Assessing the potential risk of Zika virus epidemics in temperate areas with established *Aedes albopictus* populations

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Based on 2015 abundance of *Aedes albopictus* in nine northern Italian municipalities with temperate continental/oceanic climate, we estimated the basic reproductive number R_0 for Zika virus (ZIKV) to be systematically below the epidemic threshold in most scenarios. Results were sensitive to the value of the probability of mosquito infection after biting a viraemic host. Therefore, further studies are required to improve models and predictions, namely evaluating vector competence and potential non-vector transmissions.

In 2015, the largest recorded epidemic of Zika virus (ZIKV) started in Brazil and has since then expanded progressively to most countries in Central and South America [1]. We provide estimates of the basic reproduction number (R_0) of ZIKV in northern Italy, based on estimates of the mosquito abundance from entomological surveillance data.

Entomological surveillance in northern Italy

Mosquito monitoring was carried out fortnightly from May to October 2015 in the provinces of Belluno and Trento, Italy (Figure 1).

Aedes albopictus mosquitoes were collected using 54 Biogents Sentinel traps (Biogents AG, Regensburg, Germany, hereafter abbreviated as BG) baited with BG lures and CO_2 from dry ice, running for 24 hours and placed by entomologists at selected locations in nine municipalities (Figure 1) at altitudes ranging from 74 m a.s.l. to 650 m a.s.l and geographical coordinates between 10°49'04.9"E and 12°12'54.2"E longitude and 45°53'26.9"N and 46°09'59.4"N latitude. Temperatures at trap locations were obtained from land surface temperature satellite data with a resolution of 250 m [2] (Figure 2).

Mosquito population dynamics

We developed a population model representing the developmental cycle of mosquitoes by means of temperature-dependent parameters (Figure 3) and fitted it to capture data in order to estimate the density of female adult mosquitoes per hectare over time at each municipality. For two towns (Belluno and Feltre), human landing captures were carried out (seven and five sessions, respectively) where BG traps were positioned. Two experts performed the catches, rotating between the two sites, acting as human baits and collectors. The mosquitoes were collected by a handheld aspirator during the three hours preceding sunset. Human landing data were used for independent validation of the local mosquito abundance predicted by the model.

The four main stages of the *Aedes albopictus* life cycle (eggs, larvae, pupae and adults) are modelled. Biological parameters encoding mortalities, developmental rates and the length of the gonotrophic cycle depend on the average daily temperature recorded at the site of capture, according to equations provided in [6] and based on experimental data [20]. The site-specific density-dependent factors and the capture rate (common to all sites) are free model parameters estimated by fitting model outputs to experimental capture data.

Given the model-predicted daily number of mosquitoes N_V and the number of bites per mosquito per day k, the following relation should hold:

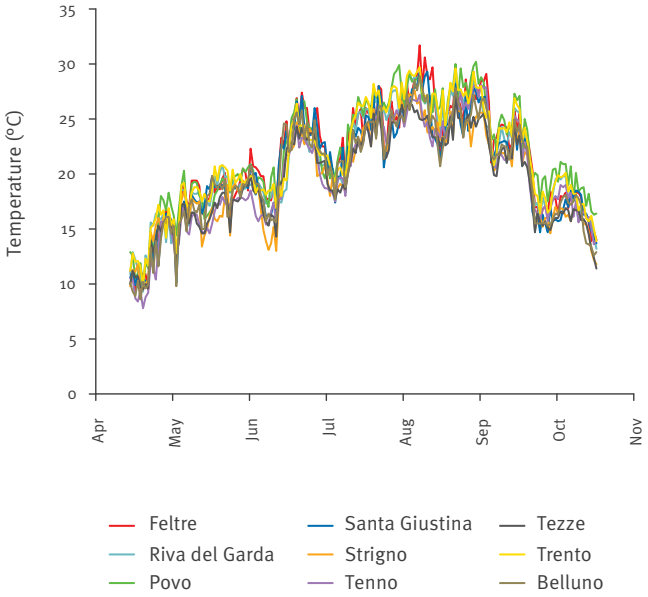
$$k\, N_V = HLR\, T,$$

Figure 1

Location of the study area (inset) and mosquito traps (red points) within the study area, Italy, 2015

Figure 2

Average temperatures recorded in the nine municipalities with mosquito traps, Italy, May–October 2015



where HLR is the hourly human landing rate estimated from data and *T* is the average duration of biting activity during a day (set to 12 hours, based on several studies on daily landing patterns, e.g. [3]).

Figure 4 shows a comparison between observed trapping captures and corresponding model estimates over time for all nine sites considered. Values of the coefficient of determination R^2, ranged between 0.47 and 0.87, depending on the site (average across sites: 0.71). Model-predicted hourly HLR (i.e. $k \times N_V / T$) were in good agreement with the observed HLR during 2015 (Figure 5; $R^2 = 0.57$), thereby validating the use of model-predicted mosquito densities.

Basic reproduction number of Zika virus

We assumed that the only route of transmission for ZIKV is via mosquito bites. R_0 can be calculated from densities of human and mosquito populations and several epidemiological parameters according to the following Formula [4]:

$$R_0 = k^2 p_V p_H g \frac{l_V}{m_V (l_V + m_V)} \frac{V}{H}.$$

Symbols, interpretations, values and literature references are reported in the Table.

When $R_0 < 1$ (epidemic threshold), the probability of observing sustained transmission of ZIKV after importation of a case is negligible. When $R_0 > 1$, the outbreak probability is given by the following Formula [5]:

$$p_0 = 1 - \frac{R_{VH} + 1}{R_{VH}(R_{HV} + 1)},$$

where $R_{VH} = k p_V g \frac{l_V}{l_V + m_V} \frac{V}{H}$

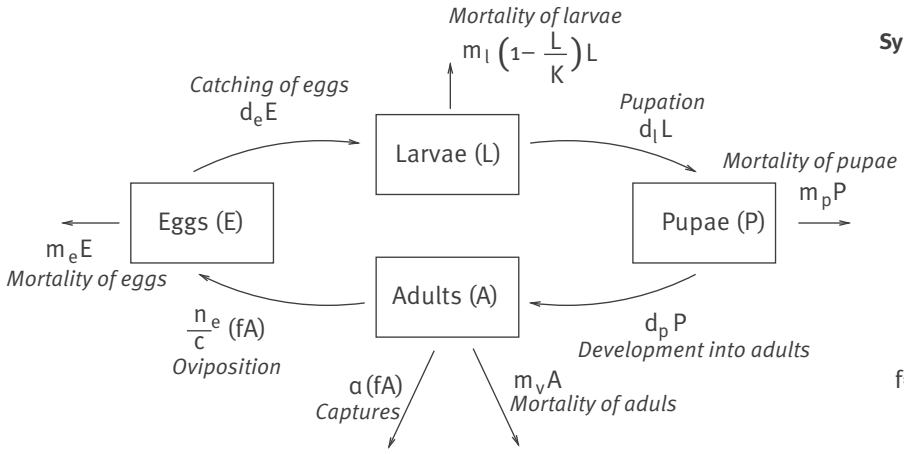
and $R_{HV} = k \frac{p_H}{m_V}$.

Using baseline parameter values (Table), the expected value of R_0 stayed far below the epidemic threshold of 1 at all sites and times in our simulations (Figure 6A), resulting in a low risk of autochthonous transmission of ZIKV.

We re-computed the values of R_0 under a range of worst-case scenarios for parameter values and model assumptions. In all scenarios, all epidemiological parameters but one were fixed at their baseline values and sensitivity was assessed against variations of the selected parameter. Firstly, we set the mosquito biting rate (k) to the largest estimate for the 2007 Italian chikungunya virus outbreak ($k = 0.16$ days^{-1} [6]). In this scenario, the peak value of R_0 never exceeded 0.8. Secondly, we assumed daily temperatures in the upcoming mosquito season to be 2 °C higher than those recorded in 2015 (an extreme scenario in climatological terms) under baseline parameter values. This resulted in an increase of the peak mosquito abundance of 17% to 95%, depending on the town; however, even in this case, R_0 remained far from the epidemic threshold (peak values below 0.4 at all sites). Thirdly, R_0 remained below 1 even when considering 100% human susceptibility to infection given a bite from an infected mosquito (p_H) [7,8].

Figure 3

Model for mosquito population dynamics



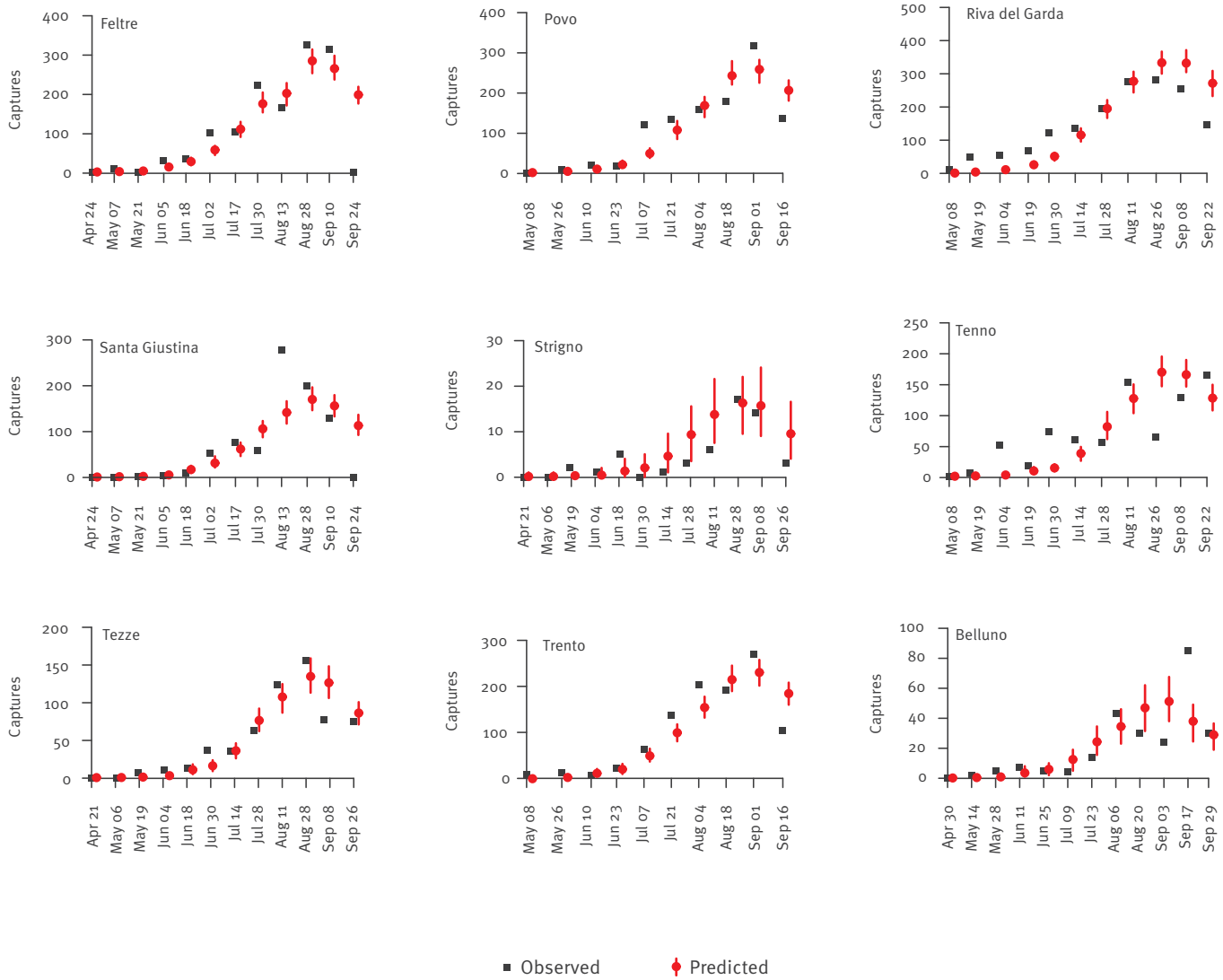
Symbol Description

n_e	*Number of eggs laid per oviposition*
c	*Duration of gonotrophic cycle*
d_e	*Developmental rate from eggs to pupae*
d_p	*Developmental rate from pupae to larvae*
d_l	*Developmental rate from larvae to adults*
m_e	*Mortality rate of eggs*
m_l	*Mortality rate of larvae*
m_p	*Mortality rate of pupae*
m_v	*Mortality rate of adults*
K	*Site-specific density-dependent factor*
α	Capture rate
$f=1/2$	*Proportion of female adults*

The four main stages of the Aedes albopictus life cycle (eggs, larvae, pupae and adults) are modelled. Biological parameters encoding mortalities, developmental rates and the length of the gonotrophic cycle depend on the average daily temperature recorded at the site of capture, according to equations provided in [6] and based on experimental data [20]. The site-specific density-dependent factors and the capture rate (common to all sites) are free model parameters estimated by fitting model outputs to experimental capture data.

Figure 4

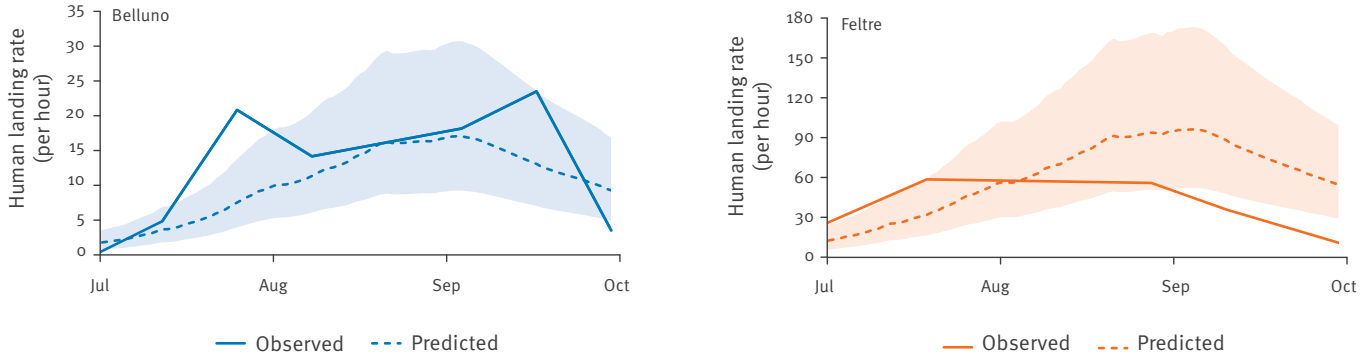
Comparison between observed and predicted numbers of mosquitoes captured over time at all sites, Italy, 2015



Model predictions shown as average and 95% confidence intervals over 10,000 stochastic simulations

Figure 5

Comparison between observed and predicted hourly human landing rate for the two sites where data were available, Italy, 2015



Shaded areas represent the uncertainty of the value for the biting rate *k*.

Table

Parameter values used in the model

	Parameter description	Unit	Baseline	Range	Reference
k	Number of bites to humans per mosquito per day	$Days^{-1}$	0.09	0.05–0.16	[6]
p_V	Vector susceptibility to infections: probability of transmission per bite from infectious hosts to susceptible mosquitoes	%	6.65	0.8–100	[7,8]
p_H	Human susceptibility to infections: probability of transmission per bite from infectious mosquitoes to susceptible hosts	%	50	1–100	[7,8]
g	Average infectious period in humans	Days	5.8	4–7	[18]
$1/l_V$	Average extrinsic incubation period in mosquitoes	Days	10.5	7–14	[7,19]
m_V	Temperature dependent (in the range 10–30 °C) average mosquito mortality rate	$Days^{-1}$	0.031	0.031–0.032	[6,20]
H	Urban population density of humans	Ha^{-1}	Town-specific	39.4–88	[21]
V	Female adult mosquito density	Ha^{-1}	Town-specific time-dependent	8–508 (peak value)	This study

Finally, we considered the variability of R_0 with respect to the probability of a mosquito being infected upon biting of a viraemic human host, p_V. The very low baseline value (6.7%) was suggested by a recent experimental study [7], but previous work had estimated a value of 100% [8]. Resulting predictions were very sensitive to the value of this parameter. When we used the value provided by the latter study ($p_V = 100\%$), the peak value of R_0 exceeded the epidemic threshold in seven of nine towns, with values as high as 3.8 in the highly mosquito-infested towns of Feltre and Riva del Garda (Figure 6B). In Strigno and Belluno, R_0 remained systematically below the epidemic threshold because of the low ratio of mosquitoes per human (V/H in equations above). In all other towns, the minimum value of p_V required to have R_0 above 1 ranged from 25% to 50%.

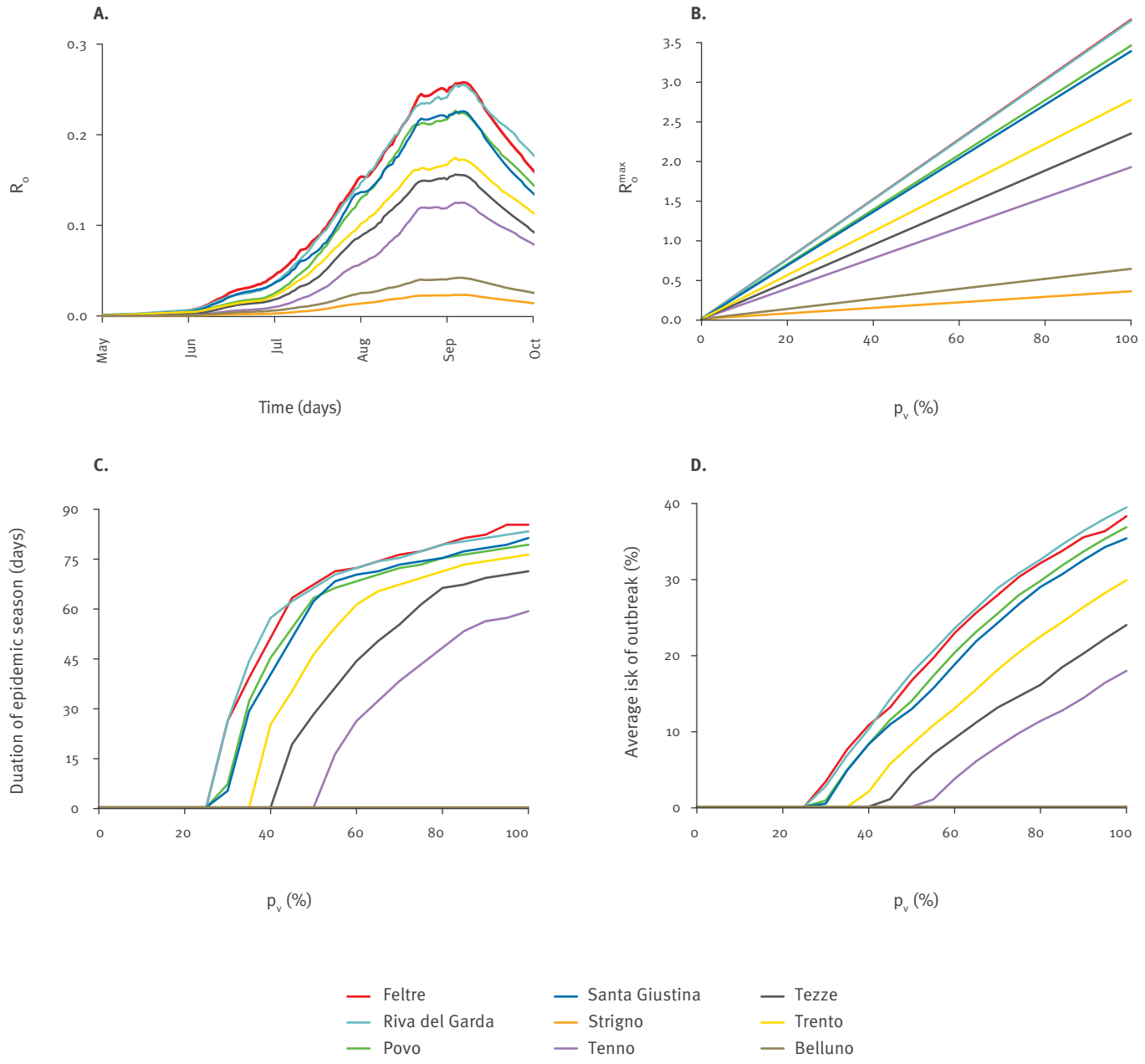
We call epidemic season the time of the year when the local mosquito abundance is sufficiently high for R_0 to exceed the epidemic threshold. According to model estimates, the epidemic season in the worst-case scenario of $p_V = 100\%$ was predicted to last between two and three months in the seven towns at higher risk (Figure 6C). In this scenario, for every ZIKV case imported within the epidemic season, the average probability of observing an outbreak of local transmission ranged from 18% in Tenno to 39% in Feltre and Riva del Garda (Figure 6D).

Discussion

Although ZIKV infection in humans is generally asymptomatic or very mild, there is growing evidence of association with Guillain–Barré' syndrome [9] and congenital neuronal defects in newborns [10,11]. The flow of international travellers to and from Latin America raises potential concerns for the occurrence of outbreaks also in Europe during the summer months when the mosquito activity is higher [12]. The Latin-American epidemic is likely to be driven by *Ae. aegypti*, a mosquito species that is currently present in Europe only in Madeira (Portugal) and around the Black Sea [13]. However, in many European countries *Ae. albopictus* is now endemic [13]. This species has been demonstrated to transmit ZIKV both in the laboratory [7,8] and in the

Figure 6

Estimated temporal changes of R0, using baseline parameter values (A) and sensitivity of model predictions with respect to all possible values of the mosquito probability of infection (B-D), Italy, 2015



B: Maximum value of Ro during the year. C: Duration of the epidemic season, defined as the time interval of the year when Ro>1. D: Average risk of outbreaks per imported case over the epidemic season.

wild [14], although its estimated transmission efficiency is much lower than measured for *Ae. aegypti* [7]. Based on data-driven estimates of the abundance of *Ae. albopictus* mosquitoes in nine municipalities of northern Italy, we expect a low risk of autochthonous mosquito-borne transmission of ZIKV. In addition, it must be considered that there is not yet sufficient evidence of the real vector competence of *Ae. albopictus* in the wild for the circulating strain. Indeed, there have not been any documented ZIKV outbreaks in Europe in the last decades, despite the repeated introductions of the virus by viraemic travellers. Our findings may be applicable to other areas of Europe with temperate climate [15] and with established *Ae. albopictus* populations [13], such as eastern France, central Europe and the Balkan states. Our predictions do not apply to Mediterranean areas where the risk may be substantially higher because climate conditions for *Ae. albopictus* are more favourable.

The most important source of variability in our results was the value for the mosquitoes' susceptibility to infection. Two studies on vector competence provide tentative estimates: one where *Ae. albopictus* mosquitoes from a humid subtropical climate (Central Florida, United States) were infected with the Asian

ZIKV genotype involved in the large South American outbreak [7], and one using *Ae. albopictus* from a tropical rainforest climate (Singapore) infected with an Ugandan ZIKV genotype [8]. We chose the first study as a baseline, because the viral strain used in the experimental setting was more relevant for the ongoing epidemic, and the second study to set the worst-case scenario ($p_V = 100\%$).

Additional sources of uncertainty come from sexual transmission of ZIKV [16]; much higher viral loads have been found in semen than in blood [17]; however, the relative contribution of non-vector transmission is currently not quantified. To improve models and predictions, further studies are required that evaluate the vector competence and capacity of European populations of *Ae. albopictus* for the circulating strain of ZIKV and the potentially related contributions of non-vector transmission.

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Conflict of interest

None declared.

Authors' contributions

GG, PP, AR, RR, GC and SM conceived of the study. FM and FB supervised field work. GG and PP performed the analysis. All authors contributed to interpret results. GG drafted the first version of the manuscript. All authors read and approved the final version of the manuscript.

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