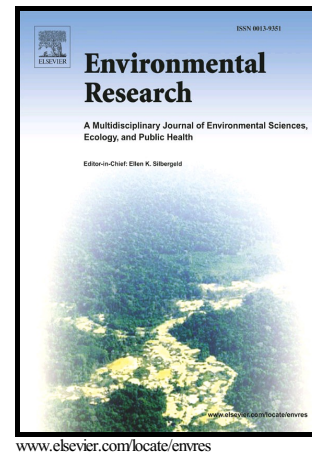


Author's Accepted Manuscript

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PII: S0013-9351(19)30106-9
DOI: <https://doi.org/10.1016/j.envres.2019.02.026>
Reference: YENRS8338

To appear in: *Environmental Research*

Received date: 3 December 2018
Revised date: 15 February 2019
Accepted date: 16 February 2019

Cite this article as: Jing Liu-Helmersson, Joacim Rocklöv, Macquin Sewe and Åke Brännström, Climate change may enable *Aedes aegypti* infestation in major European cities by 2100, *Environmental Research*, <https://doi.org/10.1016/j.envres.2019.02.026>

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Climate change may enable *Aedes aegypti* infestation in major European cities by 2100

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Declarations of interest: none

Abstract

Background: Climate change allows *Aedes aegypti* to infest new areas. Consequently, it enables the arboviruses the mosquito transmits -- e.g., dengue, chikungunya, Zika and yellow fever -- to emerge in previously uninfected areas. An example is the Portuguese island of Madeira during 2012-13.

Objective: We aim to understand how climate change will affect the future spread of this potent vector, as an aid in assessing the risk of disease outbreaks and effectively allocating resources for vector control.

Methods: We used an empirically-informed, process-based mathematical model to study the feasibility of *Aedes aegypti* infestation into continental Europe. Based on established global climate-change scenario data, we assess the potential of *Aedes aegypti* to establish in Europe over the 21st century by estimating the vector population growth rate for five climate models (GCM5).

Results: In a low carbon emission future (RCP2.6), we find minimal change to the current situation throughout the whole of the 21st century. In a high carbon future (RCP8.5), a large parts of southern Europe risks being invaded by *Aedes aegypti*.

Conclusion: Our results show that successfully enforcing the Paris Agreement by limiting global warming to below 2°C significantly lowers the risk for infestation of *Aedes aegypti* and consequently of potential large-scale arboviral disease outbreaks in Europe within the 21st century.

Key words: *Aedes aegypti*; vector invasion; Europe; climate change.

Abbreviations:

RCP - greenhouse gas representative concentration pathways.

r_1 - vector growth rate annually.

r_{10} - vector growth rate decadal.

Funding

This work was supported by the European Union Seventh Framework Programme FP7/2007-2013 [282589], the Swedish Research Council [2015-03917] and the Swedish research funding agency Formas [2017-01300].

Highlights

- *Ae. aegypti* has caused major dengue outbreaks in Europe: Athens 1927 and Madeira 2012.
- The current European climate does not support its invasion except in small coastal areas.
- Future European infestation of *Ae. aegypti* depends on the level of global warming.
- Under the worst climate scenario, *Ae. aegypti* may infest most of southern Europe.
- A majority of infestation could be avoided if the temperature rise is kept under 2°C.

Introduction

Aedes aegypti is an invasive arboviral vector transmitting diseases with large global impact [1, 2]. While increasing trade and travel have catalysed the spread of the *Aedes* mosquitoes and consequently enabled the arboviruses it transmits (e.g., dengue, chikungunya, zika and yellow fever) to emerge or re-emerge in uninfected areas, climatic conditions determine the mosquitoes' viability [3, 4]. *Aedes aegypti* is currently not present in Europe, with the exception of a small coastal area of Georgia and the Southwest of Russia, and the Atlantic Portuguese island of Madeira [5]. Climate change may possibly enable the vector to invade elsewhere in the years to come, but the timing and likelihood of this outcome will depend critically on global achievements in enforcing climate policy, such as the Paris Agreement (UNFCCC) [6]. Here, we assess the risk of *Aedes aegypti* invading new areas in continental Europe under two salient future emission scenarios.

Despite the importance of understanding changes in vector distributions under climate change, only a handful of studies have attempted to project the future distribution of *Aedes aegypti* [1, 7, 8]. These studies have predominantly used statistical vector-distribution models aiming to describe the patterns, not the mechanisms, of the association between vector occurrences and

environmental conditions in relation to climate [3, 9] and vegetation [4]. They are further based on empirical observations of occurrence of the vector, which are known to be patchy and to suffer from systematic surveillance and reporting biases [10]. Recognizing that new approaches will be needed to significantly improve the ability to predict vector distributions under climate change, the White House report *The Impacts of Climate Change on Human Health in the United States: A Scientific Assessment* [11] stressed the need for development of new dynamic evidence-based mechanistic models.

Mechanistic models use process-based descriptions of the vector demography and life cycle. They can describe discrete but intertwined events that are fundamental to the different stages of the vector or a disease development [11]. This is accomplished by incorporating causal relationships, such as experimental findings on vector development under different environmental conditions. For *Aedes aegypti*, this includes time-dependent influences of climate, natural environment, and human demography (i.e., breeding sites, population, and lifestyle). For dengue, process-based models have mainly been used to study vector and disease transmission dynamics in specific locations, while considering the environmental drivers as either temperature and photoperiod for *Aedes albopictus* [12-14] or temperature and precipitation for *Aedes aegypti* [15, 16].

We present the first application of a process-based mathematical model with time-dependent parameters to predict changes in the European distribution of *Aedes aegypti* – vector growth rate, under anticipated global warming scenarios. We estimate the invasion risk of *Aedes aegypti* in Europe over the 21st century by using an ensemble of five global circulation climate models, CMIP5 [17], under two representative greenhouse gas concentration pathways (RCP) [18]. By drawing on empirical data from a range of complementary sources, we are able to provide predictions of *Aedes aegypti*'s European distribution that span a full century into the future.

Method

We use a process-based model (see Figure S1) with three compartments for larvae, pupae, and adults [19] to represent the lifecycle of *Aedes aegypti*. All vital rates (birth, death, fecundity, and stage-transition rates) depend on temperature and/or precipitation. The fecundity rate of adult females depends additionally on the local human population density. The whole lifecycle from

egg to adult takes one to a few weeks, depending on temperature and precipitation. Three ordinary differential equations are used to describe the rates of change of individuals for each of the life-history stages:

$$\frac{dL}{dt} = \Phi \square A q Z_e(L) f - \mu_l L - \sigma_l L, \quad (1)$$

$$\frac{dP}{dt} = \sigma_l L - \mu_p P - \sigma_p P, \quad (2)$$

$$\frac{dA}{dt} = \sigma_p P - \mu_a A. \quad (3)$$

Here L , P , and A are the total female larva, pupa, and adult populations per area, with the area being either a city/location or a 0.5 x 0.5 degree grid when we generate global maps. All the variables are explained in Table 1 in the Supplementary Information. From the top down, the three equations describe the rates of change of their respective densities. Female adults lay eggs at rate Φh of which a fraction $q Z_e(L)$ are viable, and of which a fraction f become female. Here q is the fraction of eggs hatching at low larva population density and $Z_e(L)$ is density-dependent probability for the viable eggs to survive and develop into larvae. Larvae die at rate μ_l and develop into pupae at rate σ_l . Similarly, pupae die at rate μ_p and emerge as female adults at rate σ_p .

The adult female fecundity rates Φh are expressed as the product of two factors. The first is the oviposition rate Φ as determined in laboratory studies in which sufficient blood meals were provided. Under natural conditions, the availability of blood meals is limited by human population density ρ , as described by the second factor h (human blood-meal factor). We do not make any specific assumption about the form of the density-dependent egg survival probability $Z_e(L)$ other than that it should be a smooth function taking values between 0 and 1, such that $Z_e(0) = 1$. A full description of the model parametrization is given in Supplementary Information, S1.

To assess whether the environmental conditions during a given time period enable vector invasion, we determine the long-term growth rate of an invading vector population under two assumptions: 1) density dependence is negligible, i.e., $Z_e(L) = 1$ and 2) the environmental conditions are periodic, i.e., they repeat themselves after the end of the time span considered. The

first assumption, which should be reasonable in the early phase of an invasion when the invading population remains small, allows the following representation of equations (1-3) in matrix form,

$$\begin{pmatrix} L' \\ P' \\ A' \end{pmatrix} = \begin{pmatrix} -\sigma_1 - \mu_1 & 0 & \Phi h q f \\ \sigma_1 & -\sigma_p - \mu_p & 0 \\ 0 & \sigma_p & -\mu_a \end{pmatrix} \begin{pmatrix} L \\ P \\ A \end{pmatrix}. \quad (4)$$

For populations described by periodic linear differential equations such as equation (4) above, their long-term exponential growth rate can be derived based on Floquet theory [20]. This means solving a corresponding matrix differential equation over one period τ , from which the so-called dominant eigenvalues can be calculated. Specifically, writing $\mathbf{M}(t)$ for the matrix of coefficients (the above 3x3 matrix in Eq. (4)), we solve

$$\frac{d\mathbf{F}}{dt} = \mathbf{M}(t)\mathbf{F}, \quad (5)$$

for a matrix solution \mathbf{F} satisfying $\mathbf{F}(0)=\mathbf{I}$ (the identity matrix). $\mathbf{F}(t)$ is called a principal fundamental matrix solution of Eq. (5) if it is non-singular at all times. The eigenvalues (λ_i , $i=1,2,3$) of $\mathbf{F}(\tau)$ are called Floquet multipliers and determine the long-term behaviour of the system. The population growth rate, r , is given by $r = \log(\lambda)/\tau$ in which λ is the largest eigenvalue of $\mathbf{F}(\tau)$. For n periods ($t = n\tau$), the vector population grows geometrically as λ^n but the growth rate r is the same as for one period. If $\lambda > 1$ or $r > 0$, the vector population will grow and on average multiply geometrically over each time period and the population will eventually establish itself. Otherwise, it will diminish and die out over time. To obtain the eigenvalues λ_i over one period, we solve Equation (5) numerically. *Wolfram Mathematica* 11 and *R* (package *expm*) [21] were used for calculation and mapping.

From the Climate Research Unit (CRU) online database, time series (CRU TS 3.25) of gridded (0.5 x 0.5 degrees) monthly mean temperature and precipitation were obtained for Europe (1901 – 2015) [22]. For future climate data, projected monthly temperature and precipitation from five global circulation models (GCM), from ISMIP based on CMIP5 [23], were used as input in our model under the two extreme scenarios RCP2.6 and RCP8.5 (2006-2099). The annual global human population data were also obtained from ISMIP (1901-2099, gridded 0.5 x 0.5 degrees).

We used an interpolation function (Spline function) to obtain continuous temperature and precipitation time series. As described in Supplementary Information S6, using interpolated time series from monthly data in lieu of actual daily data does not significantly affect our results. The vector growth rate was calculated for each decade over the past century (1910-2009) and for the future during this century (2011-2099) for each GCM and under the two RCPs.

Results

Predicting the current vector distribution, we find negative population growth rate (r_{10} , day^{-1}) of *Aedes aegypti* over most of the European continent over the recent decade, 2005-2014 (Figure 1), which agrees with the absence of the vector in the area. However, smaller parts of southern Italy, Spain, Portugal, Greece, and Turkey show population growth rates ($r_{10} > 0$) at the border of establishment. For the early decades of the past 100 years (1910-2009), the decadal vector growth rates are presented for Europe in the Supplementary Information – See Figure S4. There was hardly any infestation in the early part of last century but infestation slowly increased over time.

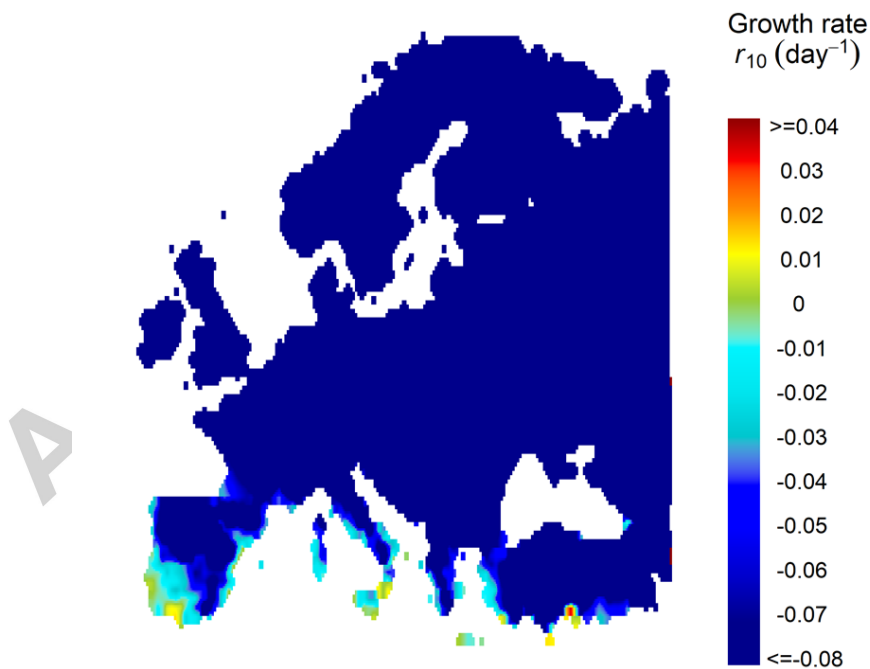


Figure 1. *Aedes aegypti* growth rate (r_{10} in unit day^{-1}) for the current decade (2005-2014). Vector parameters are based on interpolated CRU TS3.25 monthly temperature and precipitation data. Yellow, orange and red colours correspond to positive growth rates and green and blue colours to negative growth rates. The reported growth rates are for an initially small invading population.

Future projections at the middle and end of this century are shown in Figure 2 with the two greenhouse emission scenarios shown in columns – A & B for RCP8.5 and C&D for RCP2.6. The five rows show the decadal growth rates for five climate models (GCMs). We found an increasing risk of *Aedes aegypti* establishing in Europe, especially for the high emission RCP8.5 scenario – global temperature rising to 4.9°C by end of 2100 as compared to the pre-industrial level (Figure 2A and 2B). For this scenario, the growth rate increases to positive values in southern European fringe zones by the 2050s (Figure 2A), and increases further to indicating establishment risk of *Aedes aegypti* in large parts of southern Europe along the Mediterranean coast by the 2090s (Figure 2B). The difference to a low emission future RCP2.6 (global temperature rising under 2°C during this century), such as the one outlined in the Paris Agreement, is striking (Figure 2C-D). By the middle of this century (Figure 2C), only scattered smaller areas along the Mediterranean Sea coasts show positive but small growth rates, and no further change is detectable at the end of the century (Figure 2D). This indicates that warming above 2°C may lead to exceeding a tipping point in the risk of *Aedes aegypti* infestation (Figure 2A-D). Although the degree varies among the five GCMs, the trend is clear between the two RCPs, and over time in all the five GCMs. In the Supplementary Information, the details of decadal growth rate as European infestation maps are presented for each decade from 2011 to 2099. See Figure S5A and S5B.

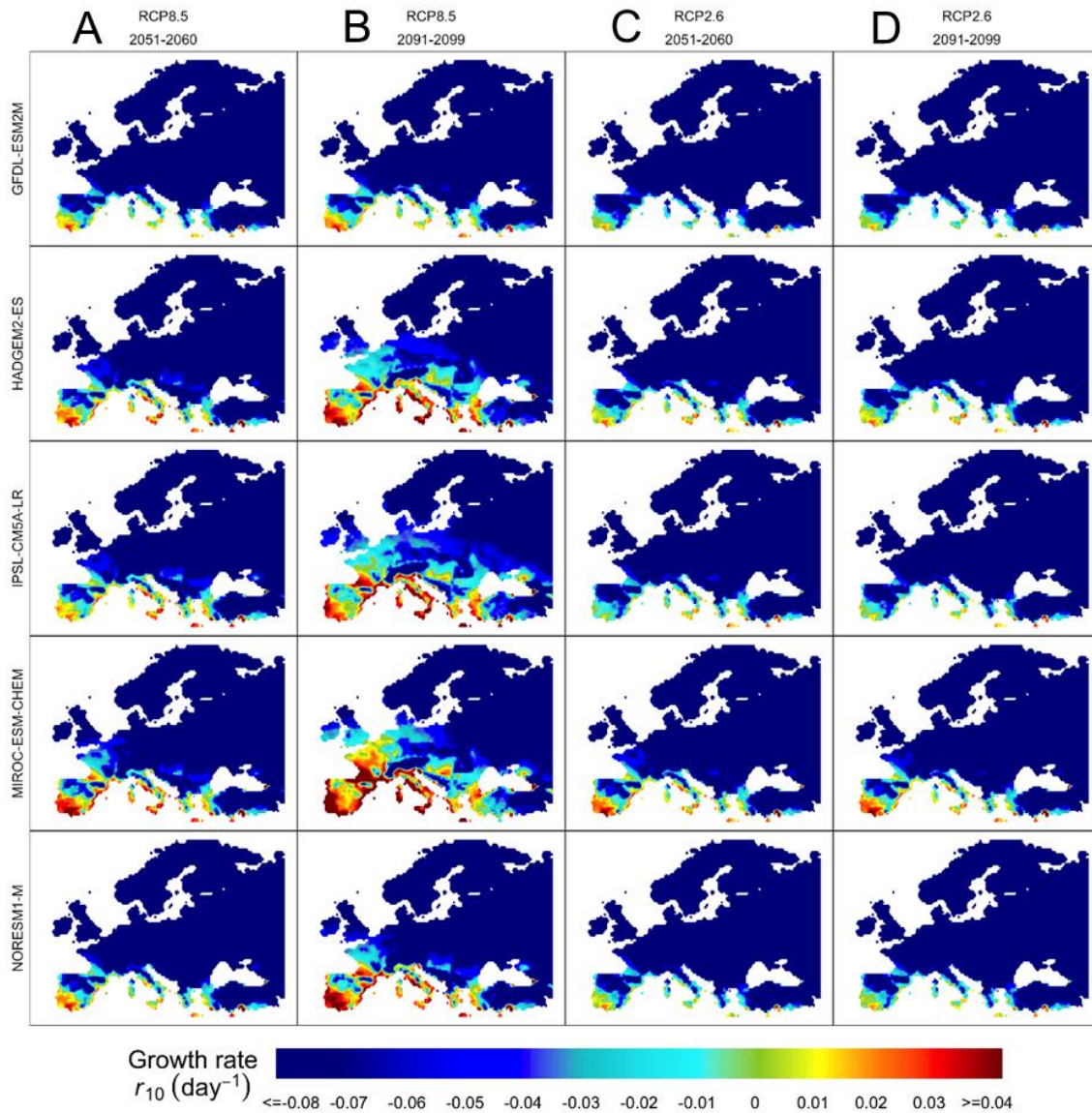


Figure 2. The predicted future *Aedes aegypti* decadal growth rate (r_{10}) in Europe. Maps show the results of different greenhouse gas emission pathways – RCP8.5 (A & B) and RCP2.6 (C&D), during the middle of this century (A & C) and the end of this century (B & D). The reported growth rates are for an initially small invading population.

The trend of the total vector-invasion risk area in Europe over the 21st century is shown in Figure 3 for two carbon-emission scenarios, RCP2.6 and RCP8.5. Temperature changes in Europe for the same period (relative to the 1910s) is also presented. The vector-infested area increases with the temperature. Under RCP8.5, as European temperature rises continuously into the end of this century (1.7-6.7°C, Fig. 3C), the European vector invasion area increases from 0.6% (0.4% -

0.8%) to 5.3% (1.9% – 8.7%, Fig. 3A) and the increasing trend continues into the 22nd century; under RCP2.6, as temperature rises by 1.6 - 2.9 °C (Fig. 3D), invasion area increases first, then reaches a plateau at about 1.5% (0.7% - 1.5%, Fig. 3B) by the 2060s and then slightly decreases to 1.2% (0.6%-2.3%) by the end of the century.

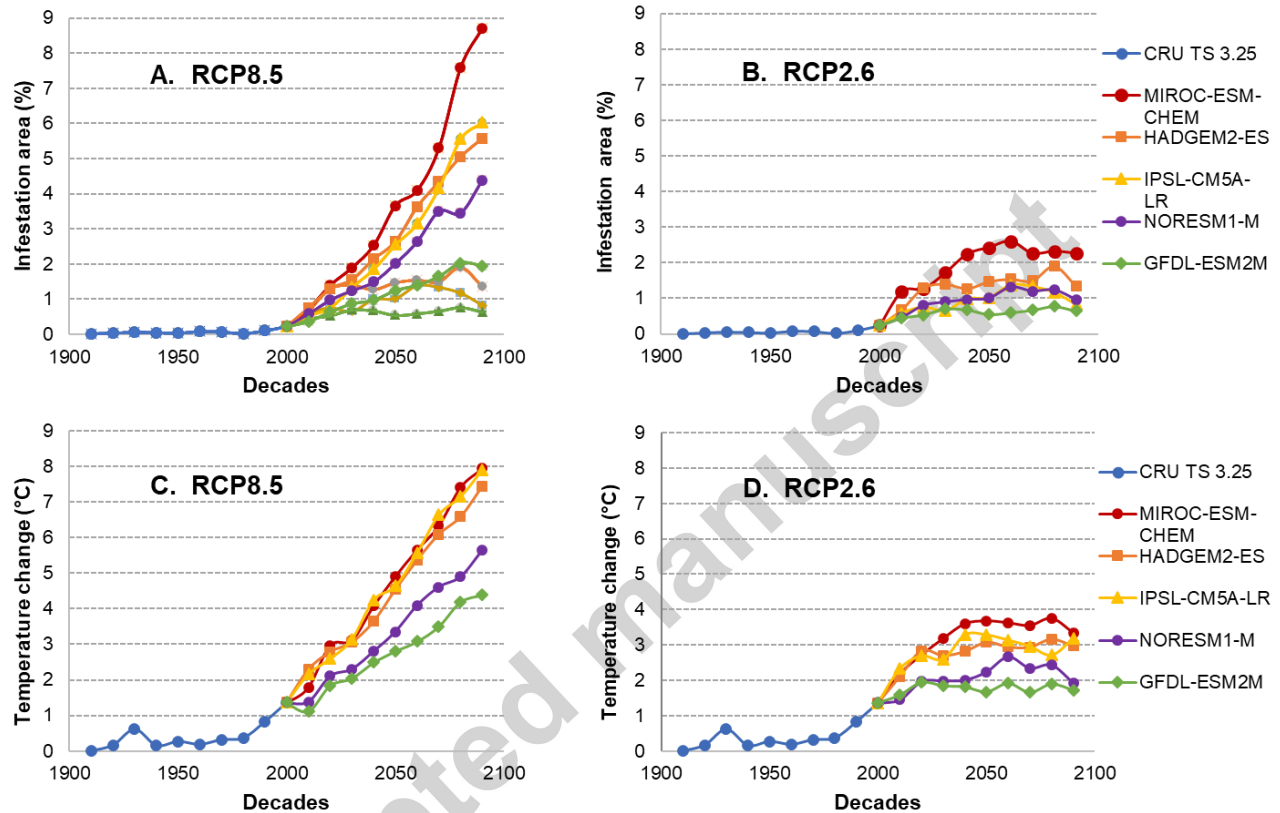


Figure 3. Trend of vector infestation area in Europe over two centuries under two RCPs (A&B, 1910-2099). The plot also shows the corresponding European temperature change per decade (C & D). The decadal vector population growth rates were calculated to estimate the infestation area from the past using CRU-TS 3.25 data to the future for all five global circulation models.

In the history of Europe, only two cities are reported to have experienced major dengue outbreaks: Athens during 1927-28 [24] and Madeira during 2012-13 [25], with *Aedes aegypti* as the vector. We examined the vector growth rate both annually (r_1) and decadally (r_{10}) in Madeira and Athens during 1901-2099 (Figure 4). Madeira had a positive and increasing trend in both annual and decadal growth rate over the last century (Figure 4A-B). The growth rates are predicted to continue to increase in the 21st century, but the degree depends on the RCP scenario, consistent with our previous findings.

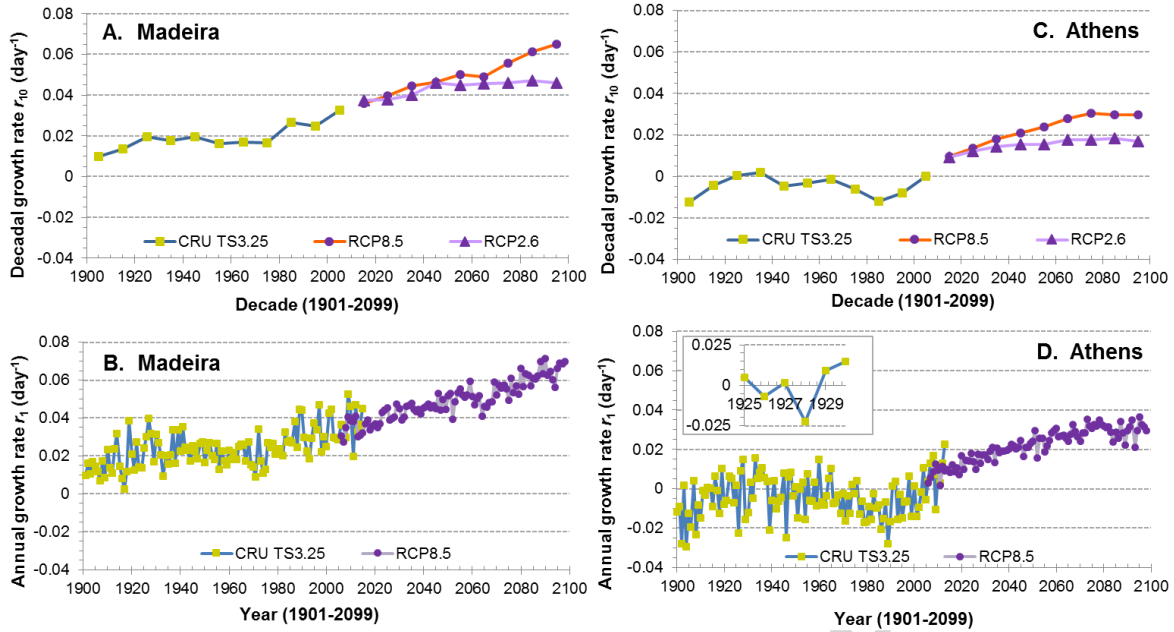


Figure 4. *Aedes aegypti* decadal and annual growth rates from 1901 to 2099 in Madeira (A-B) and Athens (C-D). These two cities in Europe have had major dengue outbreaks in the past. The annual growth rate in Athens with the insert in Fig. 4D illustrates the possibility of temporary *Aedes aegypti* presence in a place (Athens, 1927) without long-term establishment.

Athens (Figure 4C-D), on the other hand, shows decadal growth rates close to zero over the 20th century with the highest r_{10} in the 1920s-1930s. By 2000, decadal growth rate was positive but close to zero ($< 0.01 \text{ day}^{-1}$). This is consistent with the fact that no vectors have been reported in Athens recently. But still, temporary invasion is possible as the annual growth rate r_1 shows. The insert in Figure 4D illustrates the six-year r_1 around the dengue outbreak period, 1925-1930. Positive r_1 in 1927 when dengue outbreak peaked was followed by negative r_1 in 1928 when the dengue outbreak died out in the early part of 1928 – consistent with the actual dengue reports. The future trend differs depending on the climate change scenarios.

In the Supplementary Information, we present the temperature and rainfall relationships of all the vector parameters used and their influence on the estimated growth rates (Figures S2A and S3). In addition, we also present growth rates for Europe in maps from the past (Figure S4, 1910s-2000s) to the future for two RCPs and five GCM (Figure S5, 2010s-2090s). We present as well results for 10 European cities plus three tropical and subtropical cities for comparison – decadal (Figure S6, 2010s-2090s) and annual growth rates (Figure S7, 2001-2014 and Figure S8, 2006-2099), and a seasonal map for Europe (Figure S9, summer 2015). Our model is validated by a

good agreement between the global map of decadal growth rate (Figure S10, 2007-2016) and the vector occurrence data [10]. From the comparison, we also show the percentage of occurrence area per category of growth rate (Figure S11).

Discussion

Historically, Europe has been invaded by *Aedes aegypti* that was called the Yellow Fever mosquito [26]. As early as the 1920s-30s, *Aedes aegypti* was reported in quite a few countries in Europe, from Badajos, Portugal (38 °N.) in Southern Europe to as far north as Dol (48° 31' N.) and Brest (48° 24' N.) in France and including the countries of Spain (Ebro), Italy (Genoa, Ravenna), Bosnia, Macedonia, and Russia (Odessa - Ukraine, Sukkum and Baku – Azerbaijan) (See Table 1 from reference [26]). However, recent reports limit occurrence of *Aedes aegypti* to only the Southwest of Russia and the west of Georgia [5]. The other areas may be similar to the case of Athens (Fig. 4C) where the 1920s-30s had a higher vector invasion risk than the later years. The disappearance of *Aedes aegypti* from most of Europe could have many reasons. One example is the economic development and associated vector control to reduce malaria, as in Portugal, which generated fewer breeding sites for other mosquitoes like *Aedes* mosquitoes to develop. In addition, the stochastic nature of fluctuation in vector survival and development may account for some part of the die-out during the initial growth phase of the vector introduction to a new area.

The future invasion risk depends on the carbon emission scenarios. Under a low carbon-emission scenario limiting global warming below 2°C, the risk of invasion continues to be small and confined in both the middle and the end of the 21st century (<1.5% area). Only a few coastal areas along the Mediterranean Sea allow vector establishment. However, under continued high carbon-emissions and global warming centred at 4.9°C, the risk zone of *Aedes aegypti* infestation expands considerably. The risk zone then includes many today densely inhabited areas of southern Europe and up to 5.3% of Europe's land area. This scenario, if not mitigated, is likely to correspond sooner or later to large-scale epidemics and maybe even lead to endemicity of arboviral diseases in Europe. For the European population, our findings challenge the current belief that arboviral diseases are going to increase only incrementally due to climate change as postulated by the IPCC in their last report [27].

Comparing with previous studies using statistical models, our results agree on the current zones of presence [4, 28], but differ in the future projections [8, 29]. Two statistical models predict globally a future increase in risk area with very different results. One predicts an overall global expansion in 2050 that goes as far north as Sweden and Alaska [8], while the other predicts a reduction of risk in the 2070s relative to the 2030s [29]. These data-based statistical models suffer from various biases arising from systematic surveillance, reporting, to prediction, due to scarce data with limited geographical range. For example, the control areas used to train the model limits to a 5-degree latitude and longitude of vector presence. This forces the model to omit climate association at the wider geographical scale [1]. Causality of detected correlations is a critical issue for the use of the statistical models, as the correlation between input parameters may be different in different places and hence problems can arise when extrapolating in space and time [30, 31].

This study uses growth rate (r) over one year or decade to evaluate the establishment of the *Aedes aegypti* mosquito to a new place after it is introduced. This is the first time that growth rate has been used for such threshold estimation. Traditionally in the health field, reproduction number, R_0 , is used to estimate the threshold for an outbreak of disease. R_0 represents the threshold for a mosquito to reproduce over one lifecycle of the mosquito. If $R_0 > 1$, the vector is likely to develop or the disease is likely to spread. r and R_0 are not the same. But they are equivalent in sign: i.e. $r > 0$ if and only if $R_0 > 1$. They make identical predictions of when invasion may be possible. Following this study, we calculated R_0 to repeat this study and we obtained the same results.

Our model accounts for only macro climate influence on infestation of *Aedes aegypti* into Europe. This mechanistic model does not include the stochastic nature of fluctuation in vector survival and development. In addition, the climate data used is gridded, which takes averaging temperature over a certain area (50x50 km near the equator) and GCM does not include local variations such as urban heat islands. As a result, some of the coastal areas have lower growth rate or risk of invasion than would be found using finer resolution of climate data; urban centres may have different growth rates than what we have estimated. Nevertheless, our results show that there is currently risk of contemporary establishment of *Aedes aegypti* over an area of 0.23% of the European continent. Furthermore, since *Aedes aegypti* lives close to human dwellings, there are many possible places to find this mosquito where the climate should in principle not allow its

survival over the winter. An example is Windsor Canada in 2017 [32]. Therefore, the actual places of invasion depend not just on macroclimate but also on local microenvironment and human factors such as living habits, socioeconomic factors, vector controls, etc. Accounting for these additional factors is an important challenge for future research.

Conclusion

Our study is the first to apply a process-based mechanistic model with explicit temperature and precipitation-dependent vector vital rates to predict changes in *Aedes aegypti* invasion potential under climate change. Our results strongly support the necessity of enforcing global carbon emission policy, as signed in the Paris Agreement, to prevent wider scale infestation of *Aedes aegypti* in Europe and other locations where future climatic conditions may enable establishment.

Authors' contributions

JLH carried out the modelling, generated the calculations, and drafted the manuscript. JR conceived the research idea, assisted with modelling and editing of the manuscript. MS obtained climate datasets, created the maps, and assisted with the calculations. ÅB guided the modelling method and helped with the writing of the paper. All authors discussed the results and contributed to the final version of this manuscript.

Acknowledgements

We thank Prof. Hyun MoYang from Universidade Estadual de Campinas, (UNICAMP), Campinas, SP, Brazil for valuable discussion and input for the early stage development of this model. We also thank Mikkel Quam for developing the earlier version of the *R* code for generating the European map. We especially thank Samuel Brändström for critically reviewing the manuscript. We are grateful to Lawrence Lerner, Professor Emeritus at California State University Long Beach, USA, for language proof reading of this manuscript and the Supplementary Information.

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