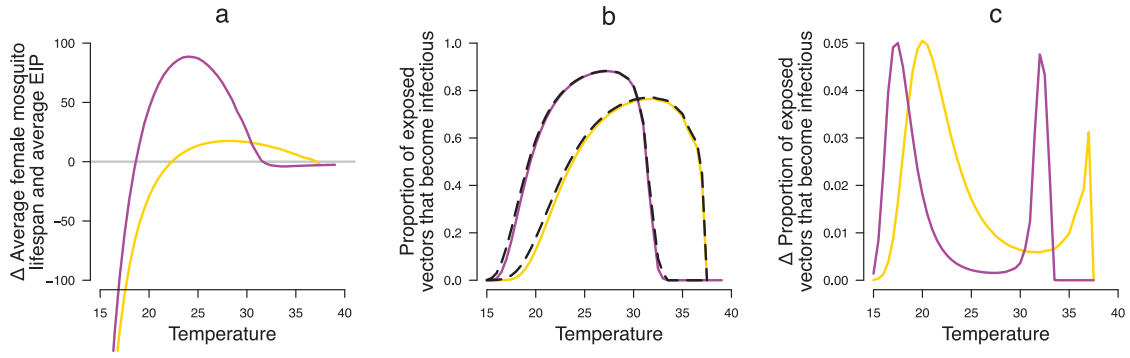

Fig. 1. At low and high temperatures, dengue viruses face a tight race against time to complete incubation before the vector dies. (a) The difference between the expected lifespan of female adult mosquitoes and the expected duration of EIP. Below the grey line, the average incubation period exceeds the average vector lifespan. (b) The proportion of exposed vectors that become infectious calculated based on the population average EIP, $e^{-\mu \mathrm{E[EIP]}}$ (solid lines), and the proportion calculated with realistic distribution of EIP duration, $\mathrm{E}[e^{-\mu \mathrm{EIP}}] = \int_0^\infty e^{-\mu \mathrm{EIP}} \mathrm{PDF(EIP)} d\mathrm{EIP}$ where *PDF*(EIP) refers to the probability density function of the EIP distribution. For dengue virus, *PDF*(EIP) is best described by the log-normal distribution for a given temperature (Chan and Johansson, 2012) (black dashed lines). (c) The elevated proportion of exposed vectors that become infectious due to incubation variation peaks at both ends of the temperature range suitable for dengue transmission. The colours, yellow and purple, indicate the two primary mosquito vectors of dengue, *Aedes aegypti* and *Aedes albopictus*, respectively. The estimates for mosquito mortality and EIP distributions were adopted from Mordecai et al. (2017b) and Chan and Johansson (2012), respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

example, pollutants, solar radiation, and predation. As a result, there is an accelerating benefit in reducing EIP, and hence parasites with a short EIP enjoy a disproportionate fitness advantage through increased incubation success.

Crucially for understanding temperature-dependent disease risks, temperature affects both the mean and variability of the duration of EIP: in dengue virus, it has been shown that both the expected duration of EIP and the variation around that expectation decrease with increasing temperature (Fig. 2) (Chan and Johansson, 2012). The understanding of how temperature mediates EIP variation is important for its impact on the proportion of exposed vectors that survive to become infectious (i.e., probability of successful incubation), an effect that can be explained mathematically by Jensen's Inequality (reviewed in Denny, 2017). Assuming a constant rate of extrinsic mortality, μ, the probability that an exposed vector survives a period of time, $e^{-\mu t}$, decays exponentially with time, t. Therefore, the probability that an exposed vector survives to become infectious, $e^{-\mu \mathrm{EIP}}$, is a convex function of time, as supported by mark-recapture data of female *Aedes aegypti* in the field (Harrington et al., 2014). Due to this convex relationship, Jensen's Inequality implies that the expected proportion of exposed vectors that become infectious for a distribution of EIP values, $\mathrm{E}[e^{-\mu \mathrm{EIP}}]$, is greater than, or equal to, the conventional estimate, $e^{-\mu \mathrm{E[EIP]}}$, which is the same proportion calculated based on the population average EIP (Fig. 1b). Failing to incorporate realistic EIP variation (Chan and Johansson, 2012) will, therefore, lead to underestimating the proportion of vectors that survive to become infectious. Focusing on two primary mosquito vectors of dengue, Fig. 1c shows that the maximum difference between $\mathrm{E}[e^{-\mu \mathrm{EIP}}]$ and $e^{-\mu \mathrm{E[EIP]}}$ is estimated at approximately 5%. The biological intuition behind this increase is that exceptional cases completing incubation faster than the population average have greater odds of surviving the duration of EIP.

Despite being a key component of the vector-borne disease lifecycle, a large fraction (~38%) of epidemiological models ignore extrinsic incubation altogether (Reiner et al., 2013). Furthermore, even models that consider the process often opt for mathematically convenient simplifications of the biology, for example by ignoring variation (i.e., assuming EIP follows a Dirac delta distribution, e.g.,Paaijmans et al., 2009), or assuming that EIP is exponentially distributed (e.g., Carvalho et al., 2019). Importantly, these contrasting assumptions about EIP variation can quantitatively alter the estimation of disease risks (Kamiya et al., 2017). With growing attention to the causes and consequences of variability in extrinsic incubation (Rudolph et al., 2014; Christofferson et al., 2016; Ohm et al., 2018), several recent epidemiological models have relaxed conventional assumptions of EIP distribution to reflect empirical evidence. For example, realistic EIP variation has been shown analytically to elevate conventional disease risk estimates (Brand et al., 2016), and variation has been incorporated into differential equation models of disease dynamics by assuming a Gamma distribution (i.e., using a linear chain trick) (Robert et al., 2019). An increasing number of studies make use of the distributions of viral and vector traits to estimate uncertainty in epidemiological properties such as the basic reproductive number, vectorial capacity, generation interval and epidemic growth (Karl et al., 2014; Perkins et al., 2016; Siraj et al., 2017; Codeço et al., 2018). Furthermore, empirically measured EIP variability has been incorporated into individual-based simulations to reveal variation in disease risks among dengue genotypes (Fontaine et al., 2018).

Here, we use dengue virus as a case study to illustrate the impact of

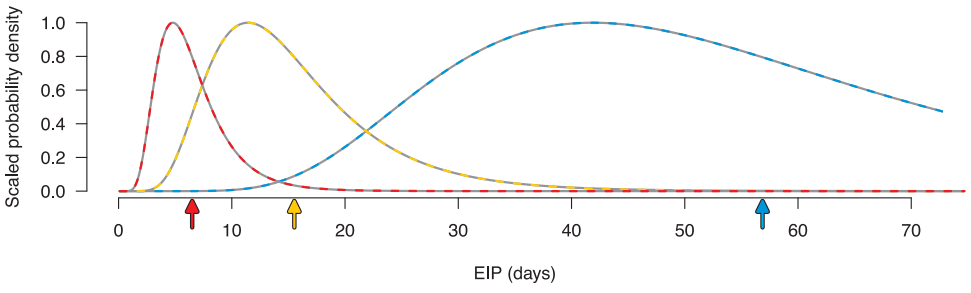

Fig. 2. Both the mean and variation of the duration of dengue extrinsic incubation period (EIP) are temperature-sensitive. The lines indicate the log-normally distributed duration of EIP estimated in *Aedes* mosquitoes by Chan and Johansson (2012) with colours (blue, yellow, and red) representing temperatures (20, 25, 30 °C, respectively). The arrows indicate the average EIP at the corresponding temperature. The dataset used to estimate the temperature-dependent probability distributions contained both *Aedes aegypti* and *A. albopictus*, though *A. aegypti* was overrepresented in the data (140 versus 6 observations) (Chan and Johansson, 2012). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

temperature-dependent EIP variation on disease emergence using a stochastic individual-based simulation approach. We take advantage of the meta-analytic estimates of empirical EIP distributions published by Chan and Johansson (2012) who compiled EIP data for dengue virus from 35 studies to determine that the variation in EIP is best described by the log-normal distribution (Fig. 2). We predict the probability of dengue virus emergence and epidemic size in a human population given the introduction of a single infected human across a range of temperatures and mosquito-to-human ratios. We find that variation in the EIP elevates the disease risk because exceptionally rapid incubation — which would be ignored by modelling only the average — increases the chance of disease emergence, even outside the temperature range where dengue transmission is commonly expected. We show that the proportional increase in the risk of disease emergence due to EIP variation is greater at cooler temperatures where the mean EIP is long, and its variation is large. This finding has implications for predicting the geographical distribution and the transmission season of dengue virus.

2. Methods

We used a stochastic algorithm to simulate a classic Ross–Macdonald model as a system of delay differential equations that mirror the epidemiology of dengue virus in a human population (reviewed in Smith et al., 2012). Following Barrio et al. (2006), we implemented a fixed duration process (viral incubation within mosquitoes) in an otherwise standard method for stochastically simulating ordinary differential equations (i.e., Gillespie algorithm). The dynamics of the mosquito population are governed by:

$$\frac{\mathrm{d}M_S(t)}{\mathrm{d}t} = \lambda M_T(t) - (\mu + rT_{\mathrm{MH}}H_I(t))M_S(t) \tag{1a}$$

$$\frac{\mathrm{d}M_E(t)}{\mathrm{d}t} = rT_{\mathrm{MH}}H_I(t)M_S(t) - \mu M_E(t) - r(T_{\mathrm{MH}}H_I(t-\mathrm{EIP})M_S(t-\mathrm{EIP})\mathrm{e}^{-\mu\,\mathrm{EIP}} \tag{1b}$$

$$\frac{\mathrm{d}M_I(t)}{\mathrm{d}t} = r(T_{\mathrm{MH}}H_I(t-\mathrm{EIP}))M_S(t-\mathrm{EIP})\mathrm{e}^{-\mu\,\mathrm{EIP}} - \mu M_I(t). \tag{1c}$$

In this model, susceptible mosquitoes, M_S, were born at a per-capita rate, λ. We kept the mosquito population size constant (so, $\lambda = \mu M_T$, where M_T and μ are the total population size and the rate of mosquito extrinsic mortality, respectively), in order to forgo the vast complexity of processes governing the larval mosquito dynamics (Beck-Johnson et al., 2013), for which there is a dearth of data on *Aedes* mosquitoes. We assumed that all mosquitoes experience the same mortality rate, μ, regardless of their infection status. In our model, mosquitoes were equally likely to bite a host of any class, so hosts get bitten by a given mosquito at the rate r, calculated as the per mosquito biting rate, b, divided by the total host population size, H_T, making disease transmission frequency-dependent (Keeling and Rohani, 2008). A susceptible mosquito becomes exposed, M_E, to the virus when it bites an infected host, H_I, with the probability T_{MH}. If a mosquito gets exposed to the virus, the process of viral incubation — i.e., transition from exposed, M_E, to infectious, M_I (Eq. (1)b and c) — takes the exact duration of EIP. In the stochastic simulation, the duration of EIP was assigned to each mosquito at birth, making the model individual-based with respect to the duration of EIP. An exposed mosquito survives the duration of EIP with probability $\mathrm{e}^{-\mu\,\mathrm{EIP}}$. The individual EIP value in a polymorphic population (with realistic EIP variation) was determined by randomly sampling from the empirically derived lognormal distribution estimated by Chan and Johansson (2012) who compiled EIP data for dengue virus from 35 studies. From their model (their Eq. (1) and Table 1) (Chan and Johansson, 2012) and parameter estimates (their Table 2; 4th row) (Chan and Johansson, 2012), we obtained the distribution of EIP across a range of temperatures (Fig. 2). In a mosquito population monomorphic for the duration of EIP (i.e., ignoring EIP variation), the average duration of EIP (often referred to as EIP_{50} (Christofferson et al., 2016)) at the appropriate temperature was assigned to every mosquito at birth.

The host population was modelled as a compartmental susceptible-exposed-infected-recovered (SEIR) model,

$$\frac{\mathrm{d}H_S(t)}{\mathrm{d}t} = -rT_{\mathrm{HM}}M_I(t)H_S(t) \tag{2a}$$

$$\frac{\mathrm{d}H_E(t)}{\mathrm{d}t} = rT_{\mathrm{HM}}M_I(t)H_S(t) - \theta H_E(t) \tag{2b}$$

$$\frac{\mathrm{d}H_I(t)}{\mathrm{d}t} = \theta H_E(t) - \gamma H_I(t) \tag{2c}$$

$$\frac{\mathrm{d}H_R(t)}{\mathrm{d}t} = \gamma H_I(t), \tag{2d}$$

where T_{HM}, θ and γ are the probability of mosquito-to-human viral transmission, viral incubation rate in humans and human recovery rate, respectively. The average latent period of dengue virus in humans has been estimated at 5.9 days (Chan and Johansson, 2012) (i.e., $\theta = 5.9^{-1}$ per day) and patients typically recover from dengue fever after a week (Guzman et al., 2016) (i.e., $\gamma = 7^{-1}$ per day). Robust immune responses against dengue confer life-long protection for a given serotype (Guzman et al., 2016); thus we did not consider waning immunity in this model. The human population size was set to 1000 and we explored a range of values for the total mosquito density, M_T, as reliable estimates of the mosquito-to-human ratio are rare. We parameterized the rest of the model with temperature-dependent empirical estimates published by Mordecai et al. (2017b). Specifically, we used GraphClick (Arizona-Software, 2010) to extract the estimated dengue virus trait values from their Fig. 1 and Fig. A in Supporting information 1 for *A. aegypti* and *A. albopictus*, respectively (Mordecai et al., 2017b). We list the parameter values used in the simulations in Supplementary Information 1. The complete collection of data by Mordecai et al. (2017b) are available online (Mordecai et al., 2017a).

We estimated the probability of disease emergence as the fraction of runs (of 10,000 replicates) for which the introduction of a single infected human to the entirely susceptible population led to at least one secondary human infection. We quantified the relative effect of EIP variation as the log risk ratio (*lnRR*, also known as relative risk) of the probability of disease emergence in simulations with realistic EIP variation to the probability of disease emergence in simulations only considering the population average EIP, keeping all other parameters constant.

3. Results & discussion

Using a stochastic simulation model parameterized for dengue virus, we found that realistic variation in EIP across exposed mosquitoes elevates disease emergence risks in human populations (Fig. 3). Specifically, our results demonstrate that EIP variation in either of the primary dengue vector species, *A. aegypti* or *A. albopictus*, increases the chance that the introduction of a single infected host causes secondary human infections in a fully susceptible population, at a given temperature. As a consequence, EIP variation extends the temperature range over which disease emergence can occur, particularly at the lower extreme. These effects are amplified with increasing mosquito-to-human ratios (Fig. 3).

The relative impact of EIP variation was most pronounced at the fringe of the temperature range that allows for dengue emergence (Fig. 4), meaning that assuming a constant, average EIP will underestimate the risk. When the climatic conditions are sub-optimal for dengue transmission — for example, when the race between incubation and mosquito mortality is tight — disease transmission is largely carried out by a small fraction of exceptional vectors that complete EIP faster than the population average. This phenomenon is ignored in a

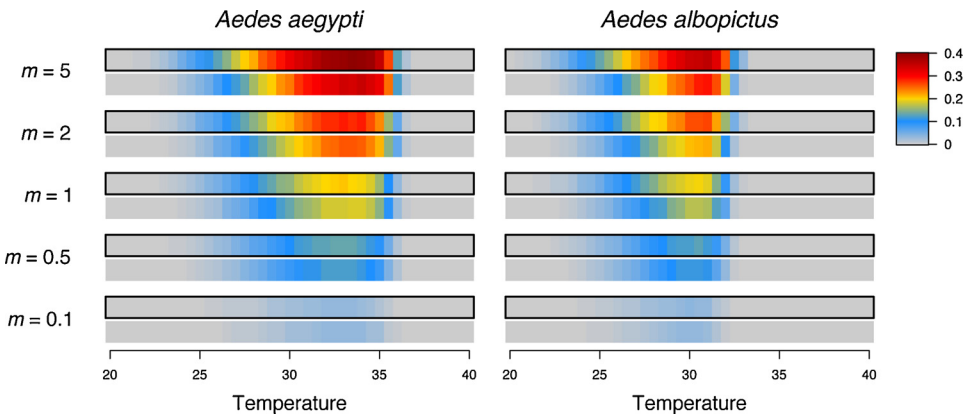

Fig. 3. Variation in viral EIP elevates the risk of dengue emergence in human populations. The model that incorporates realistic incubation variation (outlined in black) predicts elevated risk of disease emergence for human populations assuming dengue is vectored by either *Aedes aegypti* or *A. albopictus*, compared to the conventional approach that ignores variation (no outline). The probability of disease emergence (indicated by colours) given the introduction of a single infected host (i.e., production of one or more secondary human infection(s)) was calculated assuming a mosquito population comprised solely of either *A. aegypti* and *A. albopictus* across a range of temperatures (*x*-axis) and mosquito-to-human ratios, *m* (*y*-axis). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

conventional fixed-EIP approach. The finding that variation in EIP has a stronger impact at low temperatures is due to the interplay between the distribution of EIP and other temperature-dependent vital parameters. First, the distribution of dengue EIP for a given temperature is best explained by the log-normal distribution, for which the variance increases with the mean (Chan and Johansson, 2012). Therefore the variation in EIP is larger at lower temperatures where the mean duration in EIP is also long. Second, a number of other factors governing the interaction between dengue virus and mosquitoes are temperature-dependent, and so they also shape the temperature range suitable for disease emergence. For example, the spike in the proportion of exposed vectors that become infectious due to variation in *A. aegypti* at the high temperature range (Fig. 1c ~37 °C) has little effect since the probability of an exposed mosquito becoming infectious tends towards zero beyond 35 °C for this species (Mordecai et al., 2017b) (Fig. 1b ~37 °C). Thus, the influence of incubation variation at the high-temperature end, in particular, is buffered by a sharp decline in other vital parameters of the mosquito and virus.

Our model was parameterized with the most comprehensive estimates of temperature-dependent dengue EIP variation and mosquito vital parameters published by Chan and Johansson (2012) and Mordecai et al. (2017b), respectively. While primary observations are rather sparse at high temperatures in these studies, our finding that the relative impact of EIP variation is largest at lower temperatures is likely robust as parameter estimates were based on relatively more data at the lower temperature range (Mordecai et al., 2017b; Chan and Johansson, 2012). Because the relationship between mosquito and human densities is highly complex (Romeo-Aznar et al., 2018), we explored the impact of EIP variation across a range of mosquito-to-human ratios. We find that the impact of EIP variation increases with the mosquito-to-human ratio, indicating that incorporating EIP variation is most important for accurate prediction of disease risk in areas of high relative mosquito density (Fig. 4).

We next explored the size of additional epidemics expected due to EIP variation. We found an overrepresentation of minor epidemics — defined as those in which less than 10% of the human population becomes infected — under sub-optimal conditions for dengue transmission (e.g., low mosquito-to-human ratio and fringe temperatures) (Fig. 5). This result suggests that EIP variation — and the few exceptionally rapidly incubating infections that result from it — increases the chance of short transmission chains involving a small handful of humans even when the deterministic force of infection is too weak to sustain transmission. These epidemics, which are small and rare, yet still concerning from a public health perspective, would be overlooked by the conventional approach that ignores EIP variation. Put another way, EIP variation reduces the chance of disease extinction due to demographic stochasticity. As a consequence, the model that takes into account EIP variation predicts the more frequent occurrence of epidemics across the entire temperature range (Fig. 5).

To highlight the impact of temperature-dependent EIP variation in a geographical context, we predicted the probability of disease emergence across the continental United States, using average temperature in July (Matsuura and Willmott, 2018), the warmest month in North America. We note that our projection here offer insight about relative (rather than absolute) risk: while we allow temperature to determine EIP variation and other virus and vector traits, we assume all else is equal across this geographic range. Fig. 6 shows that ignoring the variation would lead to underestimation of dengue risk in its entire geographical range, but particularly at the expanding northern edge, for example in cities like Indianapolis (IN) and Philadelphia (PH), but less so in Austin (AU) — three US cities within the range of *A. albopictus* predicted by the Center for Disease Control (CDC, 2017). Furthermore, since EIP variation increases the risk at low temperatures and never reduces it (Fig. 4), the standard approach is likely to underestimate the

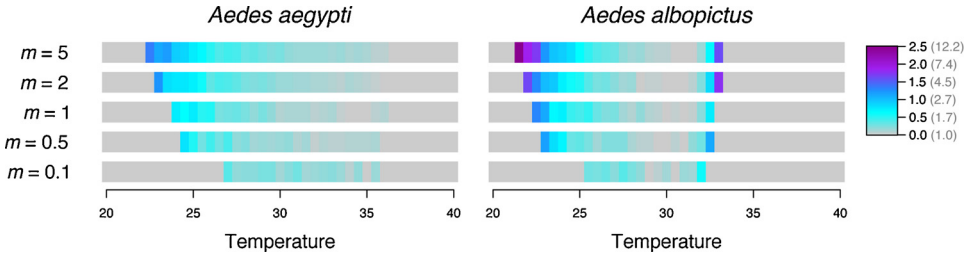

Fig. 4. The impact of EIP variation on dengue emergence is strongest at the lower fringe of the temperature range that allows for dengue transmission. The log risk ratio (*lnRR*, shown in colours) was calculated as the natural logarithm of the ratio between the probabilities of disease emergence when taking EIP variation into account versus not, i.e., the values presented in Fig. 3 with and without the black outline, respectively. The colour legend shows *lnRR* (in black) with the corresponding linear-transformed risk ratio in parentheses (in grey): for example, *lnRR* = 2 indicates a 7.4-fold increase in the probability of disease emergence. In calculating *lnRR*, we focused on simulations where the probability of disease emergence with EIP variation exceeded 1% to disregard extremely rare events. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

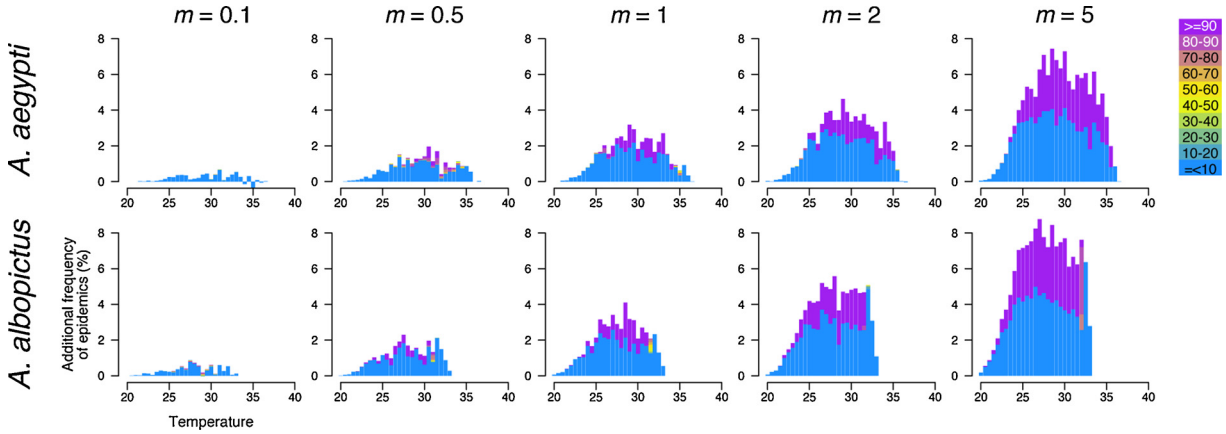

Fig. 5. Realistic EIP variation uncovers epidemics unaccounted for by the conventional approach that ignores EIP variation. Plotted in stacked histograms is the difference in the frequency of epidemics between simulations with and without EIP variation across a range of temperatures and mosquito-to-human ratios, *m*, for *Aedes aegypti* and *A. albopictus*. The colours indicate the epidemic size measured as the proportion of the human population cumulatively infected during an epidemic, with blue and purple indicating minor ($\leq$10%) and major ($\geq$90%) epidemics, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

duration of dengue transmission seasons. Again, the predicted pattern demonstrates that the impact of EIP variation increases with the mosquito-to-human ratio, indicating that ignoring EIP variation also leads to a severe underestimation of disease risk in areas with high relative mosquito density (Figs. 4 and 6). However, since mosquito abundance is climate-driven and generally lower in the fringes of the species' ranges (Li et al., 2019), the actual elevated risk may not be as exaggerated as our most extreme predictions indicate (Fig. 6, right panel). Nonetheless, accurate prediction of the risk of dengue emergence locally will rely on a fine-scale understanding of local mosquito abundance, and ultimately, the mosquito-to-human ratio.

In the present study, we assumed that female adult mosquitoes experience constant mortality due to extrinsic causes, as assumed by the standard approach in vector-borne disease modelling. In reality, extrinsic sources of mortality most likely operate alongside intrinsic causes, which leads to senescence and age-dependent mosquito survival (Harrington et al., 2014). Per Jensen's Inequality, the impact of EIP variation would differ qualitatively if young adult female mosquitoes rarely experience mortality such that mosquito survival is a concave function of time. However, we believe such a situation is unlikely because field mark-recapture data support a convex relationship between mosquito survival and time (Harrington et al., 2014), and the finding that estimated mosquito survival is lower in mark-recapture experiments carried out in the wild compared to laboratory experiments also supports the role of extrinsic mortality in wild mosquito populations (Ryan et al., 2015). Little is known about the relative importance of different sources of mortality in the wild and it appears context-dependent (e.g., with respect to the climate (Hugo et al., 2014)). Future predictive models will benefit from an understanding of mosquito survival in the wild with respect to both temperature and age, information that, to our knowledge, is currently only available for malaria vectors in a laboratory setting (Shapiro et al., 2017).

Recent years have seen sporadic re-emergence of vector-borne diseases in temperate regions where they had been absent for decades (Bouri et al., 2012; Tomasello and Schlagenhauf, 2013; Schaffner and Mathis, 2014; Lai et al., 2015). Because major dengue epidemics are unlikely to occur in these areas (Mordecai et al., 2017b), our primary focus was to better understand the impact of temperature-dependent individual heterogeneity on stochastic occurrences of small disease outbreaks that would be overlooked by deterministic modelling. Our individual-based simulations demonstrated that failing to incorporate variability in the duration of EIP across individual vectors can lead to a severe underestimation of the risk of minor epidemics and duration of potential dengue exposure in cooler climates. Although researchers should also consider more analytically tractable modelling approaches (e.g. branching process theory and Kolmogorov equations) (Lloyd et al., 2007), stochastic individual simulations are appealing for studying the impact of heterogeneities in vector-borne diseases due to their ability to accommodate comprehensive empirical knowledge (Perkins et al., 2019).

Dengue virus offers the most comprehensive documentation on temperature-sensitive measures of mosquito and pathogen traits and EIP variation to date. Nonetheless, we expect that the basic mathematical principle underlying the inflation of disease risk due to variation — Jensen's Inequality due to the convex relationship between the duration of EIP and extrinsic incubation success — applies widely across vector-borne diseases. Thus, variation in EIP is likely to elevate disease risks in other vector-borne diseases, though the exact quantitative impact is likely to vary across diseases and vector species, as we found in our comparisons of *A. albopictus* and *A. aegypti*. Furthermore,

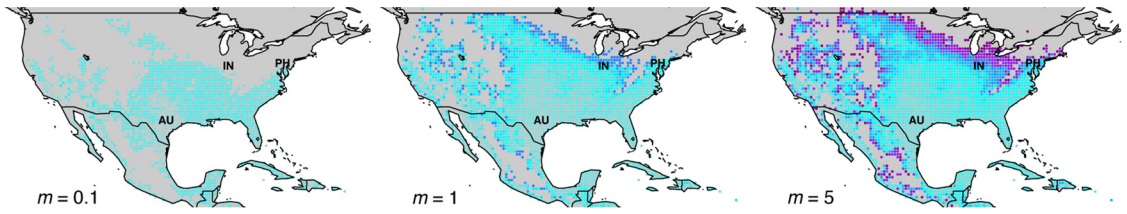

Fig. 6. Ignoring EIP variation underestimates the disease risk in its entire geographical range, but particularly at the temperate edge, for example in cities like Indianapolis (IN) and Philadelphia (PH), but less so in Austin (AU) where the climate is warmer. The colour indicates the impact of EIP variation (measured as *lnRR* of the probability of disease emergence with and without realistic EIP variation; as shown in Fig. 4, which uses the same scale) on the probability of disease emergence by *A. albopictus* in July. In calculating *lnRR*, we focused on simulations where the probability of disease emergence with EIP variation exceeded 1% to disregard extremely rare events. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

while we here focused solely on temperature-dependent variability in EIP, a future challenge is to characterize and integrate the knowledge of variability in multiple vector and parasite life-history traits and their covariation across a range of temperatures (Vazquez-Prokopec et al., 2016). Individual-based simulations, together with a growing body of experimental data, will offer further opportunities to achieve a more comprehensive understanding of the role of individual heterogeneity in vector-borne disease epidemiology.

Authors' contribution

Tsukushi Kamiya: conceptualization, methodology, software, investigation, visualization, writing – original draft preparation.

Megan A. Greischar: conceptualization, investigation, supervision, writing – reviewing and editing.

Kiran Wadhawan: methodology, visualization, investigation.

Benjamin Gilbert: conceptualization, methodology, supervision.

Krijn Paaijmans: conceptualization, supervision.

Nicole Mideo: conceptualization, founding acquisition, supervision, resources, writing – reviewing and editing.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.epidem.2019.100382.

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