

1 Impact of age-specific immunity on the timing and burden of  
2 the next Zika virus outbreak

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8 **Abstract**

9 The 2015–2017 epidemics of Zika virus (ZIKV) in the Americas caused widespread protective  
10 immunity. The timing and burden of the next Zika virus outbreak remains unclear. We used an  
11 agent-based model to simulate the dynamics of age-specific immunity to ZIKV, and predict the  
12 future age-specific risk using data from Managua, Nicaragua. We also investigated the potential  
13 impact of a ZIKV vaccine. Assuming lifelong immunity, the risk of a ZIKV outbreak will remain  
14 low until 2035 and rise above 50% in 2047. The imbalance in age-specific immunity implies that  
15 people in the 15–29 age range will be at highest risk of infection during the next ZIKV outbreak,  
16 increasing the expected number of congenital abnormalities. ZIKV vaccine development and  
17 licensure are urgent to attain the maximum benefit in reducing the population-level risk of  
18 infection and the risk of adverse congenital outcomes. This urgency increases if immunity is not  
19 lifelong.

20 **1 Introduction**

21 Zika virus (ZIKV) is a flavivirus, which is transmitted primarily by mosquitoes of the genus *Aedes*.  
22 Before 2007, circulation of the virus only occurred sporadically in African and Asian countries  
23 (Wikan and Smith, 2016; Kohl and Gatherer, 2015). Between 2007 and 2013, ZIKV caused large-  
24 scale epidemics in the populations of Micronesia (Duffy et al., 2009), French Polynesia (Cao-Lormeau  
25 et al., 2014) and other Pacific islands (Wikan and Smith, 2016). ZIKV probably became established  
26 in *Aedes aegypti* mosquitoes in the Americas between 2013–2014, (Faria et al., 2016; Zhang et al.,  
27 2017) and then spread rapidly across the continent. In 2015, doctors in Brazil started reporting  
28 clusters of infants born with microcephaly, a severe congenital abnormality, and of adults with  
29 Guillain-Barré syndrome, a paralyzing neurological condition, resulting in the declaration by the  
30 World Health Organization (WHO) of a Public Health Emergency of International Concern (PHEIC)  
31 (World Health Organization, 2016). WHO stated, in September 2016, that ZIKV in pregnancy was  
32 the most likely cause of the clusters of microcephaly, and other adverse congenital outcomes (Krauer  
33 et al., 2017; Counotte et al., 2018). The risk of an affected pregnancy appears highest during the first  
34 trimester, with estimates between 1.0 and 4.5% (Cauchemez et al., 2016; Johansson et al., 2016).  
35 By the beginning of 2018, over 220,000 confirmed cases of ZIKV infection had been reported from  
36 Latin America and the Caribbean (PAHO, 2019), which is estimated to be only 1.02% ( $\pm 0.93\%$ ) of  
37 the total number of cases, based on mathematical modelling studies (Zhang et al., 2017).

38 Protective immunity conferred by infection, combined with high attack rates and herd immunity,  
39 can explain the ending of epidemics and the lack of early recurrence (Dietz, 1975), as has been seen

40 with ZIKV (Ferguson et al., 2016). The duration of protective immunity induced by ZIKV infection  
41 remains uncertain, since immunity to ZIKV infection was not studied extensively before the 2013  
42 outbreaks. Evidence from seroprevalence studies in French Polynesia and Fiji found that levels of  
43 ZIKV neutralizing antibodies decrease with time (Henderson et al., 2019). If the fall in antibody  
44 levels means that people become susceptible to infection again, population level ZIKV immunity  
45 might be declining already. Even if protective immunity is lifelong, the risk of a new ZIKV outbreak  
46 will rise as susceptible newborns replace older individuals, lowering the overall proportion of the  
47 population that is immune. A modelling study, based on data from the 2013 epidemic in French  
48 Polynesia, estimated that ZIKV outbreaks are unlikely to occur for 12 to 20 years, assuming lifelong  
49 immunity (Kucharski et al., 2016).

50 A direct consequence of population renewal will be an unequal distribution of immunity by age  
51 group, with younger age groups at higher risk from a new epidemic than older people (Ferguson  
52 et al., 2016). That effect will be amplified if ZIKV attack rates are lower in children than adults.  
53 Assessing the risk of ZIKV infection in women of reproductive age is essential because ZIKV infection  
54 in pregnancy, leading to adverse congenital outcomes, has such important implications for individuals,  
55 for public health and for investment in surveillance and mitigation strategies, including vector  
56 control, early warning systems, and vaccines (Abbink et al., 2018; World Health Organization, 2018).  
57 However, currently no vaccine is available against ZIKV. Phase I clinical trials of ZIKV candidate  
58 vaccines have shown levels of neutralizing antibody titers that were considered protective against  
59 reinfection (Gaudinski et al., 2018; Modjarrad et al., 2018). Some vaccines have already entered  
60 phase II trials (National Institute of Allergy and Infectious Diseases, 2018), but some companies  
61 have stopped vaccine development (Cohen, 2018).

62 Researchers in Managua, Nicaragua were the first to report the age-stratified seroprevalence  
63 of ZIKV antibodies in population-based surveys (Zambrana et al., 2018). The first cases of au-  
64 tochthonous ZIKV infection in Nicaragua were reported in January, 2016, and an epidemic was  
65 observed between July and December of that year. Through case-based surveillance, the public  
66 health authorities of Nicaragua reported a total of 2,795 people with ZIKV detected by reverse tran-  
67 scriptase (RT) PCR over this period (PAHO, 2019). The number of symptomatic infections is likely  
68 much higher, owing to under-reporting. Furthermore, ZIKV infection is asymptomatic in 33 to 87%  
69 of cases [23], which are generally not identified by surveillance systems. Shortly after the end of the  
70 2016 epidemic, Zambrana et al. analyzed sera from two large population-based surveys in Managua  
71 to measure the prevalence of IgG antibodies against ZIKV in 2- to 14-year olds (N=3,740) and 15-  
72 to 80-year olds (N=2,147) (Zambrana et al., 2018). The authors reported ZIKV seroprevalence of  
73 36.1% (95% confidence interval, CI: 34.5; 37.8%) among the 2-14 year age group and 56.4% (95% CI:  
74 53.1; 59.6%) among the 15-80 year age group (Zambrana et al., 2018; Balmaseda et al., 2017). The  
75 observed post-outbreak seroprevalence in adults is in line with findings from seroprevalence studies  
76 from French Polynesia, Brazil, and Bolivia (Aubry et al., 2017; Netto et al., 2017; Saba Villarroel  
77 et al., 2018).

78 In this study, we used data from the 2016 ZIKV epidemic in Managua and developed an agent-  
79 based model (ABM) to predict the evolution of age-specific protective immunity to ZIKV infection  
80 in the population of Managua, Nicaragua during the period 2017–2097. We assessed: 1) the risk of  
81 a future ZIKV outbreak; 2) the consequences of a future ZIKV outbreak on women of reproductive  
82 age; 3) the influence of loss of immunity on future attack rates; and 4) how vaccination could prevent  
83 future ZIKV outbreaks.

## 84 2 Methods

### 85 2.1 Modelling strategy

86 We assessed the consequences of future outbreaks of ZIKV infection in Managua, Nicaragua using  
87 a stochastic ABM. The model follows a basic susceptible-infected-recovered (SIR) framework and

Table 1: Parametrization of the agent-based model. <sup>a</sup>age-dependent parameters; <sup>b</sup>the different scenarios are discussed in the text in detail under the headings corresponding to the headings of this table.

Parameter	Comment	Source
<b>ZIKV epidemic parameters</b>		
Transmission rate <sup>a</sup>	Inferred from the 2016 epidemic	Zambrana et al. (2018)
Recovery rate	Inferred from the 2016 epidemic	Zambrana et al. (2018)
<b>ZIKV immunity</b>		
Initial immunity <sup>a</sup>	Inferred from the 2016 epidemic	Zambrana et al. (2018)
Duration of immunity	Lifelong or decaying with time	5 scenarios <sup>b</sup>
<b>Demography</b>		
Initial age distribution	–	World Bank (2019a)
Birth rate	–	World Bank (2019a)
Death rate <sup>a</sup>	–	World Health Organization (2019)
Ageing	Linear ageing at each time-step	–
<b>ZIKV reintroduction</b>		
Delay until reintroduction	1 to 80 years	80 scenarios <sup>b</sup>
Cases reintroduced	1, 5 or 10 cases	3 scenarios <sup>b</sup>
<b>Risk of adverse congenital event</b>		
Exposure	Proportion of women in the first semester of pregnancy	World Bank (2019a)
Risk of microcephaly	Upon infection during exposure time (3 levels of risk)	Cauchemez et al. (2016); Johansson et al. (2016)
<b>Targeted vaccination</b>		
Date of implementation	In 2021, 2025 or 2031	3 scenarios <sup>b</sup>
Effective coverage	Proportion of 15 year old girls vaccinated (0% to 80%)	5 scenarios <sup>b</sup>

88 integrates processes related to ZIKV transmission, immunity, demography, adverse congenital outcomes and vaccination (Table 1). We parameterized the model based on published estimates or  
89 inferences from data about the 2016 ZIKV epidemic (Table 1). We considered different scenarios  
90 about the duration of immunity, the timing and scale of ZIKV reintroductions in the population,  
91 and the timing and scale of a hypothetical vaccination program targeted towards 15 year old girls.  
92

## 93 2.2 Model structure

94 We simulated a population of 10,000 individuals for 80 years (2017–2097). We assigned agents age  
95 and ZIKV infection status (susceptible *S*, infected *I* or immune *R*). Initial conditions reflected the  
96 situation in Managua, Nicaragua in 2017, when there was no documentation of active transmission.  
97 In the outbreak-free period, we only considered demographic and immunity processes: births, deaths,  
98 ageing and, if applicable, loss of immunity and vaccination. Given the scarcity of these events  
99 at the individual level, we select a long time-step of seven days and stochastically applied the  
100 transition probabilities at each time step for each agent. After a given time, ZIKV-infected cases  
101 were reintroduced in the population. Upon reintroduction, the time step was reduced to 0.1 days, and  
102 we evaluated the epidemic-related transition probabilities: Susceptible agents may become infected  
103 at a rate  $\beta_a I/N$ , where  $\beta_a$  is the age-dependent transmission rate and  $N$  the total population size.  
104 Infected individuals may recover with a rate  $\gamma$ . We ignored the influence of the vector population

105 and assumed that the force of infection is directly proportional to the overall proportion of infected  
 106 individuals. We allowed six months for the outbreak to finish after introduction. Simulations  
 107 were conducted independently for each combination of scenarios and repeated 1,000 times. In the  
 108 baseline scenario, we assumed no vaccination, no loss of immunity and a reintroduction of 10 infected  
 109 individuals.

110 We implemented the model in ‘Stan’ version 2.18 (Carpenter et al., 2017) and we conducted  
 111 analyses with R version 3.5.1 (R Core Team and Team, 2008). The Bayesian inference framework  
 112 Stan permits the use of probability distributions over parameters instead of single values, allowing  
 113 for the direct propagation of uncertainty. Stan models are compiled in C++, which improves the  
 114 efficiency of simulations. Algorithm 1 (Appendix A.1) describes the ABM in pseudo code. The  
 115 model code and data are available from <http://github.com/ZikaProject/SeroProject>.

## 116 2.3 Parametrization

### 117 2.3.1 ZIKV epidemic parameters

118 We inferred the probability distributions for the age-specific transmission rate  $\beta_a$  and the recovery  
 119 rate  $\gamma$  from data on the 2016 ZIKV epidemic in Managua, Nicaragua. We used surveillance data  
 120 (Zambrana et al., 2018), which give weekly numbers of incident ZIKV infections, confirmed by  
 121 RT-PCR (dataset A, n=1,165), and survey data on age-stratified ZIKV seroprevalence, measured  
 122 among participants of pediatric and household cohort studies in Managua during weeks 5–32 of 2017  
 123 (dataset B, n=3,740 children and 1,074 adults) (Zambrana et al., 2018).

124 We conducted statistical inference using a deterministic, ordinary differential equation (ODE)-  
 125 based version of the ABM with three compartments ( $S$ ,  $I$  and  $R$ ) and two age classes ( $a \in \{1, 2\}$   
 126 corresponding to ages 0–14 and  $\geq 15$ ):

$$127 \frac{dS_a}{dt} = -\beta_a S_a \frac{\sum I_a}{N} \quad (1)$$

$$128 \frac{dI_a}{dt} = \beta_a S_a \frac{\sum I_a}{N} - \gamma I_a \quad (2)$$

$$129 \frac{dR_a}{dt} = \gamma I_a \quad (3)$$

131 We ignored demography in this model because it covers a short time span. We recorded the overall  
 132 cumulative incidence of ZIKV cases using a dummy compartment:

$$133 \frac{dC}{dt} = \sum_a \beta_a S_a \frac{\sum I_a}{N} \quad (4)$$

134 in order to compute the weekly incidence on week  $t$ :

$$135 D_t = C(t) - C(t-1) \quad (5)$$

136 We fitted the model to weekly incidence data A using a normal likelihood after a square-root  
 137 variance-stabilizing transformation (Guan, 2009):

$$138 \Pr(\mathbb{A}|\beta_a, \gamma, \rho, \sigma) = \prod_t \mathcal{N}(\sqrt{\mathbb{A}}|\sqrt{\rho D}, \sigma) \quad (6)$$

139 where  $\rho$  is a reporting rate parameter and  $\sigma$  an error parameter. In addition, we also fitted the  
 140 model to the number of individuals with anti-ZIKV antibodies at the end of the epidemic by age  
 141 group  $\mathbb{B}_a$  using a binomial likelihood:

$$142 \Pr(\mathbb{B}|\beta_a, \gamma) = \prod_a \mathcal{B}(\mathbb{B}_a|n_a, p_a) \quad (7)$$

143 where  $\mathbb{B}_a$  the number of individuals with antibodies,  $n_a$  is the sample size in each age group, and  
 144  $p_a = R_a(t_{end})/N_a(t_{end})$  the proportion of immune at the end of the epidemic. The full likelihood  
 145 was obtained by multiplying Eq. 6 and Eq. 7. We chose weakly-informative priors for all parameters  
 146 and fitted the model in Stan (Table 2). We describe the calculation of the basic reproduction number  
 147  $\mathcal{R}_0$  in appendix A.2. We used one thousand posterior samples for  $\beta_a$  and  $\gamma$  obtained by Hamiltonian  
 148 Monte Carlo in the ABM model, ensuring the full propagation of uncertainty. Parameter values can  
 149 translate from deterministic to agent-based versions of an epidemic model if the time step is small  
 150 (Roche et al., 2011a), which was the reason for using a time step of 0.1 days.

Table 2: Parameter estimates inferred from incidence and sero-prevalence data on the 2016 ZIKV epidemic in Managua, Nicaragua. CrI: Credible interval.

Parameter	Interpretation	Prior	Posterior (median and CrI)	95%
$\beta_1$	Transmission for age group 0-14	Expon(0.1)	0.19 (0.16; 0.22)	
$\beta_2$	Transmission for age group $\geq 15$	Expon(0.1)	0.32 (0.30; 0.36)	
$1/\gamma$	Duration of infectious period	Gamma(1, 0.1)	4.8 (4.3; 5.4)	
$\rho$	Reporting rate	Beta(1, 1)	0.24% (0.21; 0.26)	
$I(0)$	Initial number of infectious	Expon(0.1)	74 (40; 134)	
$\mathcal{R}_0$	Basic reproduction number	—	1.58 (1.56; 1.59)	

### 151 2.3.2 ZIKV immunity

152 We used the deterministic model, described in the previous section, to infer the proportion of people  
 153 with protective immunity within each age group at the end of the 2016 epidemic  $\tilde{p}_a$ . We used one  
 154 thousand posterior samples of  $\tilde{p}_a$  in the ABM to allow the propagation of uncertainty. Protective  
 155 immunity to ZIKV after infection was lifelong in our first scenario, so the reduction of the overall  
 156 proportion of immune individuals in the population decreased only because of population renewal.  
 157 Given the absence of evidence about the duration of immunity to ZIKV, we considered four scenarios  
 158 assuming exponentially distributed durations of immunity with means of 30, 60, 90, or 150 years.  
 159 These values correspond to a proportion of initially immune agents that loses immunity after 10  
 160 years of 28%, 15%, 11% or 6%, respectively (Appendix A.3).

### 161 2.3.3 Demography

162 We based the initial age distribution of the population on data from the World Bank (World Bank,  
 163 2019b). We used age-dependent death rates for 2016 from the World Health Organization (World  
 164 Health Organization, 2019). For births, we computed a rate based on an average birth rate in  
 165 Nicaragua of 2.2 births per woman, which was uniformly distributed over the female reproductive  
 166 lifespan (World Bank, 2019a). We defined the period of reproductive age between 15 and 49 years.  
 167 The ageing process was linear, increasing the age of each agent by 7 days at each 7-day time step.

### 168 2.3.4 ZIKV reintroduction

169 We reintroduced ZIKV in the population after a delay of  $d = \{1, \dots, 80\}$  years in independent  
 170 simulations. We chose this approach rather than continuous reintroductions to remove some of  
 171 the stochasticity and assess more clearly the association between immunity decay and risk of an  
 172 outbreak. As the probability of an extinction of the outbreak depends on the number of ZIKV cases  
 173 reintroduced in the population, we considered three different values for the seed (1, 5 or 10 cases)  
 174 and compared the results (Appendix A.4). Simulations using continuous reintroductions each year  
 175 are presented in the appendix A.5.

176 **2.3.5 Risk of adverse congenital outcomes**

177 The estimated number of microcephaly cases resulting from the reintroduction of ZIKV depended  
178 on the exposure, i.e. the number of pregnant women infected by ZIKV during their first trimester,  
179 to which we applied three different levels of risk, based on published estimates (Cauchemez et al.,  
180 2016; Johansson et al., 2016). We obtained the number of ZIKV infections among women aged  
181 15–49 years from ABM simulations. As gender was not explicitly considered in the model, we  
182 assumed that women represented 50% of the population. We assumed a uniform distribution of  
183 births during the reproductive period, and considered that the first trimester constituted a third  
184 of ongoing pregnancies at a given time. We explored three different levels of risk of microcephaly  
185 in births to pregnant woman with ZIKV infection during the first trimester, as reported by Zhang  
186 et al., based on data from French Polynesia (0.95%, called low risk) and Brazil (2.19% and 4.52%,  
187 called intermediate and high risk, respectively) (Cauchemez et al., 2016; Johansson et al., 2016).

188 **2.3.6 Vaccination**

189 We examined the effects of a potential ZIKV vaccine, given to 15-year-old-girls. This vaccination  
190 strategy was used for rubella virus, which also causes congenital abnormalities, before the vaccine  
191 was included in the measles, mumps and rubella vaccine given in childhood (Vyse et al., 2002). The  
192 main objective of vaccination would be the prevention of adverse congenital outcomes, including  
193 microcephaly. We simulated this intervention in the ABM, assuming vaccine implementation starting  
194 in 2021, 2025 or 2031. From that date, half of the agents reaching age 15, representing females, could  
195 transition to immune status  $R$  regardless of their initial status, with an effective vaccination coverage  
196 ranging from 20% to 80%.

197 **2.4 Outcome analysis**

198 From the simulations, we collected 1) the evolution of the age-specific ZIKV immunity in the pop-  
199 ulation; 2) the attack rate resulting from the reintroduction of ZIKV at year  $d$ ; 3) the age of newly  
200 infected individuals. We fitted a binary Gaussian mixture model to dichotomize the observed attack  
201 rates into either outbreaks or non-outbreaks. We defined the outbreak threshold as the 97.5% upper  
202 bound of the lower distribution. This corresponded to a threshold of 1%, so that attack rates  $\geq 1\%$   
203 were considered as outbreaks. The age structure of newly infected individuals was used to compute  
204 relative risks of infection by age group.

205 **3 Results**

206 **3.1 2016 ZIKV epidemic**

207 The fitted model (Figure 1), resulted in a reporting rate of 0.24% (95% credible interval, CrI: 0.21;  
208 0.26). The transmission rate in the 0–14 age group was 42% (95% CrI: 35; 48) lower than in the  
209  $\geq 15$  age group. This corresponded to an overall basic reproduction number  $\mathcal{R}_0$  of 1.58 (95% CrI:  
210 1.56; 1.59). The predicted percentage of immune at the end of the epidemic was 36% (95% CrI: 34;  
211 38) for the 0–14 age group and 53% (95% CrI: 50; 57) for the  $\geq 15$  age group.

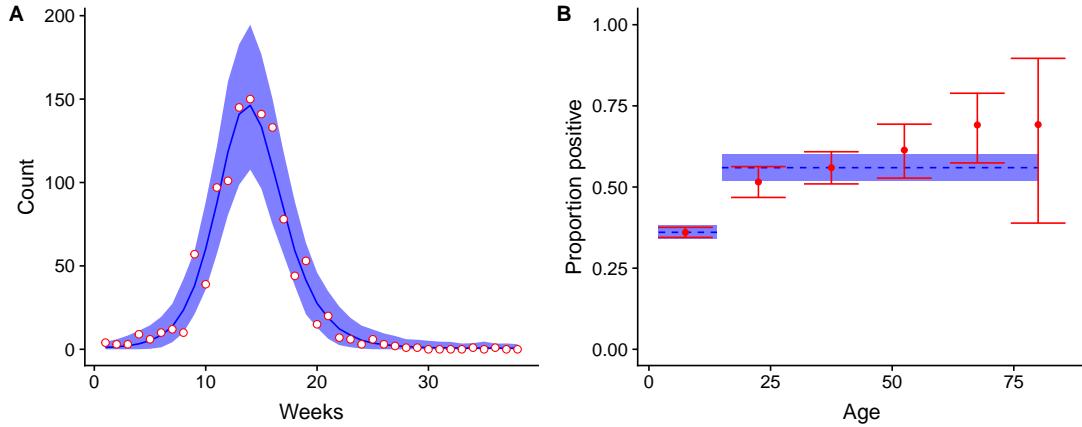


Figure 1: Model fit for (A) weekly incidence data and (B) post-epidemic sero-prevalence data from the 2016 ZIKV epidemic in Managua, Nicaragua. Data points are in red and the corresponding model fit (posterior median and 95% credible interval) is in blue.

### 212 3.2 Immunity and population

213 In our forward simulations, the expected population size increased by 42% between 2017 and 2097.  
214 Under the assumption that ZIKV infection results in lifelong protective immunity, population re-  
215 newal will create an imbalance in the proportion immune in different age groups. We expect the  
216 overall proportion of the population with protective immunity to have halved (from 48% to 24%)  
217 by 2051 and to be concentrated among the older age classes (Fig. 2A). The 0–14 year old age group  
218 will become entirely susceptible by 2031 and the 15–29 year old age group by 2046.

### 219 3.3 Future risk of ZIKV outbreak

220 Reintroductions of ZIKV in the population of Managua are unlikely to develop into sizeable outbreaks  
221 before 2035, 24 years after the 2016 epidemic, assuming lifelong immunity for individuals infected in  
222 2016 (Fig. 2B). After this point, attack rates resulting from ZIKV reintroduction will rise steeply.  
223 By 2047, we predict that ZIKV reintroductions will have a 50% probability of resulting in outbreaks  
224 with attack rates greater than 1% (Fig. 2C).

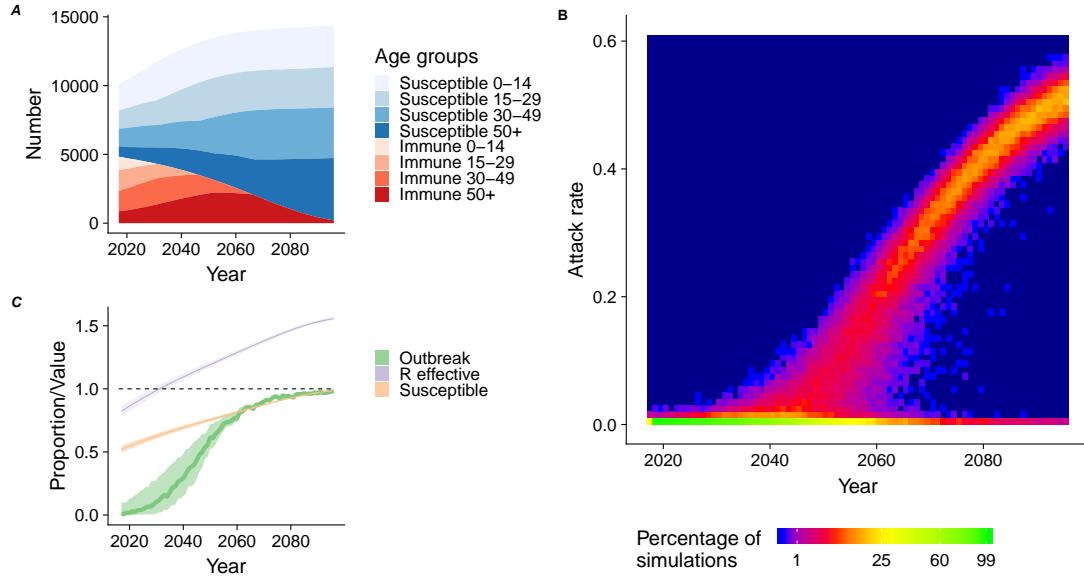


Figure 2: (A) The evolution of the immunity status per age group in a population of 10,000 agents for the next 80 years based on the demographic structure of Nicaragua. (B) Heat map of the distribution of the attack rates resulting from the reintroduction of ZIKV in the population at each year (1000 simulations for each year). (C) The evolution of the proportion of reintroductions resulting in outbreaks (with a threshold of 1%) with time (green), proportion of susceptible (orange), and effective reproduction number  $R_e$  (purple).

### 225 3.4 Risk of infection and microcephaly births in women of reproductive 226 age

227 The differences between age groups in both immunity and transmission will result in a dispropor-  
228 tionate burden of infection in the 15–29 age class. The relative risk of infection in this age group  
229 ranges from 1.2 to 1.6, compared with the general population if an outbreak occurs during the pe-  
230 riod 2032–2075 (Fig. 3A). As most pregnancies occur in this age group, these women are also the  
231 most likely to experience a pregnancy with an adverse outcome. The increased risk of infection in  
232 this group implies that the number of adverse congenital outcomes resulting from a ZIKV outbreak  
233 during this period is likely to be higher than expected with a homogeneous distribution of immunity  
234 across ages. Assuming different values for the added risk of microcephaly after a ZIKV infection  
235 during the first trimester, we expect the mean number of additional microcephaly cases due to ZIKV  
236 infection resulting from the reintroduction of the virus in Managua, Nicaragua to reach 1 to 5 cases  
237 per 100,000 population in 2060 (Fig. 3B).

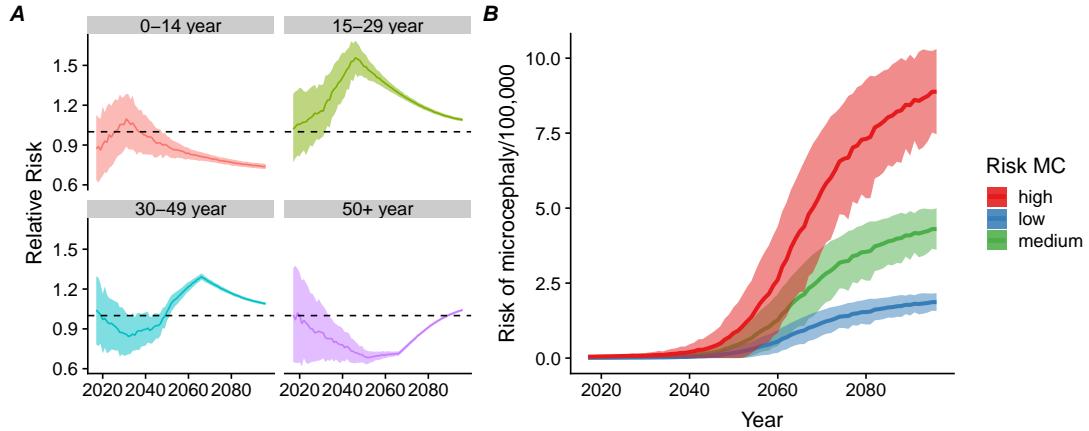


Figure 3: (A) Relative risk of ZIKV infection during a ZIKV outbreak per age group compared to the general population by year (median, interquartile range). (B) Expected number of additional microcephaly events associated with ZIKV infection during pregnancy per 100,000 total population according to three different risk scenarios.

### 238 3.5 Loss of immunity

239 If protective immunity to ZIKV is not lifelong, the time window before observing a rise in the attack  
 240 rates resulting from ZIKV reintroduction will shorten (Fig. 4A). For instance, if 15% of the those  
 241 who were infected in 2016 lose their immunity after 10 years (a mean duration of immunity of 60  
 242 years), the time until the risk of outbreak upon reintroduction reaches 50% would be 14 years earlier  
 243 (2033) than with lifelong immunity (2047). Loss of immunity over time would reduce the relative  
 244 risk in the 15-29 year old age group (Fig. 4B).

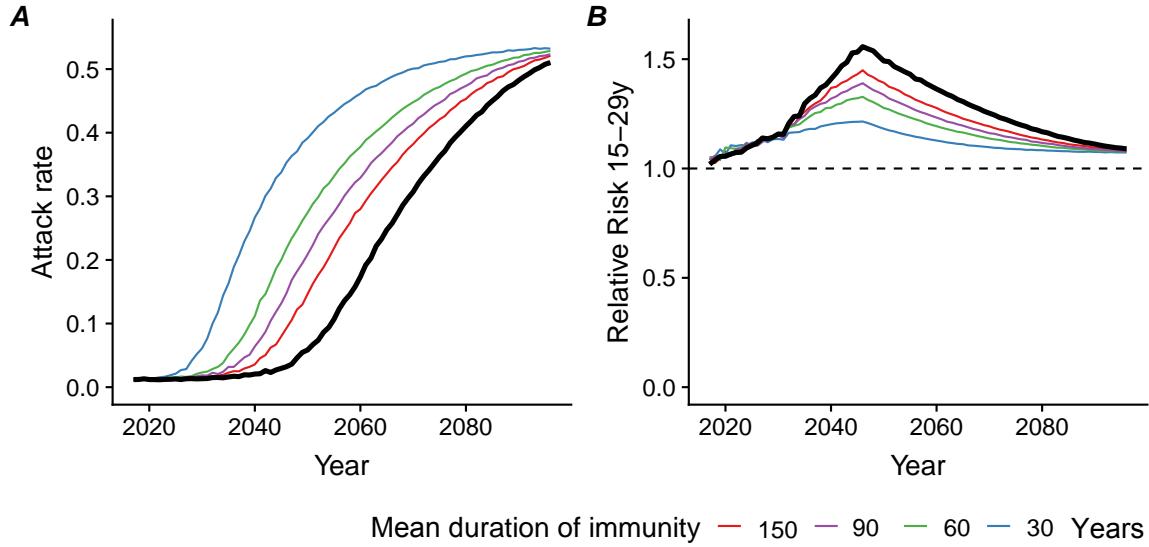


Figure 4: Consequences of alternative scenarios regarding the mean duration of protective immunity (30, 60 and 150 years), compared with lifelong immunity (thick black line): (A) median attack rate of ZIKV among reintroductions resulting in outbreaks (with a threshold of 1%) and (B) relative risk of ZIKV infection during an outbreak in the 15–29 year age group compared with the general population.

### 245 3.6 Targeted vaccination

246 The implementation of a vaccination program targeted towards 15 year old girls between 2021 and  
247 2031 would reduce the risk of infection in women aged 15–29 years and would also indirectly reduce  
248 the overall risk of a ZIKV outbreak in the population (Fig. 5). If effective vaccine coverage is  
249 60–80% amongst 15 year old girls, the prolongation of herd immunity could effectively mitigate the  
250 overall risk of a ZIKV outbreak in the population. The reduction in the number of microcephaly  
251 cases would then exceed what would be expected by considering only the direct protection granted  
252 by a vaccine to future mothers. A later implementation of the intervention would be less effective,  
253 as it becomes more difficult to maintain the herd immunity (Fig. 5B).

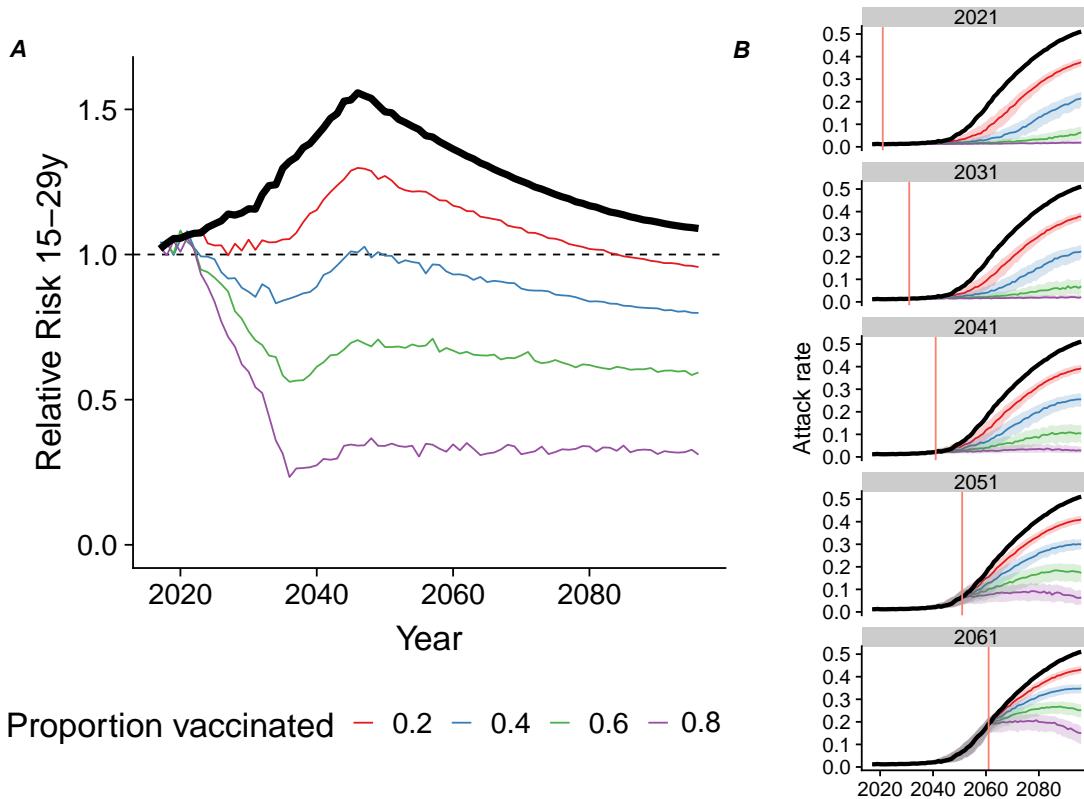


Figure 5: Consequences of implementing a targeted vaccination program among 15-year-old-girls from 2021 onwards with various levels of effective vaccination coverage (from 20 to 80%) compared with no vaccination (thick black line): (A) relative risk of ZIKV infection during an outbreak in the 15–29 year age group compared with the general population and (B) attack rate of ZIKV among reintroductions resulting in outbreaks (median, interquartile range, with a threshold of 1%), when vaccination is introduced from 2021, 2031, 2041, 2051 or 2061 onwards (red vertical line).

## 254 4 Discussion

255 In this mathematical modelling study, we show that a new ZIKV outbreak in Nicaragua would affect  
 256 proportionally more women in the young reproductive age range (15–29 years) than the general  
 257 population, owing to the age-dependent infection pattern and population renewal. The risk of a  
 258 new ZIKV outbreak in Nicaragua, after reintroduction, will remain low before 2035 because of herd  
 259 immunity, then rise to 50% in 2047. If protective immunity to ZIKV decays with time, ZIKV  
 260 recurrence could occur sooner. Timely introduction of targeted vaccination, focusing on females  
 261 aged 15 years would both reduce the risk of adverse congenital outcomes and extend herd immunity,  
 262 mitigating the overall risk of an outbreak and resulting in lower attack rates if an outbreak occurs.

### 263 4.1 Strengths and limitations of the study

264 A strength of our approach is that it allows for the full propagation of uncertainty from the initial  
 265 data into the risk assessment, by transferring the posterior distributions of the parameters from  
 266 the deterministic model fitted to surveillance and seroprevalence data on the 2016 epidemic into

267 the ABM used for simulations. Roche et al. showed that, when a sufficiently small time step was  
268 chosen, stochastic and deterministic models using the same parameter values led to similar results  
269 (Roche et al., 2011b). Additionally, we benefited from the availability of high quality data from  
270 population-based surveys that included participants from age 2 to 80 years in Managua, Nicaragua.  
271 The age-stratified seroprevalence data allowed us to investigate the risk in different age groups and  
272 better assess the evolution of the age-specific immunity, which is crucial when studying adverse  
273 congenital events caused by ZIKV infection during pregnancy.

274 We chose a simple approach based on an SIR structure, similar to the model used by Netto et al.,  
275 to focus on the dynamics of infection and immunity in the human population. We did not model  
276 vector populations and behavior explicitly, as in some other studies (Kucharski et al., 2016; Cham-  
277 pagne et al., 2016; Ferguson et al., 2016). This simplification limits the mechanistic interpretation of  
278 the epidemic parameters, but provides a phenomenological description of the transmission dynamics.  
279 We believe that this approach is appropriate because our main objective was to determine the risk  
280 of an outbreak after reintroduction of ZIKV, which is mostly influenced by the level of protective  
281 immunity in the human population. We acknowledge that the future occurrence of ZIKV in the area  
282 also depends on the presence of a competent vector. Our choice is supported by sensitivity analyses  
283 that show that more complex model structures (delayed SIR and Ross-MacDonald-type models)  
284 were not superior to a simple SIR structure in describing the 2016 ZIKV epidemic of Managua  
285 (Appendix A.6). Similarly, Pandey et al. (2013) showed that additional model complexity does not  
286 result in a better description of the dynamics of transmission of dengue virus (another Aedes-borne  
287 virus) in a human population compared with a SIR model (Pandey et al., 2013). In our model,  
288 the transmission rate ( $\beta_a$ ) captures both human-mosquito and mosquito-human transmission; we  
289 assumed a constant transmission rate, as observed in the 2016 outbreak.

290 Another limitation of our model is that we did not take migration or changes in population  
291 distribution into account in our model. An influx of people with lower levels of protective immunity  
292 or higher birth rates would increase the speed at which the population becomes susceptible again.  
293 Nicaragua has an urbanization rate that exceeds the world average (Maria et al., 2017). If rural  
294 populations have lower seroprevalence for ZIKV, as was shown in Suriname (Langerak et al., 2019),  
295 an inflow of rural inhabitants into Managua could increase the risk of ZIKV outbreaks. Uncertainty  
296 remains, as factors such as the political instability in Nicaragua could drive migration and influence  
297 disease transmission, as we currently observe in Venezuela and bordering countries (Tuite et al.,  
298 2018).

## 299 4.2 Interpretation in comparison with other studies

300 This study shows that the lower attack rate of ZIKV in children than in adults will hasten the  
301 emergence of a population that will be fully susceptible to infection, especially if immunity is not  
302 lifelong. The advantage of our approach is that we used the age-specific attack rates to model  
303 the processes of ageing in relation to protective immunity to ZIKV explicitly. Even with lifelong  
304 immunity, our model predicts that children aged 0–14 years will become entirely susceptible by 2031  
305 and 15–29 year olds by 2046. In future outbreaks, the attack rate will then be highest amongst  
306 15–29 year olds, including women who will be at risk of ZIKV infection in pregnancy. If immunity  
307 wanes, the time until the next ZIKV outbreak will be reduced and, in that case, the distribution of  
308 infection risk would be more equal across age groups (Fig. 4). Several authors have studied the time  
309 to a next ZIKV outbreak, but none studied the effect of the loss of immunity over time in relation to  
310 age. Assuming lifelong immunity, our estimates of the time until the risk increases are similar to the  
311 12–20 years before re-emergence estimated for French Polynesia (Kucharski et al., 2016). Netto et al  
312 (2017) used an SEIR model to show that in Salvador, Brazil, the effective reproduction number was  
313 insufficient to cause a new outbreak during the “subsequent years” (Netto et al., 2017). Lourenço  
314 (2017) showed the same for the whole of Brazil: herd immunity should protect the population from  
315 a new outbreak in the coming years (Lourenço et al., 2017). Ferguson et al. (2016) concluded that

316 the age distribution of future ZIKV outbreaks will likely differ and that a new large epidemic will  
317 be delayed for “at least a decade” (Ferguson et al., 2016).

318 Other ZIKV vaccination studies confirm our findings. However, they do not show the effect in  
319 risk groups nor assume herd immunity from previous outbreaks like we did here; Durham et al.  
320 (2018) showed that immunizing females aged 9 to 49 years with a 75% effective vaccine and a  
321 coverage of 90%, would reduce the incidence of prenatal infections by at least 94%. Similarly,  
322 Bartsch et al. (2018) showed that women of childbearing age or young adults would be an ideal  
323 target group for vaccination. Valega-Mackenzie and Ríos-Soto (2018) formulated a vaccination model  
324 for ZIKV transmission that included mosquito and sexual transmission. They found that vaccination  
325 works if well administered, both when sexual transmission is most important and when vector-born  
326 transmission is most important.

### 327 **4.3 Implications and future research**

328 Our finding that people in the 15–29 age range are more at risk of infection implies that we expect  
329 a higher number of congenital abnormalities due to ZIKV infection. Thus, vaccine development  
330 efforts should be increased. Our conclusions are drawn based on data from Managua, Nicaragua,  
331 but should be relevant to many regions in the Americas and the Pacific that have documented high  
332 post-epidemic levels of seropositivity (Aubry et al., 2017; Netto et al., 2017; Saba Villarroel et al.,  
333 2018). In regions where ZIKV has not yet caused an epidemic but competent vectors are present,  
334 vaccination would be in place as well. Further age-stratified seroprevalence studies, using sensitive  
335 and specific tests and with longitudinal follow-up, are needed to improve our understanding of ZIKV  
336 antibody distribution in populations and to quantify the duration of immunity. This information  
337 will provide important information to improve mathematical modeling of ZIKV risk.

338 ZIKV vaccine development faces considerable hurdles. First, the evaluation of vaccine efficacy  
339 has stalled because the reduced circulation of ZIKV has reduced the visibility of ZIKV-associated  
340 disease (Cohen, 2018). Second, it remains unclear if neutralizing antibodies induced by vaccination  
341 are sufficient to protect women against vertical transmission and congenital abnormalities (Diamond  
342 et al., 2018). Third, it is not clear whether or how vaccine-induced antibodies against ZIKV will  
343 cross-react with other flaviviruses. To move vaccine development forward, we need to find regions  
344 where disease will occur to be able to conduct trials. This requires identifying populations that are  
345 at risk, and implementing surveillance there. These can either be regions where ZIKV is endemic, or  
346 where ZIKV outbreaks are likely to occur; throughout the Americas, there might be regions that did  
347 not experience an outbreak, but do have suitable conditions such as competent vectors. Conducting  
348 vaccine trials in disease outbreaks is complex, but there are tools to facilitate planning (Bellan et al.,  
349 2019). ZIKV in an endemic setting, such as in Africa and Asia, could prove a suitable setting as  
350 well. However, ZIKV circulation in endemic setting is not well described and the occurrence of  
351 adverse outcomes in this context is less documented Counotte et al. (2018). Further research in  
352 understanding the transmission of the virus in an endemic context is therefore needed.

### 353 **4.4 Conclusion**

354 Preparedness is vital; the time until the next outbreak gives us an opportunity to be prepared.  
355 The next sizeable ZIKV outbreak in Nicaragua will likely not occur before 2035 but the probability  
356 of outbreaks will increase. Young women of reproductive age will be at highest risk of infection  
357 during the next ZIKV outbreak. Vaccination targeted to young women could curb the risk of a  
358 large outbreak and extend herd immunity. ZIKV vaccine development and licensure are urgent to  
359 attain the maximum benefit in reducing the population-level risk of infection and the risk of adverse  
360 congenital outcomes. The urgency of ZIKV vaccine development increases if immunity is not lifelong.

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## 365 6 Competing interests

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# 522 Appendices

## 523 A Appendix

### 524 A.1 ABM algorithm

525 Here, we provide the pseudo code of the ABM (Algorithm 1).

---

#### Algorithm 1 ABM

---

```

1: procedure INITIALIZATION                                 $\triangleright$  Add initial conditions S/R and sex per  $n$  individual
2:   for  $n \leftarrow 1, popMax$  do
3:      $R[n] \leftarrow$  select random 1 or 0 with probability( $age[n]$ )
4:      $S[n] \leftarrow 1 - R[n]$ 
5:      $I[n] \leftarrow 0$ 
6:      $sex[n] \leftarrow$  select random 1 or 0 with probability 0.5
7:   end for
8: end procedure
9: procedure SIMULATION                                      $\triangleright$  Simulation over  $wkMax$  weeks
10:  for  $wk \leftarrow 1, wkMax$  do
11:    for  $n \leftarrow 1, popMax$  do                                 $\triangleright$  Loop over  $popMax$  individuals
12:      if individual is alive then
13:        procedure POPULATION DYNAMICS                          $\triangleright$  Pre-outbreak
14:          Birth, Death, Ageing
15:        end procedure
16:        procedure LOSS OF IMMUNITY                            $\triangleright$  Loss of immunity
17:           $[R \rightarrow S]$  with probability RateToProb( $\xi$ )
18:        end procedure
19:        procedure VACCINATION                                 $\triangleright$  Vaccination
20:           $[S \rightarrow R]$  with probability vaccinationProb, at  $age[n]$ 
21:        end procedure
22:        procedure INFECTION, RECOVERY                          $\triangleright$  During outbreak
23:           $[S \rightarrow I]$  with probability RateToProb( $\beta, age[n]$ )
24:           $[I \rightarrow R]$  with probability RateToProb( $\gamma$ )
25:        end procedure
26:      end if
27:    end for
28:    procedure START OUTBREAK                             $\triangleright$  Introduction of infection
29:      if  $wk = introductionWk$  then
30:        Change timestep: 7 days to 0.1 days
31:        Collect summary statistics pre-outbreak
32:        Introduce  $introductionN$  infections
33:      end if
34:    end procedure
35:    total number alive
36:    total number infected                                 $\triangleright$  Collect summary of week  $wk$ :
37:  end for
38: end procedure

```

---

526 **A.2  $\mathcal{R}_0$**

527 We used the next generation matrix method described by Diekmann et al. to calculate  $\mathcal{R}_0$  (eq. 8  
 528 - 10).  $\beta_1$  is the transmission rate for the 0–14 age group;  $\beta_2$  for the >15 group;  $\gamma$  is the common  
 529 recovery rate.

$$F = \begin{pmatrix} \beta_1 & \beta_1 \\ \beta_2 & \beta_2 \end{pmatrix} \quad (8)$$

$$V = \begin{pmatrix} -\gamma & 0 \\ 0 & -\gamma \end{pmatrix} \quad (9)$$

$$\mathcal{R}_0 = \sqrt{\text{eig}(FV^{-1})} = \sqrt{\frac{\beta_1 + \beta_2}{\gamma}} \quad (10)$$

530 **A.3 Loss of immunity scenarios**

531 We explored plausible scenarios of loss of immunity (Fig. A.1).

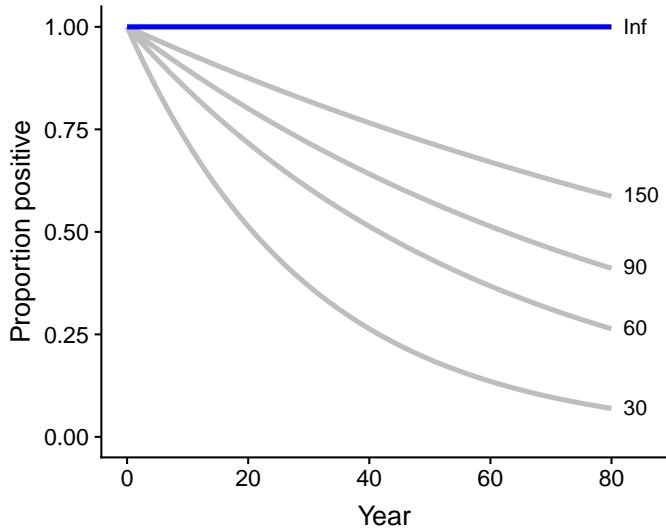


Figure A.1: Different scenarios of loss of immunity. No loss of immunity (blue) and scenarios explored (grey, exponential function with mean durations 30, 60, 90 and 150 years).

532 **A.4 The number of infections introduced does influence the probability  
 533 of an outbreak, but not the attack rate of successful outbreaks**

534 The proportion of outbreaks (1% threshold) after introduction depends on the number of infections  
 535 introduced; the attack rate of the successful outbreaks does not depend on the number of infections  
 536 introduced (Fig. A.2).

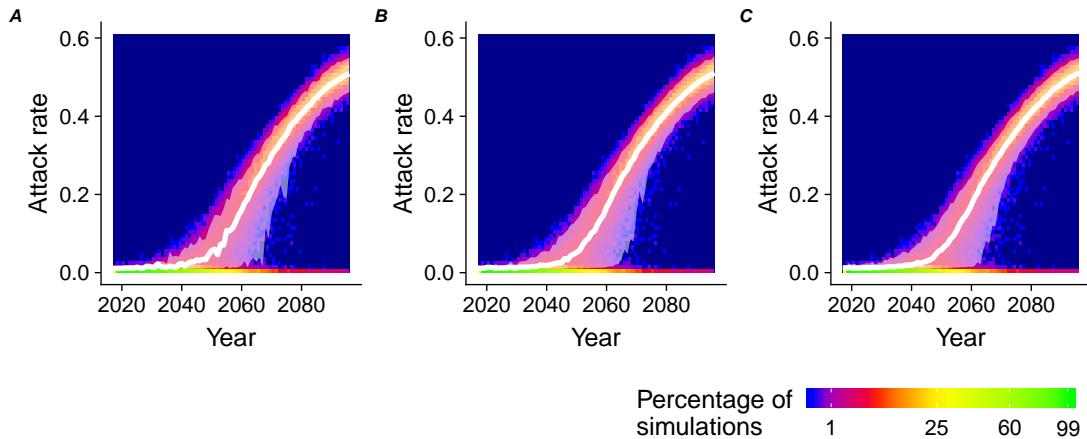


Figure A.2: Attack rate over time for the introduction of (A)  $n=1$ , (B)  $n=5$ , (C)  $n=10$  infections.

537 **A.5 Once per simulation introduction vs once per year introduction of  
538 infection**

539 Using the ABM (model B) we explored the effect of yearly introduction of one infectious individual  
540 in the population ( $n=10,000$ ). In the main text, we assumed a single introduction of  $n$  individuals  
541 per simulation. Here we introduce on a yearly basis the infectious individuals; previous outbreaks  
542 during the simulation affect the likelihood of a next outbreak and observed patterns are more  
543 stochastic. However, the pattern of the attack rate over time remains similar to the findings of the  
544 once/simulation introduction (Fig. A.3); the variation is larger due to a more stochasticity.

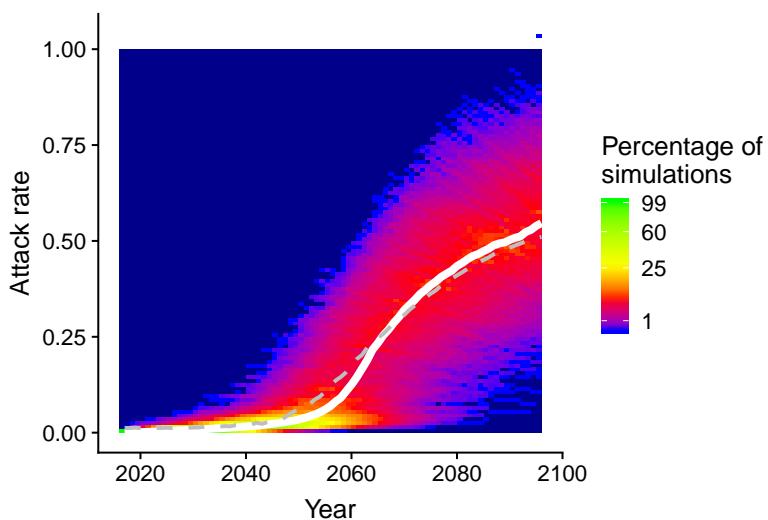


Figure A.3: Heat map of attack rate per time for simulations where every year one infectious individual is introduced in a population of 10,000. The median (white line) of this simulation is compared with the median of the simulation where once per simulation an infection is introduced (dashed grey line).

545 **A.6 Comparison of SIR model with SEIR model and the Pandey model.**

546 We compared the SIR model with a SEIR and model that explicitly models the vector; the Pandey  
547 2013 model as implemented in Champagne et al. (2016) (Champagne et al., 2016). The model fit  
548 of the more complex models does not outperform the fit of the simplest (SIR) model (Table A.1),  
549 justifying the model choice.

Model	LOOIC (SE)	$\Delta$ LOOIC (SE)
SIR	95.2 (8.7)	Ref.
SEIR	93.9 (8.9)	-1.3 (1.6)
Pandey	99.5 (8.3)	4.3 (3.6)

Table A.1: Model comparison