Assessing Seasonal Risks for the Introduction and Mosquito-borne Spread of Zika Virus in Europe

Joacim Rocklöv [a,*], Mikkel Brandon Quam [a,1], Bertrand Sudre [b,1], Matthew German [c,1], Moritz U.G. Kraemer [d], Oliver Brady [e], Isaac I. Bogoch [f,g], Jing Liu-Helmersson [a], Annelies Wilder-Smith [a,h], Jan C. Semenza [b], Mark Ong [i], Kaja Kaasik Aaslav [b], Kamran Khan [c,f]

[a] Department of Public Health and Clinical Medicine, Epidemiology and Global Health, Umeå University, Sweden
[b] European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
[c] Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, ON, Canada
[d] Spatial Ecology and Epidemiology Group, Department of Zoology, University of Oxford; Oxford, UK
[e] Wellcome Trust Centre for Human Genetics, University of Oxford; Oxford, UK
[f] Department of Medicine, Division of Infectious Diseases, University of Toronto, Toronto, ON, Canada
[g] Divisions of Internal Medicine and Infectious Diseases, University Health Network, Toronto, Canada
[h] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[i] Geomatics Program, University of Waterloo, Waterloo, ON, Canada

ARTICLE INFO

ABSTRACT

The explosive Zika virus epidemic in the Americas is amplifying spread of this emerging pathogen into previously unaffected regions of the world, including Europe (Gulland, 2016), where local populations are immunologically naïve. As summertime approaches in the northern hemisphere, *Aedes* mosquitoes in Europe may find suitable climatic conditions to acquire and subsequently transmit Zika virus from viremic travellers to local populations. While *Aedes albopictus* has proven to be a vector for the transmission of dengue and chikungunya viruses in Europe (Delisle et al., 2015; ECDC, n.d.) there is growing experimental and ecological evidence to suggest that it may also be competent for Zika virus(Chouin-Carneiro et al., 2016; Grard et al., 2014; Li et al., 2012; Wong et al., 2013). Here we analyze and overlay the monthly flows of airline travellers arriving into European cities from Zika affected areas across the Americas, the predicted monthly estimates of the basic reproduction number of Zika virus in areas where *Aedes* mosquito populations reside in Europe (*Aedes aegypti* in Madeira, Portugal and *Ae. albopictus* in continental Europe), and human populations living within areas where mosquito-borne transmission of Zika virus may be possible. We highlight specific geographic areas and timing of risk for Zika virus introduction and possible spread within Europe to inform the efficient use of human disease surveillance, vector surveillance and control, and public education resources.

1. Introduction

On May 17th, 2015, the Program for Monitoring Emerging Diseases (ProMED-mail) published a report confirming locally acquired cases of Zika virus (ZIKV) in several northeastern Brazilian states, marking the first time this virus is known to have spread within the Americas (Promed, 2015). Eight months later, on February 1st, 2016 the World Health Organization declared the ZIKV epidemic in the Americas a Public Health Emergency of International Concern, in part due to an emerging association with congenital birth anomalies such as microcephaly (Calvet et al., 2016; Mlakar et al., 2016; Rodrigues, 2016) and Guillain-Barré syndrome (Cao-Lormeau et al., 2016). After the virus' introduction into Brazil, the epidemic has swiftly spread across Latin America and the Caribbean (Faria et al., 2016; Petersen et al., 2016a). Potential reasons for this rapid spread include the presence of immunologically naïve populations and an abundance of *Aedes* mosquitoes (Kraemer et al., 2015) within a conducive environment.

As the epidemic expands in scale and geographic range, a growing number of travellers are exporting ZIKV to other regions of the world, including Europe, where *Aedes* vectors are known to be present (Maria et al., 2016; Zammarchi et al., 2015; http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx, n.d.). In Europe, *Aedes aegypti* is known to exist on the island of Madeira, Portugal (http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/

* Corresponding author.
  E-mail address: joacim.rocklov@umu.se (J. Rocklöv).
[1] These authors contributed equally to this work.

Pages/VBORNET_maps.aspx, n.d.) and in parts of Georgia and south-western Russia, whereas *Aedes albopictus* is established along much of the Mediterranean coast (http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx, n.d.). While virus importation events could trigger epidemics in distant geographies where competent *Aedes* mosquito vectors exist, this risk has to date, been mitigated by winter temperatures in the northern hemisphere.

Given the growing experimental and ecological evidence to suggest that *Ae. albopictus* may be a competent vector for ZIKV (Chouin-Carneiro et al., 2016; Grard et al., 2014; Li et al., 2012; Wong et al., 2013), health officials must plan for the possibility of locally acquired ZIKV infections in parts of Europe. The imminent arrival of summer in the northern hemisphere, when *Aedes* mosquito populations will peak and viral replication within these vectors will be most efficient, could lead to autochthonous transmission, not unlike the recent localized and transient European epidemics of dengue and chikungunya (Angelini et al., 2007; Wilder-Smith et al., 2014).

To assist public health decision-making, we (i) modeled the risks of ZIKV importation into Europe via airline travellers departing areas in the Americas where ZIKV activity has been confirmed or where suitable conditions exist for its transmission year round (Bogoch et al., 2016), (ii) used a temperature driven vectorial capacity model to quantify the potential for European *Aedes* mosquitoes to support autochthonous transmission of ZIKV, assuming that *Ae. albopictus* is a competent vector, and (iii) quantified the size of populations living in European areas where mosquito-borne transmission of ZIKV may be possible at the height of summer.

2. Materials & Methods

2.1. Overview

We developed a mathematical model that outputs basic reproduction numbers (R_0) for ZIKV transmission with biological anchoring in *Aedes* mosquito vectorial capacity and validation against surveillance data from the current ZIKV outbreak in Latin America and the Caribbean. We applied this vectorial capacity model to estimate R_0 potential for ZIKV in Europe this spring to autumn, while superimposing data on airline travellers arriving from areas in the Americas where ZIKV is active, as well as populations living in areas of Europe where mosquito-borne transmission of ZIKV is possible. Finally we discuss model assumptions and limitations in our approach.

2.2. Model Development

R_0 is used to characterize the epidemic potential of a pathogen. It represents the expected number of new infections generated by one infectious individual within a fully susceptible population. In the context of a mosquito-borne illness, R_0 is a function of vectorial capacity (VC), and the period of viremia in humans (T_h) (Anderson and R, 1991), given mathematically by: $R_0 = VC \times T_h$. Transmission increases when R_0 exceeds 1 (i.e. potential for an epidemic), and diminishes when R_0 is less than 1. VC in turn is a function of vector competence (inherent ability of the vector to transmit a particular pathogen), vector lifespan, and the extrinsic incubation period (Lambrechts et al., 2011). Since *Aedes* mosquitoes are ectotherms, VC is highly dependent upon mean
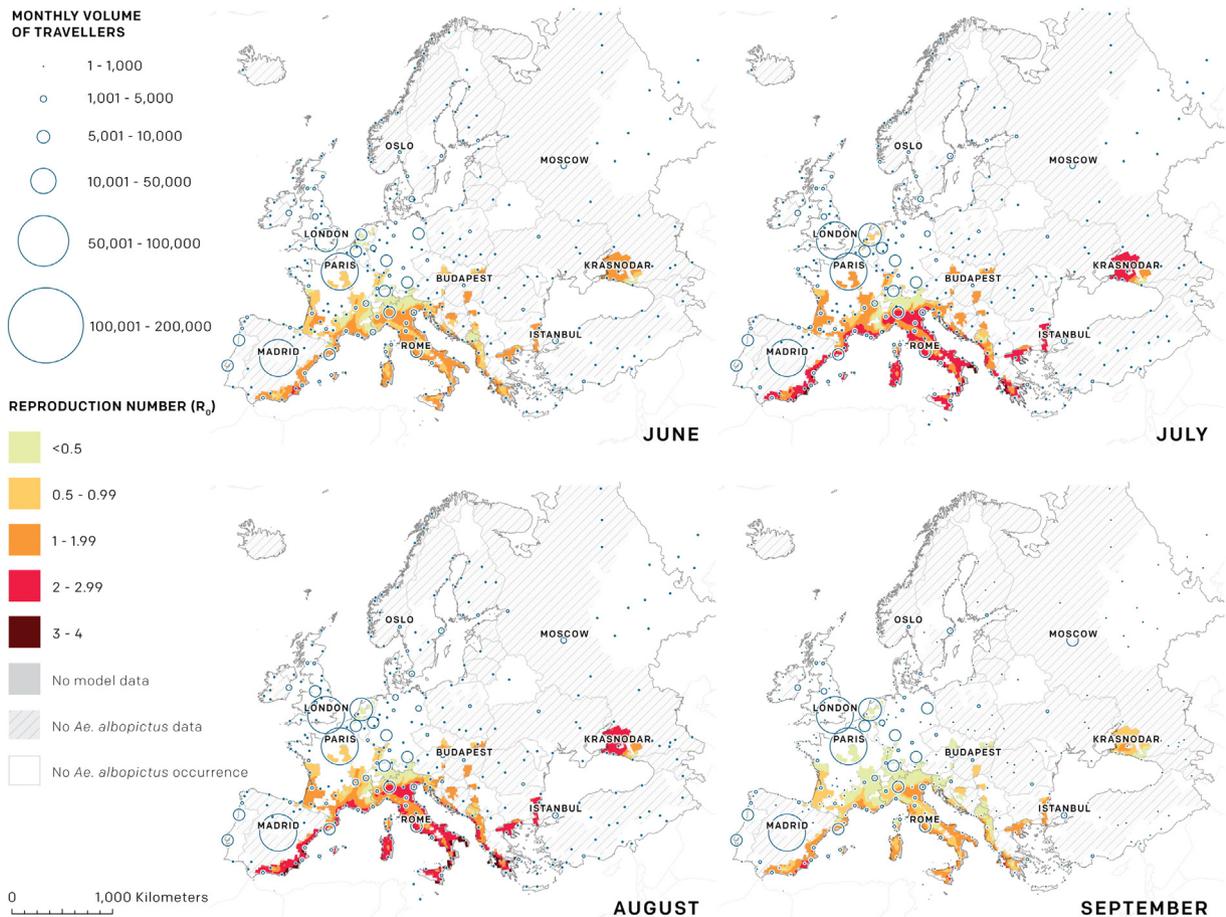

Fig. 1. Monthly stratified maps (June–Sept) of the potential basic reproduction number (R_0) of Zika virus in Europe via *Aedes albopictus* overlaid with monthly estimates of airline travellers arriving from areas with potential for year-round Zika transmission in the Americas.

Table 1

Observed and predicted R_0 for Zika for *Ae. aegypti* (Ae) and *Ae. albopictus* (Aa).

Location	Period	Number of cases	Mean Observed R_0	Mean R_0 predicted		
				Model 1: Ae, Aa	*Model 2: Ae, Aa*	*Model 3: Aa, Ae*
Guadeloupe, French overseas region	29 Jan. to 10 March, 2016	717[b]	2.1	3.7, 3.2	1.0, 0.80	2.0, 1.6
Martinique, French overseas region	21 Dec. to 21 Jan., 2015–2016	102[a]	7.2	4.4, 3.9	1.3, 0.96	2.6, 1.9
Dominican Republic, whole country	30 Jan. to 27 Feb., 2016	573[b]	1.8	3.3, 2.9	1.1, 0.75	2.2, 1.5
Mexico, 1 administrative region	1 Jan. to 13 March, 2016	129[a]	2.1	3.4, 3.0	0.94, 0.79	1.9, 1.6
Guatemala, 8 administrative regions	16 Nov. to 15 Feb., 2015–2016	386[c]	5.0	4.1, 3.6	1.2, 0.96	2.4, 1.93
Panama, 1 administrative region	1 Jan. to 13 March, 2016	49[a]	1.9	2.6, 2.2	0.73, 0.61	1.5, 1.2
Puerto Rico, whole country	26 Nov. to 24 Feb., 2015–2016	198[a]	3.7	4.2, 3.7	1.2, 0.96	2.4, 1.93
El Salvador, 11 administrative regions	1 Jan. to 13 March, 2016	5618[b]	4.8	5.5, 4.8	1.8, 1.2	3.6, 2.4
Colombia, 15 administrative regions	1 Jan. to 13 March, 2016	1593[a]	3.2	3.0, 2.7	1.1, 0.68	2.2, 1.4
Ecuador, 2 administrative regions	1 Jan. to 13 March, 2016	96[b]	7.0	4.4, 3.8	1.2, 0.96	2.4, 1.93
		Total	Mean			
		9461	3.9	3.9, 3.4	1.2, 0.87	2.4, 1.74

[a] Confirmed cases

[b] Suspected cases

[c] Confirmed plus suspected cases

temperature and diurnal temperature variation (Lambrechts et al., 2011; Brady et al., 2014; Liu-Helmersson et al., 2014; Liu-Helmersson et al., 2016). It is given mathematically by(Liu-Helmersson et al., 2016):

$$VC = \frac{ma^2 b_h b_m e^{-\mu_m n}}{\mu_m}$$

The six vector parameters in the above equation include: 1) the average vector biting rate a, 2) the probability of vector-to-human transmission per bite b_h, 3) the probability of human-to-vector infection per bite, b_m, 4) the duration of the extrinsic incubation period (i.e. this represents the duration between acquisition of a pathogen by a vector and the ability for that vector to then transmit the same pathogen to a susceptible host), n, 5) vector mortality rate μ_m, and 6) the female vector-to-human population ratio, m.

Dengue virus (DENV) for example, is also transmitted by *Ae. aegypti* and *Ae. albopictus* mosquitoes, for which the aforementioned parameters and their relationship to temperature has been described (Lambrechts et al., 2011; Brady et al., 2014; Liu-Helmersson et al., 2014; Liu-Helmersson et al., 2016). This has relevance for ZIKV transmission by *Ae. albopictus* and *Ae. aegypti*, as the mortality rate, μ_m, and biting rates, a, for *Aedes* mosquitoes are independent of whether they carry ZIKV or DENV. Further, the competence of *Aedes* mosquito species to transmit ZIKV, as described by n, b_h and b_m, is driven by the infection, dissemination, and transmission rates of the virus in an infected vector, measuring the rate of virus presence in the mosquito midgut after a blood meal, and the time and efficiency of its replication to the mosquito's salivary glands. Recent data suggests that *Aedes* mosquitoes may have the same vectorial competence for ZIKV dissemination and transmission rate as DENV at 29 °C (Chouin-Carneiro et al., 2016; Li et al., 2012; Wong et al., 2013; Lambrechts et al., 2011; Brady et al., 2014; Liu-Helmersson et al., 2014; Liu-Helmersson et al., 2016).

However, geographical differences in vector competence may exist, as *Aedes* mosquitoes from Brazil, the U.S. and Martinique have been reported as being less potent in their ability to replicate ZIKV, while *Aedes* mosquitoes from French Guiana and Guadeloupe appear competent and efficient (Chouin-Carneiro et al., 2016). The extrinsic incubation period of ZIKV (n) is not yet determined, but recent studies estimate it to be 7 days (Chouin-Carneiro et al., 2016; Li et al., 2012; Wong et al., 2013), while n for DENV is estimated to be 8–9 days at 28–29 °C (Liu-Helmersson et al., 2016).

The duration of viremia for ZIKV (T_h) is also currently under investigation however recent evidence suggests that the virus may be detectable in blood for 1 to 10 days (Musso et al., 2015a; Lessler et al., 2016). Similarly, DENV is detected in the blood for 3 to 12 days, with most individuals being viremic for about 5 days (Liu-Helmersson et al., 2016). The serial time window between pairs of infected human cases, encapsulating part of the period of viremia and the extrinsic and intrinsic incubation periods, has been estimated to be 15 days for ZIKV and 17 days for DENV(Majumder et al., 2016) indicating similarities between ZIKV and DENV in real-world settings. For both *Ae. aegypti* and *Ae. albopictus* mosquitoes, the female vector-to-human population ratio (m), is temperature dependent and presumed to be similar across species. In the absence of valid vector abundance data, as an indicator of vector populations, we used a method described in previous studies relating population density to survival (Lambrechts et al., 2011; Brady et al., 2014; Liu-Helmersson et al., 2014; Liu-Helmersson et al., 2016).

We developed three vectorial capacity models for *Aedes* mosquitoes to transmit ZIKV and selected the model that best fit observed transmission dynamics in the Americas. Each model was developed by adapting existing temperature-driven models for DENV transmission via *Ae. aegypti* and *Ae. albopictus* (Liu-Helmersson et al., 2016) while incorporating current data on ZIKV parameters. Our best fitting model was then adapted to Europe using European climatic data to estimate R_0
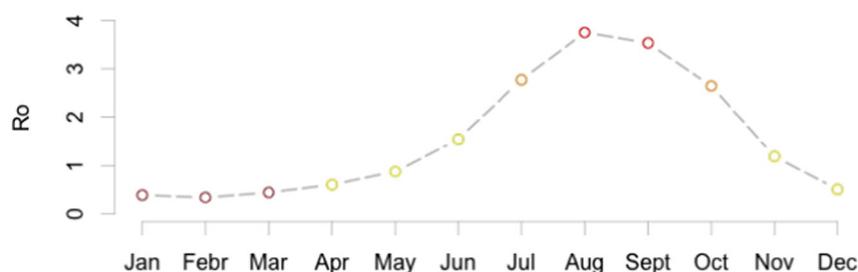

Fig. 2. Potential basic reproduction numbers (R_0) for Zika virus in Madeira, Portugal via *Aedes aegypti*.

potential this spring to autumn. Below we synthesize the findings described above into three alternative models describing the vectorial capacity and basic reproduction number of ZIKV:

- *Model 1*: characterized by high vector competence compared with dengue (Liu-Helmersson et al., 2016) in assuming a viremic period of 5 days.
- *Model 2*: similar to *model 1* with alternations in b_m being reduced to 76.7% and b_h reduced to 21.4% of the *model 1* values for *Ae. aegypti* (Chouin-Carneiro et al., 2016). For *Ae. albopictus*, *model 2* is similar to *model 1* however b_m are reduced to 50.0% of the *model 1* value (Chouin-Carneiro et al., 2016).
- *Model 3*: same configuration as *model 2* but with a viremic period of 10 days (Lessler et al., 2016).

The model 1–3 parameters and their relationship to temperature for both vectors are described in the supplementary information, Figs. 7–12.

2.3. Model Validation

We collected data on the number, location and time of confirmed and suspected ZIKV infections across Latin America and the Caribbean regions up until the end of March 2016 using data from national surveillance systems (see Table 1). Disease data were reported for individual countries or sub-national administrative regions. We also collected temperature measurements from terrestrial meteorological stations and satellite sensors reading land surface temperatures (see Table 3; extended data).

We estimated R_0 values for the initial phases of the epidemic in the Americas assuming a Poisson distribution using weekly count data (*R package version 1.2–5, 2014*; Wallinga, 2007). The serial time interval range of ZIKV infection was taken to be 10 to 23 days, with a mean of 16 days (Majumder et al., 2016). We then used a lognormal serial time distribution function with a mean of 16 days and standard deviation of 3 days covering the interval. Estimates of observed R_0 values were made at the sub-national administrative region level and aggregated to national averages as described in Table 1. We selected smaller countries and regions to better fulfill the assumption of homogeneous mixing in the estimation of R_0.

We tested and validated our three temperature-driven vectorial capacity models by comparing R_0 values generated for countries in Latin America and the Caribbean to R_0 estimates derived from the same region using ZIKV surveillance data (Table 1). We used temperature data from one month prior to and two months into the epidemic (Table 3; extended data). R_0 values were computed assuming that *Ae. aegypti* or *Ae. albopictus* alone were the sole vector for ZIKV transmission.

2.4. Estimating R_0 in Europe

Since *Model 1* best fit observed data on ZIKV transmission in the Americas, we used it to estimate potential for mosquito-borne transmission, outputted as R_0 values, across Europe in 2016. We did this by integrating daily temperature observations (mean, minimum, maximum) from the E-OBS 12.0 dataset at locations gridded at 0.25 × 0.25° (approximately 25 × 25 km at the equator) latitude and longitude (Haylock et al., 2008) for the period between January 1st 2006 to December 31st 2015. Daily R_0 estimates required interpolating diurnal temperature values from daily temperature observations. We estimated R_0 values for Europe for geographic areas where *Ae. aegypti* or *Ae. albopictus* mosquito populations have been reported by the European Centre for Disease Prevention and Control in 2016 (http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx, n.d.). Maps were presented for each

month from May to October after averaging daily R_0 observations. Model outputs were classified into R_0 zones for ease of interpretation (<0.5, 0.5–0.99, 1–1.99, 2–2.99, and 3–4).

2.5. Airline Travellers into Europe from the Americas

To estimate the potential for travellers infected with ZIKV arriving into European cities from the Americas, we analyzed worldwide airline ticket sales data from the International Air Transport Association (IATA). This dataset includes anonymized, full-route, flight itinerary data on an estimated 90% of all passenger trips on commercial flights worldwide, while the remainder is modeled using airline market intelligence. Each flight itinerary includes information on passengers' initial point of embarkation, final destination, and where applicable, connecting flights.

To select commercial airports in the Americas where departing travellers might be infected with ZIKV, we assumed that ZIKV would be active in all countries in the Americas except Canada and Chile by the summer of 2016. Subsequently, we narrowed this list of countries to those that have experienced *significant* transmission of chikungunya virus since the onset of the 2013 outbreak in the Americas (Musso et al., 2015b). In this step, we excluded the United States as it has only experienced limited autochthonous transmission of chikungunya virus in Florida. Conversely, we included Argentina because it is currently experiencing a DENV epidemic (Gil et al., 2016). Within each country in our remaining list, we identified subnational areas with potential for year-round ZIKV transmission by either *Ae. aegypti* or *Ae. albopictus* based upon an ecological suitability analysis (Bogoch et al., 2016). We then created a 50 km buffer zone around these areas to accommodate for the potential movements of individuals travelling by land from areas of ZIKV activity to neighboring commercial airports, where travellers could embark upon international trips. After selecting our final list of commercial airports in the Americas, we quantified and mapped the monthly final European destinations of all travellers departing these airports between May and October 2015.

2.6. Populations at Risk for Locally Acquired Infection

To estimate the size of populations living in areas at risk for mosquito-borne ZIKV transmission, we extracted population data from LandScan 2014, a satellite-based dataset of ambient population density worldwide in 1-km^2 grids (Dobson et al., 2000). To link our vectorial capacity model data with LandScan population density data, our R_0 map (at 25-km^2 resolution) was resampled to 1-km^2 pixels using a nearest-neighbor sampling algorithm. Population estimates were then extracted for each R_0 zone for each country across Europe in the month of August, when vectorial capacity was at its peak.

3. Results

3.1. Travellers Arriving to Europe from the Americas

In continental Europe, the leading final destinations of airline travellers departing areas in the Americas with known ZIKV activity or suitable conditions for year-round autochthonous transmission, from May to October 2015 were i) Paris (~120,000 to 200,000 travellers peaking in July and August), ii) London (~100,000 to 130,000 travellers peaking in August), iii) Madrid (~75,000 to 125,000 travellers peaking in July), iv) Amsterdam (~50,000 to 70,000 travellers peaking in August), v) Frankfurt (~40,000 travellers with no clear peak), vi) Milan (~25,000 to 40,000 travellers peaking in August), vii) Lisbon (~20,000 to 40,000 travellers peaking in July), viii) Barcelona (~25,000 to 35,000 travellers peaking in September and October), and ix) Rome (~20,000 to 35,000 travellers peaking in August; see Fig. 1). Outside of continental Europe, Madeira, Portugal (where *Ae. aegypti* is established) receives ~500 to 2500 monthly travellers with peak flows in July.

3.2. Basic Reproductive Number for Zika virus in Europe

Based on temperature inputs, our vectorial capacity model predicted a basic reproduction number (R_0) of 3.9 (assuming transmission by *Ae. aegypti*), and 3.4 (assuming transmission by *Ae. albopictus*) for the current ZIKV epidemic in the Americas. We compared these R_0 estimates with those derived using ZIKV surveillance data in the Americas and found agreement between our predictions and observations as summarized in Table 1. Adapting our vectorial capacity model to Europe using empirical temperature data from 2006–2015, we estimated R_0 values for *Ae. albopictus* across southern Europe from France and Spain in the west to southwestern Russia in the east (see Fig. 1; higher resolution monthly maps are supplied in the supplementary information, Figs. 1–6). Most of the potential for autochthonous transmission was centered on Italy, southeastern France including the island of Corsica, the southern and eastern coasts of Spain, and western regions of the Balkans from Slovenia and Croatia in the north, to Albania and Greece in the south. While predicted R_0 values begin to exceed 1 (i.e. indicating epidemic potential) across areas of southern Europe in June, they increase in July (R_0 values of 2–3) and peak in August (R_0 values of 3–4) before falling again in September (R_0 values of 1–2) and October (R_0 falls below 1). For the sub-tropical island of Madeira in Portugal, R_0 values for the vector *Ae. aegypti*, were estimated to exceed 2 from July through October (see Fig. 2).

3.3. Populations at Risk in Europe

Of the total population residing within the geographic range of our analysis (i.e. 779 million people), we find that in the month of August (i.e. when temperatures and vectorial capacity in Europe are peaking), approximately 47% of people (i.e. 366 million) reside in areas with no known occurrences of *Ae. albopictus*, 35% (i.e. 272 million) in areas where data on *Aedes* mosquito occurrences are absent, 11% (i.e. 83 million) in areas where R_0 estimates from our model exceed 1, 4% (i.e. 31 million) in areas where R_0 estimates are less than 1 (i.e. low risk for sporadic transmission), and 3% (i.e. 27 million) in areas where our model lacked data to estimate R_0.

Countries with a large proportion of their population residing in areas where our R_0 estimates exceeded 1 in August included: Albania (83%), Croatia (44%), France (20%), Greece (25%), Italy (78%), Montenegro (39%), Slovenia (28%), and Spain (19%). Population sizes in these areas were largest for Italy (45 million people), France (12 million), and Spain (8 million). For Greece and Spain, more than half of their populations resided in areas with either no *Aedes* mosquito surveillance data or no data outputs from our model. The geographic extents of *Ae. albopictus* mosquitoes overlaid with our model's R_0 outputs are shown in Fig. 1, while actual values of populations affected are found in Table 2 (extended data).

4. Discussion

Our analysis indicates that the peak flow of travellers departing areas in the Americas where they might be exposed to ZIKV (and who have final destinations in Europe) coincides with the peak in vectorial capacity for ZIKV transmission in Europe (i.e. in July and August). These intersections in risk are most apparent within or adjacent to several major cities such as Barcelona, Milan and Rome.

Since *Ae. albopictus* mosquitoes might prove to be competent vectors for ZIKV (Chouin-Carneiro et al., 2016; Grard et al., 2014; Li et al., 2012; Wong et al., 2013), the public, healthcare providers and public health officials across Europe could use these findings to identify regions at greatest risk for the importation of ZIKV, and its potential transmission within ecologically suitable areas. Although the volume of travellers arriving from the Americas to Madeira, Portugal is substantially lower compared to other major cities in continental Europe, the known occurrence of *Ae. aegypti*, a longer season with high vectorial capacity, the

explosive epidemic of dengue fever in 2012 (Wilder-Smith et al., 2014), and the recent Zika epidemic in nearby Cape Verde (Attar, 2016), collectively highlight the potential for autochthonous transmission of ZIKV on this sub-tropical island.

Our analysis highlights necessary, but not always sufficient conditions for autochthonous transmission of ZIKV. While the introduction of ZIKV into Europe, the presence of competent mosquito vectors, and suitable climatic conditions are all prerequisites for local mosquito-borne transmission, a multitude of other factors, including but not limited to, population density, housing conditions, and socioeconomic factors, could influence the likelihood of observing ZIKV epidemics, as seen with other arbovirus infections such as dengue (Clark, 2008; Reiter et al., 2003).

Our model is founded on a number of assumptions, most notably that continental European strains of *Ae. albopictus* possess competence for the transmission of ZIKV. While there is growing evidence to suggest that *Ae. albopictus* can become infected with ZIKV under experimental conditions (Chouin-Carneiro et al., 2016; Li et al., 2012), empirical data on its role as a vector in nature exist (Grard et al., 2014), but are limited. Recent evidence from the Americas also suggests that *Ae. aegypti* and *Ae. albopictus* may be less competent vectors than anticipated (Chouin-Carneiro et al., 2016), and that other factors such as population density, immunologically naïve populations, additional modes of transmission (e.g. sexual (Oster et al., 2016; Foy et al., 2011)), and possibly even other mosquito species might play a role in this epidemic (Ayres, 2016). A key strength of our study is that our model's R_0 outputs were comparable to estimates we derived using ZIKV surveillance data from the ongoing epidemic in the Americas. However, we assumed that our model, validated against ZIKV data from the Americas where *Ae. aegypti* is thought to be the primary driver for transmission, would be transferrable to a European setting where *Ae. albopictus* is the dominant vector.

Cities across Europe are already experiencing an increase in ZIKV importations via travellers from the Americas (Maria et al., 2016; Zammarchi et al., 2015). Two recent studies assessed the risk of transmission of ZIKV in Europe reaching contrasting conclusions (Guzzetta et al., 2016; WHO, 2016). One of the studies finds minimal risk based on an assumed low vectorial capacity of European *Ae. albopictus* (Guzzetta et al., 2016), while the other study, aligning climatic suitability of vectors and coarse patterns in air traffic, estimate and identify European countries at high risk for Zika transmission (WHO, 2016). Our study increases output resolution through our transmission model and passenger-level air travel data, while drawing from epidemiological data from the current outbreak in the Americas. We conclude, that while there remains uncertainty about the capacity for *Ae. albopictus* to transmit ZIKV in nature, European health officials must consider the possibility of mosquito-borne transmission within Europe during warmer periods of the year. With the imminent arrival of summer, our findings could help guide the efficient use of finite resources for human disease surveillance, vector surveillance and control, and public education following guidelines from the European Centre for Disease Prevention and Control (European Centre for Disease Prevention and Control, 2016), for vector and non-vector borne modes of ZIKV transmission. Furthermore, our travel analysis can help target efforts to educate the public and healthcare providers alike about the potential for Zika virus transmission via travellers returning from Zika affected areas in the Americas to their sexual partners living in Europe (Oster et al., 2016; Petersen et al., 2016b).

4.1. Assumptions and Limitations

The overall range and average values of the basic reproduction number for ZIKV estimated in our study for Latin America and the Caribbean is supported by several recent studies indicating similarities to dengue (Funk et al., 2016; Kucharski et al., 2016) at least for transmission via *Ae. aegypti*. Data on the competence of *Ae. albopictus* as a vector to

transmit ZIKV in natural settings are limited. While recent experimental studies have indicated that North American *Ae. albopictus* strains may not be highly competent (Chouin-Carneiro et al., 2016), others support a higher vector competence (Li et al., 2012; Wong et al., 2013), including one study where *Ae. albopictus* appears to have been the principal vector in an urban ZIKV outbreak in Gabon (Grard et al., 2014). In this analysis, we assumed that *Ae. albopictus* would be capable of transmitting ZIKV in continental Europe. New experimental results indicate European *Ae. albopictus* mosquitoes may exhibit lower competence to transmit ZIKV (Di Luca et al., 2016; Jupille et al., 2016) contrasting to African (Grard et al., 2014) and Asian (Wong et al., 2013) varieties. However, more evidence is needed to fully understand vector competence in Europe.

We also assumed that DENV and ZIKV have similar temperature dependencies in relation to vector competence. While the similarities between our model's R_0 outputs for ZIKV and R_0 estimates derived from the current ZIKV epidemic in the Americas supports this assumption, we recognize that other factors, related to human behavior, socioeconomic, and environmental factors may create differential vector-to-human contacts rates between Europe and Latin America. These differences could contribute to different transmission dynamics not accounted for in our predictive models. For example, during a recent DENV outbreak along the Texas-Mexico border, non-climatic factors significantly influenced transmission dynamics (Clark, 2008; Reiter et al., 2003). The observed transmission of chikungunya and dengue in Europe, however, support that European vectors and environment are capable of supporting local transmission (Angelini et al., 2007; Wilder-Smith et al., 2014). We further note that vector populations, as measured by ovitraps, indicate high abundance in Europe (Bellini et al., 1996), and further, that human population densities are higher in some European areas compared with areas in Latin America with persistent transmission (http://www.worldpop.org.uk/). In relation to European vector populations it is important to note that the vector surveillance is limited in some European regions, with no reported surveillance data. Thus, our estimates of the geographic range of European areas potential suitable for ZIKV transmission are conservative (Kraemer et al., 2015).

Due to a lack of detailed parameterization data, we did not consider the effects of wind, humidity and precipitation in our model. The impact of precipitation, interacting with human behavior (e.g. storing of water and irrigation), appear unrelated to fluctuations in vector abundance in Thailand (Lambrechts et al., 2011). Tran *et al.* modeled *Ae. albopictus* abundance in Europe and demonstrated that cycles were highly seasonal and related to vector lifespan (Tran et al., 2013). While we were unable to include vector abundance data in our models, we created a proxy for abundance derived from a temperature-dependent mosquito survival function (Brady et al., 2014; Liu-Helmersson et al., 2016). We also note that populations of *Aedes* mosquitoes in the Netherlands have not established outside greenhouses, suggesting that they are tropical strains not adapted to temperate climates.

Although DENV and chikungunya viruses may offer certain insights into the unknowns of ZIKV spread and control (Musso et al., 2015b), differences between ZIKV, DENV and chikungunya vector-virus interactions and transmission routes cannot be ignored (Christofferson, 2016), In addition to mosquito-borne transmission, other modes of spread including via sexual contact (Oster et al., 2016) were not accounted for in this analysis. Current data suggest that ZIKV can be found in semen, and hence could potentially be transmitted for months post-infection (Mansuy et al., 2016).

The 2015 IATA data used in this analysis is the most current available to quantify the flow of travellers from the Americas to Europe across this spring to autumn. Although the ZIKV epidemic may decrease traveller flows to and from affected countries, we assumed that the seasonal patterns and proportions of travellers arriving to various European cities would be preserved relative to 2015. Another consideration not accounted for in our analysis is the potential impact of the Summer Olympic Games in Rio in August on travel patterns between Brazil and Europe. However, the local transmission of Zika during the Olympics might decrease due to seasonal transmission changes (Funk et al., 2016; Kucharski et al., 2016).

Our weather driven models use averaged monthly temperature values over the most recent 10-year period (i.e. 2006–2015). However, 2016 weather patterns may vary under the influence of El Nino this year, which in turn, might increase or decrease vectorial capacity.

Finally, stochasticity plays a key role in the appearance of any epidemic. In this analysis, we present conditions that are necessary, but alone may be insufficient for the emergence of an epidemic. Hence our analysis assesses the potential for ZIKV transmission within Europe, not the probability of ZIKV epidemics. The purpose of this analysis is to highlight geographies and times where epidemic potential is greatest as a way to help guide public health resources to prepare for, and if required, mobilize an appropriate response to mosquito-borne ZIKV transmission in Europe later this year, in accordance with guidelines developed by the European Centre for Disease Prevention and Control (European Centre for Disease Prevention and Control, 2016).

Disclosure Statements

Kamran Khan is the founder of BlueDot, a social benefit corporation that develops public health tools and analytics to help prepare for and respond to global epidemics. Matthew German has been employed by BlueDot and Isaac I. Bogoch has consulted to BlueDot.

Author Contributions

Joacim Rocklöv and Kamran Khan conceived the research idea, made the first analyses and drafted the text. Mikkel Quam helped develop the Zika mathematical models. Bertrand Sudre helped gather the Zika surveillance data and update the manuscript based on literature reviews on Zika epidemiology and entomology. Matthew German conducted the analyses of commercial air travel flows. Moritz Kraemer and Oliver Brady helped to develop the method for the Zika transmission zones in Latin America. Mark Ong produced estimates of populations living in areas at potential risk for autochthonous transmission of Zika virus across Europe. All authors made significant contributions to the editing and critical assessment of the manuscript.

The following are the supplementary data related to this article.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebiom.2016.06.009.

References

Mosquito maps (ECDC-EFSA, 2016 – VECTORNET) available at: http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx <http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx> (

Anderson, R.M., May, R., 1991. Infectious Diseases of Humans: Dynamics and Control. Oxford University Press.

Angelini, R., et al., 2007. Chikungunya in north-eastern Italy: a summing up of the outbreak. Euro Surveill. 12 (E071122 071122).

Attar, N., 2016. ZIKA virus circulates in new regions. Nat. Rev. Microbiol. 14, 62. http://dx.doi.org/10.1038/nrmicro.2015.28.

Ayres, C.F., 2016. Identification of Zika virus vectors and implications for control. Lancet Infect. Dis. 16, 278–279. http://dx.doi.org/10.1016/S1473-3099(16)00073-6.

Bellini, R., Carrieri, M., Burgio, G., Bacchi, M., 1996. Efficacy of different ovitraps and binomial sampling in *Aedes albopictus* surveillance activity. J. Am. Mosq. Control Assoc. 12, 632–636.

Bogoch, I.I., et al., 2016. Anticipating the international spread of Zika virus from Brazil. Lancet 387, 335–336. http://dx.doi.org/10.1016/S0140-6736(16)00080-5.

Brady, O.J., et al., 2014. Global temperature constraints on *Aedes aegypti* and *Ae. albopictus* persistence and competence for dengue virus transmission. Parasit Vectors 7, 338. http://dx.doi.org/10.1186/1756–3305–7-338.

Calvet, G., et al., 2016. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. Lancet Infect. Dis. http://dx.doi.org/10.1016/S1473-3099(16)00095-5.

Cao-Lormeau, V.M., et al., 2016. Guillain-Barre Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet http://dx.doi.org/10.1016/S0140-6736(16)00562-6.

Chouin-Carneiro, T., V.-R., A., Vazeille, M., Yebakima, A., Girod, R., Goindin, R., Dupont-Rouzeyrol, M., Lourenço-de-Oliveira, R., Failloux, A.B., 2016. Differential susceptibilities of *Aedes aegypti* and *Aedes albopictus* from the Americas to Zika virus. PLoS Negl. Trop. Dis. 10, e0004543. http://dx.doi.org/10.1371/journal.pntd.0004543.

Christofferson, R.C., 2016. Zika virus emergence and expansion: lessons learned from dengue and chikungunya may not provide all the answers. Am.J.Trop. Med. Hyg. http://dx.doi.org/10.4269/ajtmh.15-0866.

Clark, G.G., 2008. Dengue and dengue hemorrhagic fever in northern Mexico and south Texas: do they really respect the border? Am.J.Trop. Med. Hyg. 78, 361–362.

Delisle, E., et al., 2015. Chikungunya outbreak in Montpellier, France, September to October 2014. Euro Surveill. 20.

Di Luca, M., et al., 2016. Experimental studies of susceptibility of Italian *Aedes albopictus* to Zika virus. Euro Surveill. 21. http://dx.doi.org/10.2807/1560-7917.ES.2016.21.18.30223.

Dobson, J.E., Bright, E.A., Coleman, P.R., Durfee, R.C., Worley, B.A., 2000. LandScan: a global population database for estimating populations at risk. Photogramm. Eng. Remote. Sens. 66, 9.

ECDC. *Aedes albopictus*, <http://ecdc.europa.eu/en/healthtopics/vectors/mosquitoes/Pages/aedes-albopictus.aspx> (

European Centre for Disease Prevention and Control, 2016. Zika virus disease epidemic: preparedness planning guide for diseases transmitted by *Aedes aegypti* and *Aedes albopictus*. ECDC, Stockholm (2016).

Faria, N.R., et al., 2016. Zika virus in the Americas: early epidemiological and genetic findings. Science http://dx.doi.org/10.1126/science.aaf5036.

Foy, B.D., et al., 2011. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg. Infect. Dis. 17, 880–882. http://dx.doi.org/10.3201/eid1705.101939.

Funk, S., K. A. J., Camacho, A., Eggo, R.M., Yakob, L., Edmunds, W.J., 2016. Comparative analysis of dengue and Zika outbreaks reveals differences by setting and virus. bioRxiv http://dx.doi.org/10.1101/043265.

Gil, J.F., et al., 2016. Spatial spread of dengue in a non-endemic tropical city in northern Argentina. Acta Trop. 158, 24–31. http://dx.doi.org/10.1016/j.actatropica.2016.02.003.

Grard, G., Caron, M., Mombo, I.M., Nkoghe, D., Ondo, S.M., Jiolle, D., Fonenille, D., Paupy, C., Leroy, E.M., 2014. Zika virus in Gabon (central Africa) — 2007: a new threat from *Aedes albopictus*? PLoS Negl. Trop. Dis. 8.

Gulland, A., 2016. WHO warns European countries to be on alert for Zika. BMJ 352, i753. http://dx.doi.org/10.1136/bmj.i753.

Guzzetta, G., et al., 2016. Assessing the potential risk of Zika virus epidemics in temperate areas with established *Aedes albopictus* populations. Euro Surveill. 21. http://dx.doi.org/10.2807/1560–7917.ES.2016.21.15.30199.

Haylock, M.R., Hofstra, N., Klein Tank, A.M.G., Klok, E.J., Jones, P.D., New, M., 2008. A European daily high-resolution gridded dataset of surface temperature and precipitation. J. Geophys. Res. Atmos. 113. http://dx.doi.org/10.1029/2008JD10201.

Jupille, H., Seixas, G., Mousson, L., Sousa, C., Failloux, A.B., 2016. Zika virus, a new threat for Europe? bioRxiv http://dx.doi.org/10.1101/048454.

Kraemer, M.U., et al., 2015. The global distribution of the arbovirus vectors *Aedes aegypti* and *Ae. albopictus*. Elife 4, e08347. http://dx.doi.org/10.7554/eLife.08347.

Kucharski, A.J., et al., 2016. Transmission dynamics of zika virus in island populations: a modelling analysis of the 2013–14 French Polynesia outbreak. PLoS Negl. Trop. Dis. 10, e0004726. http://dx.doi.org/10.1371/journal.pntd.0004726.

Lambrechts, L., et al., 2011. Impact of daily temperature fluctuations on dengue virus transmission by *Aedes aegypti*. Proc. Natl. Acad. Sci. U. S. A. 108, 7460–7465. http://dx.doi.org/10.1073/pnas.1101377108.

Lessler, J.T., O.C.T., Carcelen, A.C., Konikoff, J.M., Williamson, J., Bi, Q., Kurcika, L.M., Cummings, D.A.T., Reich, N., Chaisson, L.H., 2016. Times to key events in the course of Zika infection and their implications: a systematic review and pooled analysis. Bull. World Health Organ. http://dx.doi.org/10.2471/BLT.16.174540.

Li, M.I., Wong, P.S., Ng, L.C., Tan, C.H., 2012. Oral susceptibility of Singapore *Aedes* (Stegomyia) *aegypti* (Linnaeus) to Zika virus. PLoS Negl. Trop. Dis. 6, e1792. http://dx.doi.org/10.1371/journal.pntd.0001792.

Liu-Helmersson, J., Quam, M., Wilder-Smith, A., Stenlund, H., Ebi, K., Massad, E., Rocklöv, J., 2016. Climate change and aedes vectors: 21st century projections for dengue transmission in Europe. eBioMedicine.

Liu-Helmersson, 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, e89783. http://dx.doi.org/10.1371/journal.pone.0089783.

Majumder, M.S., Cohn, E., Fish, D., Brownstein, J.S., 2016. Estimating a feasible serial interval range for Zika fever [submitted]. Bull. World Health Organ. http://dx.doi.org/10.2471/BLT.16.171009.

Mansuy, J.M., et al., 2016. Zika virus: high infectious viral load in semen, a new sexually transmitted pathogen? Lancet Infect. Dis. 16, 405. http://dx.doi.org/10.1016/S1473-3099(16)00138-9.

Maria, A.T., et al., 2016. Zika virus infections in three travellers returning from South America and the Caribbean respectively, to Montpellier, France, December 2015 to January 2016. Euro Surveill. 21. http://dx.doi.org/10.2807/1560-7917.ES.2016.21.6.30131.

Mlakar, J., et al., 2016. Zika virus associated with microcephaly. N. Engl. J. Med. 374, 951–958. http://dx.doi.org/10.1056/NEJMoa1600651.

Musso, D., Cao-Lormeau, V.M., Gubler, D.J., 2015b. Zika virus: following the path of dengue and chikungunya? Lancet 386, 243–244. http://dx.doi.org/10.1016/S0140-6736(15)61273-9.

Musso, D., et al., 2015a. Detection of Zika virus in saliva. J. Clin. Virol. 68, 53–55. http://dx.doi.org/10.1016/j.jcv.2015.04.021.

Oster, A.M., et al., 2016. Update: interim guidance for prevention of sexual transmission of Zika virus — United States, 2016. MMWR Morb. Mortal. Wkly Rep. 65, 323–325. http://dx.doi.org/10.15585/mmwr.mm6512e3.

Petersen, E.E., et al., 2016b. Update: interim guidance for health care providers caring for women of reproductive age with possible zika virus exposure — United States, 2016. MMWR Morb. Mortal. Wkly Rep. 65, 315–322. http://dx.doi.org/10.15585/mmwr.mm6512e2.

Petersen, L.R., Jamieson, D.J., Powers, A.M., Honein, M.A., 2016a. Zika virus. N. Engl. J. Med. http://dx.doi.org/10.1056/NEJMra1602113.

Promed, 2015. ZIKA virus - BRAZIL: confirmed. http://www.promedmail.org/post/3370768.

R₀: estimation of R_0 and real-time reproduction number from epidemics. R Package Version 1.2–5 (R).

Reiter, P., et al., 2003. Texas lifestyle limits transmission of dengue virus. Emerg. Infect. Dis. 9, 86–89. http://dx.doi.org/10.3201/eid0901.020220.

Rodrigues, L.C., 2016. Microcephaly and zika virus infection. Lancet http://dx.doi.org/10.1016/S0140-6736(16)00742-X.

Tran, A., et al., 2013. A rainfall- and temperature-driven abundance model for *Aedes albopictus* populations. Int. J. Environ. Res. Public Health 10, 1698–1719. http://dx.doi.org/10.3390/ijerph10051698.

Wallinga, J.L.M., 2007. How generation intervals shape the relationship between growth rates and reproductive numbers. Proc. R. Soc. B Biol. Sci. 274.

WHO, 2016. Zika virus technical report. Interim risk assessment for WHO European region. http://www.euro.who.int/en/health-topics/emergencies/zika-virus/technical-reports-and-guidelines-on-zika-virus/zika-virus-technical-report.-interim-risk-assessment-for-who-european-region.

Wilder-Smith, A., et al., 2014. The 2012 dengue outbreak in Madeira: exploring the origins. Euro Surveill. 19, 20718.

Wong, P.S., Li, M.Z., Chong, C.S., Ng, L.C., Tan, C.H., 2013. Aedes (Stegomyia) albopictus (Skuse): a potential vector of Zika virus in Singapore. PLoS Negl. Trop. Dis. 7, e2348. http://dx.doi.org/10.1371/journal.pntd.0002348.

Zammarchi, L., et al., 2015. Zika virus infections imported to Italy: clinical, immunological and virological findings, and public health implications. J. Clin. Virol. 63, 32–35. http://dx.doi.org/10.1016/j.jcv.2014.12.005.