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Climate Change and Aedes Vectors: 21st Century Projections for Dengue Transmission in Europe

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Abstract

Warming temperatures may increase the geographic spread of vector-borne diseases into temperate areas. Although a tropical mosquito-borne viral disease, a dengue outbreak occurred in Madeira, Portugal, in 2012; the first in Europe since 1920s. This outbreak emphasizes the potential for dengue re-emergence in Europe given changing climates. We present estimates of dengue epidemic potential using vectorial capacity (VC) based on historic and projected temperature (1901–2099). VC indicates the vectors’ ability to spread disease among humans. We calculated temperature-dependent VC for Europe, highlighting 10 European cities and three non-European reference cities. Compared with the tropics, Europe shows pronounced seasonality and geographical heterogeneity. Although low, VC during summer is currently sufficient for dengue outbreaks in Southern Europe to commence—if sufficient vector populations (either Ae. aegypti and Ae. albopictus) were active and virus were introduced. Under various climate change scenarios, the seasonal peak and time window for dengue epidemic potential increases during the 21st century. Our study maps dengue epidemic potential in Europe and identifies seasonal time windows when major cities are most conducive for dengue transmission from 1901 to 2099. Our findings illustrate, that besides vector control, mitigating greenhouse gas emissions crucially reduces the future epidemic potential of dengue in Europe.

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1. Introduction

Globalization and climate change may increase the risk of the geographic spread of vector-borne diseases (Hales et al., 2002; Liu-Helmersson et al., 2014; McMichael, 2013; Murray et al., 2013; World Health Organization (WHO), 2015). Changes in temperature variation have profound impacts on mosquito populations, and perhaps as important as changes in mean temperatures, if not more (Lambrechts et al., 2011; Vasseur et al., 2014). Since 1950, diurnal temperature extremes increased across the globe (Vasseur et al., 2014) and magnitudes of annual temperature cycles increased by 0.4 °C in temperate regions. This could result in elevated vulnerability within Europe for the introduction and re-establishment of vector-borne diseases such as dengue.

Dengue is a climate sensitive mosquito-borne viral disease that is generally found in the tropics and subtropics (Murray et al., 2013). According to the World Health Organization (WHO, 2012) and recent assessment on global burden of diseases (GBD2013) (Murray et al., 2015), dengue is now the most important arboviral disease worldwide that has the largest increases among infectious diseases over the last 20 years. The recent estimates indicate as many as 390 million infections per year (Bhatt et al., 2013). Aedes mosquitoes are the vectors for the four dengue virus serotypes: DENV 1–4 (World Health Organization (WHO), 2012). Ae. aegypti is the primary vector associated with most major dengue epidemics, while Ae. albopictus, the secondary vector, is less efficient (Lambrechts et al., 2010).

Of major concern is the geographic expansion of dengue viruses and vectors to new areas (Lambrechts et al., 2010; World Health Organization (WHO), 2009). Reasons for the expansion are complex; however, main contributing factors include the introduction of Aedes mosquitoes by shipping (Reiter, 1998) and increasingly importation of the dengue virus via viremic travelers (Leder et al., 2013; Wilder-Smith and Gubler, 2008). Subsequent establishment of vectors after introduction can only be possible if suitable climate and ecological conditions exist. Having established populations of Aedes vectors and the conducive climatic conditions, in early autumn 2014, Tokyo, Japan

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recorded the first epidemic of dengue since the Second World War (Quam et al., 2016). Europe is also suitable for the establishment and re-establishment of Aedes mosquitoes as evidenced by the following: Aedes aegypti was historically present in many European countries including UK and France (1919), Spain (up to 1953), Portugal (up to 1956), and recently the Netherlands, Russia and Georgia (European Centre for Disease Prevention and Control (ECDC), 2014; European Centre for Disease Prevention and Control (ECDC), 2015). In Madeira, Portugal, Ae. aegypti was documented until 1977–79 and then was re-established in 2004 and 2005. Madeira experienced its first major dengue outbreak in 2012/2013, with more than 2000 cases (European Centre for Disease Prevention and Control, 2012; Wilder-Smith et al., 2014a). The rapidly expanding range of Ae. albopictus in Europe (Lambrechts et al., 2010; European Centre for Disease Prevention and Control (ECDC), 2013) resulted in the first known autochthonous dengue cases in southern France and Croatia in 2010 (La Ruche et al., 2010) in addition to an importation Ae. albopictus driven outbreak of chikungunya in 2007 in Italy (Rezza et al., 2007). There are concerns that Ae. aegypti could be introduced from Russia and Georgia (Abkhazia) to Western Europe via air or sea traffic, and to Eastern Europe via road and sea traffic, in addition to the vectors’ projected establishment in Southern Europe (Rogers, 2015). Current surveillance indicates that Aedes vectors have been introduced or established in much of the Mediterranean coast and as far north as the Netherlands (European Centre for Disease Prevention and Control (ECDC), 2015). Therefore, it is important to assess the dengue epidemic potential (DEP) in Europe.

A few studies have projected dengue risk and epidemic potential for Europe. They have used either statistical models (Bouzid et al., 2014; Carrington et al., 2013). A mathematical model, however, with limited range either geographically, temporally or in terms of climate scenarios. In this study, we intend to estimate DEP for Europe using vectorial capacity with increased range of climate scenarios and temporal resolution. Although DEP depends on many factors, this study focuses on the effect of temperature – past, present, and future – on vectorial capacity of Aedes mosquitoes.

Vectorial capacity (VC) describes the threshold condition for a vector’s ability to spread disease among humans (Patz et al., 1998; Massad and Coutinho, 2012), representing the average daily number of secondary cases generated by one primary case introduced into a susceptible population (Liu-Helmersson et al., 2014). It depends on six vector parameters (Patz et al., 1998), which are highly influenced by ambient temperature, both its mean value and diurnal temperature range (DTR) (Liu-Helmersson et al., 2014; Lambrechts et al., 2011; Carrington et al., 2013). VC has been used to model DEP globally for both Aedes vectors (Patz et al., 1998; Brady et al., 2014). Very few models incorporated DTR (Patz et al., 1998) and the temperature dependent transmission probabilities per bite to both humans and vectors (Lambrechts et al., 2011) when describing DEP (Liu-Helmersson et al., 2014) or vector competence. Including these factors would change the projected estimates of the impacts of climate on DEP, given strong temperature dependence of transmission probabilities per bite in humans and vectors and strong association of DTR with VC and vector competence (Liu-Helmersson et al., 2014; Lambrechts et al., 2011).

In this study, we modeled VC to project DEP in Europe given changes in climate. Throughout this study, we have included DTR in all of our VC calculations. We expanded our previous relative VC model to VC, by including temperature dependent dynamics in the female vector-to-human population ratio (Liu-Helmersson et al., 2014) for both Ae. aegypti and Ae. albopictus under four projected emission scenarios with higher temporally and spatially resolution over two centuries. We estimated DEP for local dengue transmission, in terms of seasonality, intensity and duration, for Europe and examined ten European metropolitan cities ranging from North to South for the period 1901–2099 (for more details see Table S3 in the Supplementary information).

### 2. Methods

Vectorial capacity (VC) was used to estimate dengue epidemic potential (DEP). As shown in Equation (Hales et al., 2002; Patz et al., 1998; Massad and Coutinho, 2012), VC depends on six vector parameters:

\[
VC = \frac{ma^2b_bm_a^{e^{-n_mn_t}}}{\mu_m}.
\]

(1)

The six vector parameters used were 1) the average vector biting rate \(a\), 2) the probability of vector to human transmission per bite \(b_n\), 3) the probability of human to vector infection per bite \(b_m\), 4) the duration of the extrinsic incubation period – EIP \(n\), 5) the vector mortality rate \(\mu_m\), and 6) the female vector-to-human population ratio \(m\). The time unit is one day. Each of the vector parameters depends on temperature (Liu-Helmersson et al., 2014). The temperature relationships for the first five vector parameters, 1–5), were obtained from the peer-reviewed literature for Ae. aegypti: details are described elsewhere (Liu-Helmersson et al., 2014). For Ae. albopictus, only two vector parameters, 1 and 5), were found in the literature with temperature dependent relationships: the mortality rate \(\mu_m\) and the total biting rate \(a\), which was taken as an inverse of the duration of gonotrophic cycle (Delatte et al., 2009). The remaining three parameters, 2–4), in the VC were assumed to have the same temperature relation as those for Ae. aegypti (Liu-Helmersson et al., 2014). For Ae. Albopictus, the human biting rate is assumed to be 0.88 of the total biting rate based on the human and dogs experiment performed by Delatte et al. (2010). The probability of transmission per bite to human is assumed to be 0.7 of that for Ae. aegypti, based partially on the literature review conducted by Lambrechts et al. (2010). Due to a lack of reliable data, the female vector-to-human population ratio, \(m\), is assumed to depend on temperature the same way as the life expectancy or inverse of the mortality rate, as used in a previous study (Brady et al., 2014). The maximum value of \(m(\text{m}_{\text{max}})\) is assumed to be 1.5.

The threshold cut-off for DEP was defined as \(VC^* = 0.2\) (day−1). Here we assume that an epidemic potential is realized when VC reaches a level such that one infected person will infect at least one more person after dengue is introduced into a naïve population during his/her five-day infectious period (Liu-Helmersson et al., 2014; Nishiura and Halstead, 2007) (Supplementary information, Section S4). Sensitivity analysis was performed for the effect of the range of the infectious period (4–10 days) (World Health Organization (WHO), 2012; Centers for Disease Control and Prevention (CDC), 2015; Chan and Johansson, 2012) on the dengue transmission windows (Supplementary information Section S5.3, Fig. S5A for Ae. aegypti and Fig. S5B for Ae. albopictus). This corresponds to a range of thresholds for DEP from 0.1 to 0.25 (day−1). We have chosen the threshold value of 0.2 (day−1), which is closer to the higher end of this range, to be conservative in our results presented.

To generate recent European season-stratified maps of VC (Jan. 1, 2006–Dec. 31, 2015), daily temperature observations (minimum, maximum, and mean) from the E-OBS 12.0 dataset were used for each location gridded at 0.25 × 0.25° (about 25 × 25 km at the equator) latitude and longitude (Haylock et al., 2008). This daily VC calculation included interpolating DTR based on daily observations, then aggregated over the decade by season (Winter: December–February; Spring: March–May; Summer: June–August; Autumn: September–November). The seasonal averaged VC for the recent decade were displayed as maps for Europe for each season for both vectors and compared to a recent survey of vector distribution (European Centre for Disease Prevention and Control (ECDC), 2015) for areas known to have Aedes activity according.

To show seasonality of VC over a year, decade averages of VC for each month was displayed as a function of the month in a year. For the recent decade, 13 cities were chosen to compare seasonality of DEP. Ten
European cities were selected to represent most of the European continent with different temperature zones from the north — Stockholm (latitude = 59.3) to the south — Málaga (latitude = 36.7) within the continent and Madeira (latitude = 32.7) outside the continent. Madeira is an autonomous region of Portugal having a dengue outbreak in 2012, and for convenience in this paper, we will use the name of city for all the nine cities and Madeira region. Three reference cities from tropical and sub-tropical regions outside Europe were chosen for comparison. Colombo and Singapore are located in Asia close to the equator and display high dengue endemicity (Gubler, 2011; Gubler and Clark, 1995) despite political and financial investment in dengue control. By contrast, Miami, located in North America with a sub-tropical climate with more similarity in environmental and social economic conditions to some of Southern Europe, has reported autochthonous dengue transmission occasionally, which typically does not develop into large scale epidemics (Theiler et al., 1960).

Diurnal temperature range is known to affect the competence of dengue vector Ae. aegypti (Lambrechts et al., 2011). Inclusion of DTR in modeling DEP for Ae. aegypti using relative VC (rVC) has shown a great difference comparing without DTR (Liu-Helmersson et al., 2014), especially in the cold to temperate climate zones in Northern Europe. This is because rVC (VC) depends on DTR strongly, both the peak intensity and the position. When DTR increases from 0 °C to 20 °C, the peak height of rVC reduced from 1.37 to 0.47 day⁻¹; the peak position of VC reduces from 29 °C to 20 °C. Therefore, in models including DTR, temperate climate zones with larger DTR will have greater DEP, while tropical areas with less DTR will have lower DEP than estimated by models using mean temperature alone. This is particularly relevant to Europe, where DTR is greater than tropical areas.

From the Climate Research Unit (CRU) online database, time series (CRU-TS 3.22) of gridded (0.5 × 0.5 degrees) monthly averages of daily temperature observations (minimums, maximums, and mean) were obtained for Europe for the period January 1, 1901 to December 31, 2013 (Jones et al., n.d.). Given the importance of DTR to temperate European climate, in all the VC calculations, diurnal temperature range (DTR) was included. DTR was reconstructed using a representative daily temperature for each 30 min through a piece-wise sinusoidal function based on the monthly average of daily minimum, maximum, and mean observations for each location (same temperature for each day of the month in each 0.5 × 0.5 grid — See Supplementary information S3 for details). To illustrate the combined effect of DTR and mean temperature to VC, heat maps were generated for both Ae. aegypti vectors (Fig. S2 (d) & (d) in the Supplementary information).

To show the seasonal window and its change over time, a 30-year average was used for each monthly averaged VC at three periods — the beginning of the 20th century (1901–1930), at the turn from 20th to 21st century (1984–2013), and the end of the 21st century (2070–2099). Future VC was calculated using projected climate under four greenhouse gas emission pathways (RCP2.6, RCP4.5, RCP6.0 and RCP8.5) (Weyant et al., 2009) based on CMIP5 (Taylor et al., 2011; Warszawski et al., 2014) atmosphere-ocean general circulation models. For each emission pathway, CMIP5 temperature datasets (min, max, mean resolution 0.5 × 0.5°) were used (Taylor et al., 2011; Warszawski et al., 2014). The VC was calculated for each of the five global models (NorESM1-M, MIROC-ESM-CHEM, IPSL-CM5A-LR, HadGEM2-ES and GFDL-ESM2M) and then averaged over the five models (Taylor et al., 2011; Warszawski et al., 2014). We used these models as an ensemble to form a multi-model mean, with the intention of providing results that are based on greater consensus. The four RCP scenarios describe the possible range of radiative forcing of greenhouse gases in the year 2100 (+2.6, +4.5, +6.0, and +8.5 W m⁻², respectively) (Weyant et al., 2009). VC calculations were aggregated by decade to show the trends in DEP over two centuries. A selection of the outputs of these projection-based VC calculations was also mapped for RCP2.6 and RCP8.5 for both species to show the changes in DEP across Europe under scenarios of greater or lesser emission mitigation.

To calculate the intensity and duration of dengue transmission, a seasonality curve was generated by plotting the decadal averaged VC as a function of month for each of the 10 cities first and then for each decade over the two centuries. The intensity of DEP was estimated by averaging the VC over the highest three consecutive months in the seasonality curve. The duration of transmission season was estimated by the intersections of the seasonality curve with the line defining the threshold condition (VC = 0.2 (day⁻¹)). The differences between the two intersections gave the number of months that VC was over the threshold. This was repeated for each decade over the two centuries and for each of the 10 European cities. Over the two centuries decadal averaged VC were from year zero to nine for each decade except the two decades with 9-year period: 1901–1909, 2011–2019 due to that both CRU and CMIP5 data started from year one in the data set: 1901 and 2011.

Sensitivity analyses were carried out and the results were included in the Supplementary Information, where section and figure numbers were marked with “S”. Using Monte Carlo simulations, 95% Credible Intervals (CI) (Pericchi and Walley, 1991) of VC were estimated for temperatures ranging from 10 °C to 32.5 °C. The variability in each of the six vector parameters was simulated assuming a normal random distribution. At each temperature under the random generation of parameters, VC was calculated based on Eq. (1). Repeating this process 1000 times for each temperature, the 2.5th and the 97.5th percentiles of the VC were estimated to give the values of VC ± 5% CI. Using the fitting functions (VC ± 5% CI vs. temperature) as the basic equations and temperature data as input, we estimated VC ± 5% CI for the ten cities over two centuries, including DTR (Section S5.1–S2, Figs. S3–S4 and Table S2 in Supplementary information). In addition, sensitivity of VC to threshold values (VC*) and the maximum value of the female vector-to-human population ratio (mmax) were also estimated based on Eq. (1). We compared three values: VC* = 0.1, 0.2, 0.25 day⁻¹ based on the infectious period of 4 to 10 days. The results were expressed as dengue transmission duration over the rest of this century for two RCPs (Fig. S5). We varied mmax in three values: 1, 1.5, and 2, which was chosen to reflect partially the range of pupae-to-human population ratio (0.3 to 60) for Ae. aegypti (Focks et al., 2000). The results were expressed as the seasonality curves (averaged VC vs. months) over the recent decade for selected 13 cities (Fig. S6), and transmission intensity and duration over the two centuries for two RCPs (Figs. S7–S8) in the Supplementary information.

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3. Results

3.1. Current Seasonality of Dengue Epidemic Potential in Europe and Tropical/Subtropical Cities

Fig. 1 shows the season-stratified maps of Europe’s DEP during the recent decade (2006–2015) for Ae. aegypti (Fig. 1(i)) compared to Ae. albopictus (Fig. 1(ii)) and current distribution of Ae. vectors either introduced or established (Fig. 1(iii)) (European Centre for Disease Prevention and Control (ECDC), 2015). Currently Europe is infested by Ae. albopictus mainly in the Mediterranean area but expanding northward, while only three areas have recently reported Ae. aegypti, Georgia and southwestern portions of Russia, in addition to Madeira Island, Portugal (not shown on map) (European Centre for Disease Prevention and Control (ECDC), 2015). The threshold value of 0.2 day⁻¹ corresponds to yellow color (see color bar). In areas with VC above this threshold (yellow-orange to dark red) during a given time period, dengue outbreaks may commence assuming prerequisite populations of
vectors, susceptible human hosts, and virus introduction coincide. Areas during time periods displayed in blue to yellow green would not be expected to be suitable for dengue outbreaks to begin even if vectors were present and importations of dengue virus were persistent. Strong seasonality is apparent: VC was not sufficiently high in Europe in the winter, spring, and autumn seasons to allow dengue epidemic transmission to commence using the threshold value of 0.2 day$^{-1}$, except for small areas in the very southern parts of Southern Europe during spring and autumn. In the summer season, the majority of continental Europe for Ae. aegypti and southern and partially central parts of Europe for Ae.

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**Fig. 1.** Season stratified maps of VC for Europe for Ae. aegypti (i), Ae. albopictus (ii), and in those areas having recently established and/or introduced Aedes vectors (iii) (European Centre for Disease Prevention and Control (ECDC), 2015; Wilder-Smith et al., 2014b). VC was calculated for each day of the period (Jan. 1, 2006–Dec. 30, 2015) and then seasonally aggregated over the decade. Winter: December–February; Spring: March–May; Summer: June–August; Autumn: September–November. DTR was included and $m_{max} = 1.5$. E-OBS 12.0 daily gridded (0.25 × 0.25°) temperature datasets were used (Haylock et al., 2008). The gray colored areas in this figure (iii) are those having unknown Aedes activity or for which survey information was unavailable (European Centre for Disease Prevention and Control (ECDC), 2015). The threshold value of 0.2 day$^{-1}$ is marked with an arrow on the yellow portion color bar. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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**Fig. 2.** Seasonality of VC for 13 selected cities for Ae. aegypti (a) and Ae. albopictus (b). VC was averaged over the recent 10-year period (2004–2013) for each month of the year. DTR was included and $m_{max} = 1.5$ where $m$ is the female vector to human population ratio. CRU-TS3.22 monthly gridded (0.5 × 0.5°) temperature data (Jones et al., n.d.) were used.

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albopictus have climate conditions and corresponding VC that could sustain seasonal dengue epidemics. Therefore, if the primary vector, Ae. aegypti, established in the other parts of Europe in the future, it could have greater DEP than the established and invasive secondary vector, Ae. albopictus.

We compared 10 cities in Europe with three reference cities in tropical and sub-tropical regions. Fig. 2 shows VC averaged per month over the recent 10 years for Ae. aegypti (a) and Ae. albopictus (b). General decreases in VC were observed comparing the temperate European cities to the tropics, and the subtropics. Singapore and Colombo showed high and nearly constant year-round VC. Miami showed a broad peak from May to October, with VC values over the threshold (0.2 day⁻¹) year-round, indicating dengue epidemic transmission was theoretically possible. All European cities showed a strong and narrow seasonal transmission potential with overall lower VC values. Cities in Southern Europe exhibited higher and broader peaks in VC than the rest of Europe. Ae. aegypti showed higher VC than Ae. albopictus. Seven out of the 10 European cities were over the threshold for at least one month of the year for Ae. aegypti; only four cities were over the threshold for Ae. albopictus. For both vectors, no single city in Europe had sufficiently high VC to initiate endemic dengue transmission during the winter months. Therefore, during the past decade a dengue epidemic was possible only during the warmer months of the year in all three Southern European cities for both vectors and in some Central European cities for Ae. aegypti based on the CRU temperature data as input. Notice that this result based on monthly temperature is lower than the results shown in Fig. 1 using daily temperature as input – see limitation of this study in Discussion section and Section S1 in Supplementary information for more discussion. The rest of the results were based on monthly temperature.

3.2. Climate Change and the Dengue Epidemic Potential in Europe

Fig. 3 shows the season-stratified maps of Europe’s DEP during the last decade of the 21st century under greenhouse gas emission pathways RCP2.6 (i & iv) and RCP8.5 (ii & iii) for two Aedes vectors. DTR was included and $m_{\max} = 1.5$. Differences in VC for the four seasons are clearly shown. DEP is almost zero during the winter, then growing from small regions in the Southern Europe during the Spring, increasing intensity and expanding geographically during Summer, before contracting again in Fall. The differences in VC between the two climate scenarios and two Aedes vectors are apparent in Fig. 3. Under the most mitigation climate scenario (RCP2.6), during the Summer season, DEP is limited to the Southern and the Central Europe for both vectors. Under the business as usual climate scenario (RCP8.5), DEP extends into Northern Europe for both Aedes vectors. Under both climate scenarios, Ae. aegypti showed higher intensity in more areas than Ae. albopictus. By the end of this century, the highest DEP region during summer season would be in the Central Eastern parts of the Europe, in addition to parts of the coastal areas of Southern Europe already having high DEP in the recent decade as shown in Fig. 1.

Fig. 4 shows the trend in seasonality over two centuries (1901–2099) for the 10 European cities for Ae. aegypti (Fig. 4A) and for Ae. albopictus (Fig. 4B). For each city, 30-year averaged VC was estimated for three periods: Past (1901–1930) (i), Current (1984–2013) (ii), and Future (2070–2099) (iii–vi). We used historical temperature data from 1901 to 2013 and projected temperatures from 2011 to 2099 under five climate scenarios (CMIP5 (Taylor et al., 2011; Warszawski et al., 2014)) representing increasing emissions of greenhouse gases (Representative Concentration Pathways (RCPs) 2.6, 4.5, 6.0 and 8.5). Strong seasonality was observed in all cities over all periods and...
Compared to the past, the current period shows an increase in the magnitude and the width of the peak in $VC$ in central to Northern European cities (n = 7 including Madeira) while the Southern cities (n = 3) remained about the same (the magnitude of the peak was slightly reduced in Athens and increased in Rome).

The same trend was observed when comparing the future to the current period under different emission pathways. The higher the RCP, the higher the peak in $VC$ for the Central to Northern seven cities including Madeira and the wider the window of transmission for all 10 cities. These observations hold for both Aedes vectors.

Fig. 5 shows the intensity and duration of dengue transmission over two centuries for $Ae. aegypti$ (Fig. 5A) and $Ae. albopictus$ (Fig. 5B). 'Intensity' was defined as the averaged $VC$ over the highest three consecutive months for each decade, and 'duration' of transmission window was defined as the number of months when a decade’s averaged $VC$ was over the transmission threshold value (0.2 day$^{-1}$). Three months was used as a...
as the threshold in duration, reasoning that importation-driven epide-

mics of dengue would take several transmission generations to prop-

agate in human and vector populations before the

first reported cases of dengue are identi

dified as was observed with Madeira in 2012 (Lourenço

and Recker, 2014; Wilder-Smith et al., 2014b) and Japan in 2014 (Quam

et al., 2016). Observed temperatures were used from 1901 to 2009. From 2011 to 2099, two emission pathways (CMIP5 (Taylor et al., 2011; Warszawski

et al., 2014)) were evaluated: RCP2.6 (i & ii) and RCP8.5 (iii & iv).

In general, increasing trends in intensity and duration for DEP were

observed in all cities. The intensity and duration markedly increased

from 1970 to 2019 under both RCPs and for both vectors, except for

the three Southern European cities: Malaga, Athens and Rome, where

From 2011 to 2099, two emission pathways were evaluated: RCP2.6

(i–ii) and RCP8.5 (iii–iv).

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intensity remained nearly constant due to decreasing sensitivity to slight temperature changes around the peak temperature for VC, as shown in Supplementary information (Section S4, Fig. S2(c)-(e)) and previously described for relative VC (Liu-Helmersson et al., 2014). From 2020 to the end of this century, this increase in intensity and duration is projected to level off under RCP2.6, while continuing to increase rapidly under RCP8.5 for both vectors, leading to very different projected trends.

During the current decade (2011–2019) under both RCPs, for *Ae. aegypti* the intensity threshold (0.2 day⁻¹) will be surpassed in seven cities (n=7) (Fig. 5A (i) & (iii)) and duration threshold (three months) in four cities (n=4) (Fig. 5A (ii) & (iv)) and previously described for relative VC (Liu-Helmersson et al., 2014). From 2020 to the end of this century, this increase in intensity and duration is projected to level off under RCP2.6, while continuing to increase rapidly under RCP8.5 for both vectors, leading to very different projected trends.

Among a duration of three months over the threshold in VC (dotted line in Fig. 5 (ii) & (iv)) is required for a dengue outbreak to occur (Liu-Helmersson et al., 2014), then in the past century (1901–2009) only Málaga, Athens and Rome had the potential for dengue outbreaks. However, for *Ae. aegypti*, the number of cities with intensity over the threshold will be increased from four to five continuously (n=5) with one city (Berlin) over the threshold for only short time (2060s); the number of cities with duration over threshold remains the same (n=3). However, under RCP8.5, for *Ae. aegypti* all the 10 cities are projected to be over the thresholds in both intensity and duration (n=10 by 2050s; n=10 by 2080s); for *Ae. albopictus*, all 10 cities in intensity and seven cities in duration (n=10 by 2080s; n=7 by 2080s); this is a notable increase in DEP over the projections for RCP2.6 for both dengue vectors.

Assuming a duration of three months over the threshold in VC (dotted line in Fig. 5 (ii) & (iv)) is required for a dengue outbreak to occur (Liu-Helmersson et al., 2014), then in the past century (1901–2009) only Málaga, Athens and Rome had the potential for dengue outbreaks. However, for *Ae. aegypti*, in the current decade 2011–2019, Nice shows sufficient DEP under both RCPs. In the coming decades, under RCP2.6, there is little increase from the current to the future – only five cities (Málaga, Athens, Rome, Nice and Paris by 2020s) could have sufficient DEP. If RCP8.5 were to be realized, Paris would have sufficient DEP (2020s), followed by Madeira and Berlin (2030s), London (2060s), Amsterdam (2070s), and Stockholm (2080s). Therefore, by the end of this century, five cities under RCP2.6 and all 10 cities under RCP8.5 could have sufficient DEP – an increase of five cities from Central to Northern Europe (including Madeira) between the RCPs.

For *Ae. albopictus*, under RCP2.6 there is no difference between the future and past – only the Southern three cities, Málaga, Athens and Rome, had the potential for dengue outbreaks. Under RCP8.5, Nice will have sufficient DEP (2030s), followed by Paris (2060s), Berlin (2070s) and Madeira (2080s). Therefore, the gap in dengue epidemic duration between the two RCPs widens toward the end of this century - an increase of four cities between the two RCPs.

### 4. Discussion

Comparing to tropical and subtropical countries, Europe showed strong seasonality in DEP. No European city is projected to have year-round dengue epidemic transmission; the longest period would be eight months for *Ae. aegypti* and seven months for *Ae. albopictus* in Málaga by the end of the 21st century under RCP8.5.

As temperature increases with time from 1970s onward, Central (especially Nice) and Northern Europe has shown great increase in transmission intensity during summer while Southern Europe has shown decrease (Fig. 4). This is due to the combined effect of mean temperature and DTR as shown in Fig. S2 (c)-(f) in the Supplementary information.

Over time, the intensity and seasonal windows for DEP has increased and is projected to continue increasing. As a result, more cities will be over the VC threshold starting from the South and progressing to the North during this century. However, the rate of the increase depends on the emission pathway for both vectors, especially toward the middle of the century. The same trend is observed even when using the lower bound of VC (95% CI) for *Ae. aegypti* (see Supplementary information, Section S6.2). This implies a significant potential benefit, if policies for climate change mitigation are implemented such that future emissions more closely reflect RCP2.6.

Over the two centuries, we have observed that the DEP in Athens, Málaga, and Rome are consistently over the threshold during part of the year. Nice stands out as having the most dramatic rise; by the 2060, Nice would surpass the intensity of the three Southern European cities; by the end of this century, during July–August Nice would be near the current summer peak intensity in Miami. Consistent with this, Nice was the site of the first reported autochthonous European cases in 2010 (La Ruche et al., 2010) and Athens had a massive dengue outbreak in 1927/28 (Theiler et al., 1960). Since 1928, there has only been one dengue epidemic in Europe–Madeira 2012 with over 2000 cases transmitted through *Ae. aegypti* (European Centre for Disease Prevention and Control, 2012; Wilder-Smith et al., 2014b). Using local weather station temperature data for the current decade, VC for Madeira was well over the threshold from June to October (Fig. S1 in Supplementary information). Therefore, our findings are consistent with the large dengue outbreak that occurred in 2012 (European Centre for Disease Prevention and Control, 2012). The decline of new incident cases after November 9, 2012 was most likely due to declining VC because of cooler temperatures combined with enhanced vector control measures and public awareness.

While our findings contribute valuable insight into the timing of the outbreak potential in Madeira, the introduction of vector predated the outbreak by years, and the climate based DEP predated both for a number of months each year. This illustrates that commencement of an actual dengue outbreak involves complex processes and more factors than what we have addressed here. Of note is that VC for Athens, Rome and Málaga is higher than that for Madeira even using local weather station data (UK Meteorological Office, n.d.), yet no dengue outbreaks recently occurred in those cities likely in part due to the absence of *Ae. aegypti*. However, *Ae. aegypti* may be introduced or re-introduced at any time. Our findings underpin the suitability of temperature dependent VC in countries such as Italy, Spain and Greece that could result in autochthonous dengue transmission should *Ae. aegypti* be imported and establish. Indeed, when *Ae. aegypti* was present in Greece in the early 20th century, a major dengue outbreak occurred in and around Athens in 1927–28 (Theiler et al., 1960). Furthermore, over 20 epidemics of yellow fever, another flavivirus (like dengue) transmitted via *Ae. aegypti*, occurred during the 18th and 19th centuries around British, Portuguese, and Spanish harbors, with the last outbreak being in Barcelona, Spain in 1821 (Morillon et al., 2002). With climate change, recent studies projected the re-establishment of *Ae. aegypti* in the coastal zones of Europe in 2080 (Rogers, 2015; Kraemer et al., 2015).

* Ae. albopictus is already widely spread in much of Southern Europe, especially in the Mediterranean areas (Kraemer et al., 2015; Reiter, 2010). Comparing to VC of *Ae. albopictus* (Fig. 2a), *Ae. albopictus* (Fig. 2b) had similar seasonal windows but with lower intensity such that only Southern European cities could currently have dengue epidemics. The main reason for the absence of dengue outbreaks in these cities could be one or all of the following factors: 1) Insufficient adult vector populations that are actively biting humans for an extended period that could infect infective humans with dengue for an extended period that could infect infected humans with dengue for an extended period that could infect sufficient number of vectors to sustain a dengue outbreak (infected humans traveling back from dengue endemic areas are presumably isolated indoors or may have recovered before they traveled home); 3) *Ae. albopictus* is a less efficient vector for dengue transmission than what we estimated. We may have overestimated the VC for *Ae. albopictus*
due to limitations in temperature dependent data and studies (Lambrechts et al., 2010).

However, *Ae. albopictus* was responsible for the epidemic transmission of chikungunya, an alphavirus, in Italy in 2007 (Carriero et al., 2011). Therefore, it is unlikely that at that time factor 1) - insufficient *Ae. albopictus* population - is the main reason for not having dengue outbreaks in Europe, unless *Ae. albopictus* more effectively drives transmission of chikungunya (Paupy et al., 2009) than dengue such that the current *Ae. albopictus* population are sufficient to drive chikungunya but too few to trigger dengue outbreaks (Dubrulle et al., 2009).

Each year, certain European travelers return home with dengue (i.e. 1207 cases reported in 2012 reported in EU/EEA, 884 of which lived in the EU countries currently having *Aedes* vectors (European Centre for Disease Prevention and Control (ECDC), 2014) and the number increased over time (Quam et al., 2015; Semenza et al., 2014; Tatem et al., 2006). If factor 2) is the main reason for preventing dengue outbreaks in Europe to date, this suggests outbreaks could occur anytime in the future when the infectious person/vector is in the suitable place at a suitable time, as was the case for chikungunya in Italy in 2007. If factor 3) is true, then the main concern for Europe is the potential introduction and establishment of *Ae. aegypti*, consistent with earlier studies (Liu-Helmersson et al., 2014; Lambrechts et al., 2010). Madeira like Miami highlights the difference between DEP and actually having dengue epidemic transmission. This can be multifactorial. The temporal and geographic range of DEP is likely to be spatially and temporally broader than the actual areas of transmission events (over estimations). On the other hand, Nice had local dengue transmission reported as early as September 2010 (La Ruche et al., 2010), which may indicate that the DEP should be viewed with caution. If different threshold values were used, the general trend and order of cities that would go over the threshold will hold, but the exact decade when the DEP goes over the threshold could change. However, using the threshold of 0.2 day\(^{-1}\) in the analysis of both the outbreak in Madeira in 2012 and the 2014 dengue outbreak in Japan, we found that this threshold corresponded spatially and temporally with the novel transmission events (Quam et al., 2016). See Supplementary information (Section S6.3) for more discussion.

Third, for *Ae. albopictus*, only two parameters with temperature dependent relations were available in the literature (Delatte et al., 2009). The remaining parameters were assumed to have the same temperature dependent relationships as *Ae. aegypti*, although they were adjusted to the level of *Ae. albopictus* based on a literature review (Lambrechts et al., 2010). This would limit the accuracy of the estimated value of DEP for *Ae. albopictus*. See Supplementary information (Section S4) for more discussion.

Finally, the temperature data used from CRU and CMIP5 are monthly averages over gridded area of 0.5° × 0.5°. While the daily datasets from E-OBS for the maps in Fig. 1 have finer resolution (0.25° × 0.25°, daily), coarser resolutions (CRU and CMIP5) may underestimate DEP during the summer and overestimate during the winter for cities located along the costal lines. This accounts for the differences observed between Fig. 1 and Fig. 2 for major cities. Much of our analyses were based on outputs from the coarser temperature data sets (CRU and CMIP5). Therefore, the conclusions drawn are more conservative for the summer and overestimates for the winter (Fig. 5 intensity). See Supplementary Information (Sections S1 & S2) for more discussion.

5. Conclusion

We identified past, present, and future high-risk cities and time periods for potential dengue transmission in Europe based on temperature and daily temperature variation. Compared to countries where dengue is endemic, Europe showed strong seasonality in dengue epidemic potential (DEP) without possibility of year-round epidemic transmission. Compared over two centuries, we found a slow increase in intensity and duration of dengue transmission over the past century and more rapidly changing trajectories projected in the 21st century with the rate of change depending on the level of greenhouse gas emissions.
Although Europe currently does not have a sufficiently high DEP year round, increasing periods with higher temperatures and greater temperature variation in the future due to climate change could elevate DEP along a south to north gradient. By the end of this century, DEP for *Ae. aegypti* could expand to Northern Europe (all 10 cities studied) and up to eight months in Southern Europe under the highest emission pathway (RCP 8.5). Under the lowest emission pathway (RCP 2.6), it could expand to Nice and Paris for *Ae. aegypti* from the current three Southern European cities. For *Ae. albopictus* DEP could expand to all of the Central Europe (7 cities) under RCP 8.5; however, it would remain nearly as it is now under RCP 2.6 (three Southern Europe cities). Therefore, climate change mitigation (or lack thereof) could have a large impact on the seasonal window and geographic range for dengue transmission potential in Europe. Under the higher emission scenarios, increasingly larger parts of Europe would have the potential for autochthonous dengue transmission should *Ae. aegypti* be introduced and established. Such concerns were substantiated by the dengue outbreak in Madeira in 2012. The same concern extends to *Ae. albopictus* if higher greenhouse gas emissions than RCP2.6 would be realized.

Increasing globalization in travel and trade will intensify the importation of dengue viruses and the potential for further introduction of *Ae. aegypti* (Gubler and Clark, 1995). If such introductions coincide with the incubation period of dengue viruses and the potential for further introduction of *Aedes albopictus*, vector of chikungunya and dengue in the Indian Ocean. J. Med. Entomol. 48, 1214–1225.

Carrington, L.B., Seifert, S.N., Willits, N.H., Lambrechts, L., Scott, T.W., 2013. Large diurnal temperature fluctuations negatively influence *Aedes aegypti* (Diptera: Culicidae) ecological life-history traits. Journal of medical entomology. Proc. Natl. Acad. Sci. U. S. A. 50, 3.

Centers for Disease Control and Prevention (CDC), 2015. Mosquito-borne Transmission - Infectivity Period (About 7 Days) [Accessed: 2015-12-01], available from: http://www.cdc.gov/dengue/training/cme/ccm/page49515.html.

Chan, M., Johansson, M.A., 2012. The Incubation Periods of Dengue Viruses. PLoS One 7, e30206.

Delatte, H., Gimonneau, G., Triboire, A., Fontenille, D., 2009. Influence of temperature on immature development, survival, longevity, fecundity, and gonotrophic cycles of *Aedes albopictus*, vector of chikungunya and dengue in the Indian Ocean. J. Med. Entomol. 46, 33–41.

Delatte, H., et al., 2010. Blood-feeding behavior of *Aedes albopictus*, a vector of Chikungunya on La Réunion. Vector-Borne and Zoonotic Diseases 10, 249–258.

Dubrulle, M., Mousson, L., Moutailler, S., Vazeille, M., Failloux, A.-B., 2009. Chikungunya virus and *Aedes mosquitoes*: saliva is infectious as soon as two days after oral infection. PLoS One 4, e5895.

European Centre for Disease Prevention and Control, 2012. Epidemiological update: outbreak of dengue in Madeira, Portugal 14 Feb 2013 [Accessed: 2013-03-25], available from: http://ecdc.europa.eu/en/news/pdf/News/News.aspx?id=37–.

European Centre for Disease Prevention and Control (ECDC). *Aedes albopictus* (ECDC, Stockholm, 2013). [Accessed: 2014-01-19], available from: <http://ecdc.europa.eu/en/healthtopics/vectors/mosquitoes/Pages/aedes-albopictus.aspx>.

European Centre for Disease Prevention and Control (ECDC). 2014. Annual Epidemiological Report - Emerging and Vector-Borne Diseases. ECDC, Stockholm.

European Centre for Disease Prevention and Control (ECDC). *Mosquito Maps. Aedes aegypti - Current Known Distribution - January 2016 & Aedes albopictus - Current Known Distribution*. [Accessed: 2016-02-17], available from <http://www.ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx>.

Focks, D.A., Brenner, R.J., Hayes, J., Daniels, E., 2000. Transmission thresholds for dengue in terms of *Aedes aegypti* gape size per person with discussion of their utility in source reduction efforts. Am. J. Trop. Med. Hyg. 62, 11–18.

Gubler, D.J., 2011. Dengue, urbanization and globalization: the unholy trinity of the 21st century. J. Trop. Med. Health. 1, 1.

Gubler, D.J., Clark, G.G., 1995. Dengue/dengue hemorrhagic fever: the emergence of a global health problem. Emerg. Infect. Dis. 1, 55.

Hales, S., Weinstein, P., Woodward, A., 1996. Dengue fever epidemics in the South Pacific driven by El Nino Southern Oscillation? The Lancet 348, 1664–1665. http://dx.doi.org/10.1016/S0140-6736(96)61573-6.

Hales, S., de Wet, N., Maindonald, J., Woodward, A., 2002. Potential effect of population density and climate changes on global distribution of dengue fever: an empirical model. Lancet 360, 830–834.

Haylock, M.R., et al., 2008. A European daily high-resolution gridded dataset of surface temperature and precipitation. J. Geophys. Res. (Atmospheres) 113. http://dx.doi.org/10.1029/2007JD009308.

Hill, Y.L., Zhu, H., Ng, N., Ng, L.C., Rocklov, J., 2012. Forecast of dengue incidence using temperature and rainfall. PLoS Negl. Trop. Dis. 6, e1908. http://dx.doi.org/10.1371/journal.pntd.0001908.

Jones, P.D. & Harris, I., University of East Anglia Climatic Research Unit. NCAS British Atmospheric Data Centre, 24th September 2014. (2014) CRU TS3.22: Climatic Research Unit (CRIU) Time-Series (TS) Version 3.22 of High Resolution Gridded Data of Monthly-by-month Variation in Climate [Jan. 1901-Dec. 2013]. [Accessed: 2014-10-02], available from: http://dx.doi.org/10.5065/D6Z980Z3.

Kraemer, M.U., et al., 2015. The global distribution of the arbovirus vectors *Aedes aegypti* and *Ae. albopictus*. Nature 521, 91–94.

La Ruche, G., et al., 2010. First two autochthonous dengue virus infections in metropolitan France, September 2009. Euro Surveill. 15, 19676.

Lambrechts, L., Scott, T.W., Gubler, D.J., 2010. Consequences of the expanding global distribution of *Aedes albopictus* for dengue virus transmission. PLoS Negl. Trop. Dis. 4, e646. http://dx.doi.org/10.1371/journal.pntd.0000646.

Lambrechts, L., et al., 2011. Impact of daily temperature fluctuations on dengue virus transmission by *Aedes albopictus*. PLoS Negl. Trop. Dis. 5, e798. http://dx.doi.org/10.1371/journal.pntd.0002778.

Leder, K., et al., 2013. GeoSentinel surveillance of illness in returned travelers, 2007–2011. Ann. Intern. Med. 158, 456–468. http://dx.doi.org/10.7326/0003-4819-156-5-201303190-00005.

Li-Juhelmerson, J., Stenlund, H., Wilder-Smith, A., Rocklov, J., 2014. Vectorial capacity of *Aedes aegypti*: effects of temperature and implications for global dengue epidemic potential. PLoS One 9, e85783. http://dx.doi.org/10.1371/journal.pone.0085783.
