



A final size relation for epidemic models of vector-transmitted diseases



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ABSTRACT

We formulate and analyze an age of infection model for epidemics of diseases transmitted by a vector, including the possibility of direct transmission as well. We show how to determine a basic reproduction number. While there is no explicit final size relation as for diseases transmitted directly, we are able to obtain estimates for the final size of the epidemic.

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1. Introduction

Diseases transmitted by vectors have been of importance and interest almost since the beginning of modern epidemiological modeling. The demonstration in 1897 by Dr. R.A. Ross that malaria is transmitted from person to person through a vector, the Anopheles mosquito, was a real landmark in the early history of mathematical epidemiology. Malaria remains a cause of hundreds of thousands of death annually, mostly children less than five years old. Ninety per cent of malaria cases are in Sub-Saharan Africa.

Recently, other diseases transmitted by vectors have become serious public health problems. There have been frequent outbreaks of dengue fever and chikungunya, and the number of reported cases has been increasing rapidly recently. According to the World Health Organization, approximately 50,000,000 people worldwide are infected with dengue. Symptoms may include fever, headaches, joint and muscle pain, and nausea, but many cases are very mild. There is no cure for dengue fever, but most patients recover with rest and fluids. There are at least four different strains of dengue fever, and there is some cross-immunity between strains. Dengue fever is transmitted by the mosquito *Aedes aegypti*, and most control strategies are aimed at mosquito control. Another disease transmitted by vectors, in fact the same *Aedes aegypti* mosquito that transmits dengue, is the Zika virus. The Zika virus was first observed about 1952, but initially cases were rare. In 2007 a major epidemic occurred in Yap Island, Micronesia. Since April 2015 there has been a large continuing outbreak of Zika virus that started in Brazil and has spread to much of South and Central America. It has become a major concern because it is now established that there is some correlation with microcephaly and other very serious birth defects in babies born to infected mothers (Schuler-Faccini, 2016). A new feature of the Zika virus that has been identified is that infection may be transmitted directly by blood transfusions and sexual contact (Musso et al., 2015) as well as through vectors.

In the past, models for vector-transmitted diseases have been of *SIR/SI* or *SEIR/SEI* type, assuming that vectors do not recover from infection but are infected for life. Our purpose here is to formulate and analyze models with infectivity

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depending on age of infection. This allows arbitrary periods of stay in each compartment and also the inclusion of control measures such as treatment, quarantine, or isolation. We will describe two models, beginning with a pure vector transmission model that may be considered as a prototype of a dengue fever model, and then proceeding to a model including both vector and direct transmission that may be considered as a prototype of a zika virus model.

In the modeling of epidemics of directly - transmitted diseases, a final size relation connecting the basic reproduction number and the size of the epidemic has been an essential tool for the description of the course of the epidemic. While epidemics of vector - transmitted diseases also have a final size, there is no explicit final size relation. However, we are able to establish an estimate with an upper bound for the final size of the epidemic. The result applies also to diseases that can be transmitted directly as well as through a vector. There is also a lower bound, but it is too small to be useful. The establishment of a sharper lower bound is an important open question.

2. An age of infection epidemic model

We describe an epidemic model for a vector-transmitted disease that includes the possibility of direct transmission of disease as well. We are thinking of mosquitoes as vectors, and because a mosquito lifetime is much shorter than that of the human hosts we must include demographics in the vector population.

We consider a constant total population size N of hosts (humans) with S susceptibles and total infectivity $\varphi(t)$. Typically the total infectivity is the sum of the number of members of infected classes multiplied by the relative infectivity of the class.

We assume an average mosquito makes a bites in unit time. Thus the total number of mosquito bites in unit time is aN_v , and the number of bites received by an average host in unit time is aN_v/N_h . A host makes an average of β_h contacts sufficient to receive infection in unit time from vectors. The contact rate β_h is a product of two factors, namely the number of bites received in unit time by an average human and the probability f_{vh} that a bite transmits infection from vector to human,

$$\beta_h = a f_{vh} \frac{N_v}{N_h}.$$

The total number of contacts by humans sufficient to transmit infection is $\beta_h N$.

The number of vectors (mosquitoes) is N_v , including S_v susceptibles. Each vector makes β_v contacts sufficient to receive infection from human hosts in unit time. The contact rate β_v is a product of two factors, namely the biting rate a and the probability f_{hv} that a bite transmits infection from human to vector,

$$\beta_v = a f_{hv}.$$

There is a constant birth rate μN_v of vectors in unit time and a proportional vector death rate μ in each class, so that the total vector population size N_v is constant. Infected vectors do not recover from infection. The total number of contacts by vectors sufficient to transmit infection is $\beta_v N_v$.

Elimination of a from the expressions for β_h and β_v gives

$$f_{hv} \beta_h N_h = f_{vh} \beta_v N_v. \tag{1}$$

This balance relation must hold at every time t . We think of N, N_v, a, f_{vh} and f_{hv} as fixed. Thus β_v is also fixed and the number of effective bites of a human in unit time is

$$\beta = \beta_v \frac{f_{vh}}{f_{hv}} \frac{N_v}{N}.$$

We are assuming that the population sizes N and N_v are constant, but it is important to remember that if one of the population sizes changes, for example because of a program to kill mosquitoes, a change in the value of β would be a consequence.

A susceptible human receives β_h effective mosquito bites in unit time, of which a fraction φ_v/N_v is with an infective mosquito. Thus the number of new infective humans in unit time is

$$\beta_h S \frac{\varphi_v}{N_v}.$$

A similar argument shows that the number of new mosquito infections is

$$\beta_v S_v \frac{\varphi}{N}.$$

For the Zika virus, it has been established that in addition to vector transmission of infection there may also be direct transmission through sexual contact. The Zika virus is the first example of an infection that can be transferred both directly

and through a vector, and it is important to include direct transmission (in this case sexual transmission) in a model. To model this, we add to the model a term $\alpha \frac{S}{N} \varphi$ describing a rate α of infection of humans. This leads to the model

$$\begin{aligned}
 S'(t) &= -\beta S(t) \frac{\varphi_v(t)}{N_v} - \alpha \frac{S(t)}{N} \varphi(t) \\
 \varphi(t) &= - \int_0^\infty S'(t-s) P(s) ds \\
 &= \frac{\beta}{N_v} \int_0^\infty S(t-s) \varphi_v(t-s) P(s) ds + \frac{\alpha}{N} \int_0^\infty S(t-s) \varphi(t-s) P(s) ds \\
 S'_v(t) &= \mu N_v - \mu S_v - \beta_v S_v(t) \frac{\varphi(t)}{N} \\
 \varphi_v(t) &= \frac{\beta_v}{N} \int_0^\infty S_v(t-s) \varphi(t-s) e^{-\mu s} P_v(s) ds.
 \end{aligned} \tag{2}$$

In this model we are following the structure of the formulation of (Brauer, 2016; Diekmann, Heesterbeek, & Metz, 1995) with $S(t)$ denoting the density of susceptible hosts, $S_v(t)$ the number of susceptible vectors, $P(s)$ the expected infectivity of an individual host that became infected s time units ago, and $P_v(s)$ the expected infectivity of a vector that became infected s time units ago and still alive.

The rate α is an average over the human population; if transmission is possible only from male to female this is incorporated into α . The case $\alpha = 0$ may be regarded as a template for modeling diseases like dengue fever and chikungunya, while the case $\alpha > 0$ may be regarded as a template for modeling diseases like the zika virus. Of course, each disease has other aspects which should be included in a model for a specific disease.

We assume that the disease outbreak begins at time $t = 0$, so that $S(u) = N$ and $\varphi(u) = \varphi_v(u) = 0$ for $u < 0$ and there may be a discontinuity in $S(u)$ at $u = 0$ corresponding to an initial infective distribution.

2.1. The basic reproduction number

The basic reproduction number is defined as the number of secondary disease cases caused by introducing a single infective human into a wholly susceptible population of both hosts (humans) and vectors (mosquitoes). We separate this calculation into the vector reproduction number \mathcal{R}_v and the direct reproduction number \mathcal{R}_d . For the model (2) the vector reproduction number may be calculated directly. There are two stages. First, the infective human infects mosquitoes, at a rate $\beta_v N/N_v$ for a time $\int_0^\infty P(s) ds$. This produces $\beta_v N/N_v \int_0^\infty P(s) ds$ infected mosquitoes.

The second stage is that these infective mosquitoes infect humans at a rate $\beta N_v/N$ for a time $\int_0^\infty e^{-\mu s} P_v(s) ds$, producing $\beta N_v/N \int_0^\infty e^{-\mu s} P_v(s) ds$ infected humans per mosquito. The net result of these two stages is

$$\frac{\beta_v N}{N_v} \int_0^\infty P(s) ds \frac{\beta N_v}{N} \int_0^\infty e^{-\mu s} P_v(s) ds$$

infected humans, and this is the vector reproduction number

$$\mathcal{R}_v = \beta \beta_v \int_0^\infty P(s) ds \int_0^\infty e^{-\mu s} P_v(s) ds. \tag{3}$$

If there is sexual transmission, this operates independently of the host-vector interaction, and produces α cases in unit time for a time $\int_0^\infty P(s) ds$, giving a simple term $\alpha \int_0^\infty P(s) ds$,

$$\mathcal{R}_d = \alpha \int_0^\infty P(s) ds.$$

The basic reproduction number is the sum of the vector and direct reproduction numbers,

$$\mathcal{R}_0 = \mathcal{R}_d + \mathcal{R}_v = \alpha \int_0^\infty P(s)ds + \beta\beta_v \int_0^\infty P(s)ds \int_0^\infty e^{-\mu s} P_v(s)ds. \tag{4}$$

This calculation is consistent with that made in (Brauer et al., 2016; Chowell et al., 2007; Kucharski et al., 2016) and (Towers et al., 2016).

We could also calculate the basic reproduction number by using the next generation matrix approach (van den Driessche & Watmough, 2002). If we consider only infections of humans as new infections, with infections of mosquitoes as transitions, we would obtain the same expression for the basic reproduction number. However, if we consider both human and mosquitoes as new infections we would obtain a different expression. This approach would give the next generation matrix

$$\begin{bmatrix} \alpha \int_0^\infty P(s)ds & \beta \frac{N}{N_v} \int_0^\infty e^{-\mu s} P(s)ds \\ \beta_v \frac{N_v}{N} \int_0^\infty P(s)ds & 0 \end{bmatrix}.$$

The corresponding reproduction number is the positive eigenvalue of this matrix. Since the characteristic equation of the matrix is

$$\lambda^2 - \mathcal{R}_d\lambda - \mathcal{R}_v = 0,$$

this reproduction number is

$$\mathcal{R}^* = \frac{1}{2} \left[\mathcal{R}_d + \sqrt{\mathcal{R}_d^2 + 4\mathcal{R}_v} \right].$$

This is the choice made for the reproduction number in (Gao et al., 2016) and (Pinho, Ferreira, Esteva, Barreto, Morato e Silva, Teixeira, 2010), but our preference is for the choice (4) because it has a connection to the final size relation to be derived later. The two reproduction numbers have the same threshold: $\mathcal{R}_0 \leq 1$ if and only if $\mathcal{R}^* \leq 1$.

Example: In the special case analyzed in (Brauer et al., 2016)

$$\begin{aligned} S' &= -\beta S \frac{I_v}{N_v} - \alpha S \frac{I}{N} \\ E' &= \beta S \frac{I_v}{N_v} + \alpha S \frac{I}{N} - \kappa E \\ I' &= \kappa E - \gamma I \\ S'_v &= \mu N_v - \mu S_v - \beta_v S_v \frac{I}{N} \\ E'_v &= \beta_v S_v \frac{I}{N} - (\mu + \eta) E_v \\ I'_v &= \eta E_v - \mu I_v \end{aligned} \tag{5}$$

it is not difficult to calculate, using the approach in [(Brauer & Castillo-Chavez, 2012), Section 9.7] that

$$P(s) = \frac{\kappa}{\kappa - \gamma} \left[e^{-\gamma s} - e^{-\kappa s} \right], \quad \int_0^\infty P(s)ds = \frac{1}{\gamma},$$

$$P_v(s) = 1 - e^{-\eta s}, \quad \int_0^\infty e^{-\mu s} P_v(s)ds = \frac{\eta}{\mu(\mu + \eta)},$$

so that

$$\mathcal{R}_0 = \beta\beta_v \frac{\eta}{\gamma\mu(\mu + \eta)} + \frac{\alpha}{\gamma}.$$

2.2. The initial exponential growth rate

In order to determine the initial exponential growth rate from the model, a quantity that can be compared with experimental data, we linearize the model (2) about the disease-free equilibrium $S = N, \varphi = 0, S_v = N_v, \varphi_v = 0$. If we let $y = N - S, z = N_v - S_v$, we obtain the linearization

$$\begin{aligned} y' &= \beta \frac{N}{N_v} \varphi_v + \alpha \varphi \\ \varphi(t) &= \beta \frac{N}{N_v} \int_0^\infty \varphi_v(t-s) P(s) ds + \alpha \int_0^\infty \varphi(t-s) P(s) ds \\ z' &= -\mu y + \beta_v \frac{N_v}{N} \varphi \\ \varphi_v(t) &= \beta_v \frac{N_v}{N} \int_0^\infty \varphi(t-s) e^{-\mu s} P_v(s) ds \end{aligned} \tag{6}$$

The corresponding characteristic equation is

$$\det \begin{bmatrix} -\lambda & \alpha & 0 & \beta \frac{N}{N_v} \\ 0 & \alpha \int_0^\infty e^{-\lambda s} P(s) ds - 1 & 0 & \beta \frac{N}{N_v} \int_0^\infty e^{-\lambda s} P(s) ds \\ 0 & \beta \frac{N_v}{N} & -(\lambda + \mu) & 0 \\ 0 & \beta \frac{N_v}{N} \int_0^\infty e^{-(\lambda + \mu)s} P_v(s) ds & 0 & -1 \end{bmatrix} = 0.$$

We can reduce this equation to a product of two factors and an equation

$$\lambda(\lambda + \mu) \left[\alpha \int_0^\infty e^{-\lambda s} P(s) ds + \beta \beta_v \int_0^\infty e^{-\lambda s} P(s) ds \int_0^\infty e^{-(\lambda + \mu)s} P_v(s) ds - 1 \right] = 0.$$

The initial exponential growth rate is the largest root of the equation

$$g(\lambda) = \alpha \int_0^\infty e^{-\lambda s} P(s) ds + \beta \beta_v \int_0^\infty e^{-\lambda s} P(s) ds \int_0^\infty e^{-(\lambda + \mu)s} P_v(s) ds = 1. \tag{7}$$

Since $g(0) = \mathcal{R}_0 > 1$ if $\mathcal{R}_0 > 1$, $g'(\lambda) < 0$ for positive λ , and $g(\lambda) \rightarrow -1$ as $t \rightarrow \infty$, there is a unique positive root of the equation $g(\lambda) = 0$, and this is the initial exponential growth rate.

The initial exponential growth rate may be measured experimentally. If the measured value is ρ , then from (7) we obtain

$$\alpha \int_0^\infty e^{-\rho s} P(s) ds + \beta \beta_v \int_0^\infty e^{-\rho s} P(s) ds \int_0^\infty e^{-(\rho + \mu)s} P_v(s) ds = 1. \tag{8}$$

In the special case $\alpha = 0$ with no direct disease transmission, this reduces to

$$\beta \beta_v \int_0^\infty e^{-\rho s} P(s) ds \int_0^\infty e^{-(\rho + \mu)s} P_v(s) ds = 1,$$

which determines the product $\beta\beta_v$, and gives a way to estimate the basic reproduction number from measurable quantities. Also, because of the balance relation (1) we now have values of β and β_v separately and can simulate the model (2) to estimate the final size of the epidemic.

In the general case $\alpha \neq 0$ equation (7) gives a linear relation between α and $\beta\beta_v$, and restricts the value of α to the interval

$$0 \leq \alpha \leq \frac{1}{\int_0^\infty e^{-\rho s} P(s) ds}.$$

To obtain values for α and $\beta\beta_v$ we require another quantity that can be determined experimentally and expressed in terms of the model parameters. After an epidemic has passed, it might be possible to estimate the final size of the epidemic, and then choose values of α and $\beta\beta_v$ satisfying (7) such that simulations of the model (2) give the observed final size. This, however, is possible only after the epidemic has run its course. In a particular situation, it may be possible to infer that the epidemic can not be maintained through sexual contact alone, and therefore that $\mathcal{R}_d < 1$, giving a further constraint on the possible values of α . Without further information, all we can do is to estimate reproduction numbers for various choices of α and $\beta\beta_v$ that satisfy (8). We use the model (5) (Brauer et al., 2016) and parameter values (Towers et al., 2016) obtained for the 2015 Zika outbreak in Barranquilla, Colombia, including an analysis of the exponential rise in confirmed Zika cases identified by the Colombian SIVIGILA surveillance system up to the end of December 2015.

$$\kappa = 1/7 \quad \gamma = 1/5 \quad \mu = 1/9.5 \quad \eta = 1/13,$$

and the estimated measurement $\rho = 0.073$. With these values we have

$$11\beta\beta_v + 6.48\alpha = 2.676.$$

This implies $0 \leq \alpha \leq 0.413$. We may calculate \mathcal{R}_0 and \mathcal{R}^* for several values of α in this range, assuming population sizes of 1000 humans and 4000 mosquitoes. We obtain the following results and the corresponding epidemic final sizes by simulations (see Table 1).

We observe that \mathcal{R}^* is not very sensitive to changes in the direct contact rate while \mathcal{R}_0 is quite sensitive to changes in α . We have also shown the results of simulations of the model (5) showing how the epidemic size depends on α . These simulations suggest that the epidemic final size does vary considerably, and without some way of estimating how many disease cases arise from direct contact we are unable to estimate the epidemic final size. If we assume that the epidemic can not be sustained by sexual contact alone, so that $\mathcal{R}_d \leq 1$, our results imply that \mathcal{R}_0 is at least 3.51 and S_∞ is at most 45.

In (Gao et al., 2016) it is suggested that the contribution of sexual disease transmission is small, based on estimates of sexual activity and the probability of disease transmission. Since the probability of sexual transmission of a disease depends strongly on the particular disease, this estimate is quite uncertain. In (Gao et al., 2016), the reproduction number obtained is 2.055, but this is the form \mathcal{R}^* . The values obtained in (Gao et al., 2016) for the individual reproduction numbers are $\mathcal{R}_v = 3.84$ and $\mathcal{R}_d = 0.136$, which would give $\mathcal{R}_0 = 3.98$.

Estimates based on a possible imbalance between male and female disease prevalence are also quite dubious. Most Zika cases are asymptomatic or quite light but the risks of serious birth defects means that diagnosis of Zika is much more important to women than to men. If there are more female than male cases, it is not possible to distinguish between additional cases caused by sexual contact and cases identified by higher diagnosis rates. To the best of our knowledge, there is not yet a satisfactory resolution of this problem.

3. A final size relation

In this section we analyze the behavior of solutions of the model (2). The analysis of the model (2) without sexual transmission is contained as the special case $\alpha = 0$.

First, we divide the equation for S in (2) by S and integrate from 0 to ∞ , obtaining

Table 1
Reproduction number values.

α	$\beta\beta_v$	\mathcal{R}_d	\mathcal{R}_v	\mathcal{R}_0	\mathcal{R}^*	S_∞
0	0.243	0	4.86	4.86	2.185	14
0.1	0.184	0.5	3.69	4.19	2.187	24
0.2	0.125	1.0	2.51	3.51	2.16	45
0.3	0.0665	1.5	1.335	2.835	2.13	79
0.4	0.0076	2.0	0.152	2.152	2.074	166
0.413	0	2.065	0	2.065	2.065	185

$$\log \frac{S_0}{S_\infty} = \frac{\beta}{N_v} \int_0^\infty \varphi_v(t) dt + \frac{\alpha}{N} \int_0^\infty \varphi(t) dt. \quad (9)$$

Next, we integrate the equation for φ , obtaining

$$\begin{aligned} \int_0^\infty \varphi(t) dt &= - \int_0^\infty \int_0^\infty S'(t-s)P(s) ds dt \\ &= - \int_0^\infty S'(t-s) dt \int_0^\infty P(s) ds \\ &= \int_0^\infty [S(-s) - S_\infty] P(s) ds = (N - S_\infty) \int_0^\infty P(s) ds, \end{aligned} \quad (10)$$

since $S(-s) = N$ for $s > 0$.

Now, we integrate the equation for φ_v , obtaining

$$\begin{aligned} \int_0^\infty \varphi_v(t) dt &= \frac{\beta_v}{N} \int_0^\infty \int_0^\infty S_v(t-s) \varphi(t-s) e^{-\mu s} P_v(s) ds dt \\ &= \frac{\beta_v}{N} \int_0^\infty \left[\int_0^\infty S_v(t-s) \varphi(t-s) dt \right] e^{-\mu s} P_v(s) ds \\ &= \frac{\beta_v}{N} \int_0^\infty \left[\int_0^t S_v(t-s) \varphi(t-s) dt \right] e^{-\mu s} P_v(s) ds \\ &= \frac{\beta_v}{N} \int_0^\infty \left[\int_0^\infty S_v(u) \varphi(u) du \right] e^{-\mu s} P_v(s) ds \\ &= \frac{\beta_v}{N} \int_0^\infty S_v(u) \varphi(u) dt \int_0^\infty e^{-\mu s} P_v(s) ds \end{aligned} \quad (11)$$

Next, we write

$$\int_0^\infty S_v(u) P(u) du = S_v^* \int_0^\infty P(u) du,$$

where

$$\min S_v \leq S_v^* \leq \max S_v \leq N_v,$$

so that (11) becomes

$$\begin{aligned} \int_0^\infty \varphi_v(t) dt &= S_v^* \frac{\beta_v}{N} \int_0^\infty \varphi(u) dt \int_0^\infty e^{-\mu s} P_v(s) ds \\ &= S_v^* \frac{\beta_v}{N} [N - S_\infty] \int_0^\infty P(u) dt \int_0^\infty e^{-\mu s} P_v(s) ds. \end{aligned} \quad (12)$$

Finally, substitution of (11) and (12) into (9) gives

$$\log \frac{S_0}{S_\infty} = \left[\frac{S_v^*}{N_v} \mathcal{R}_v + \mathcal{R}_d \right] \left[1 - \frac{S_\infty}{N} \right]. \tag{13}$$

In particular, since $S_v^* \leq N_v$, we have a final size estimate

$$\log \frac{S_0}{S_\infty} \leq \mathcal{R}_0 \left[1 - \frac{S_\infty}{N} \right].$$

In order to obtain a lower bound estimate for $\log(S_0/S_\infty)$, we need an estimate for the minimum of S_v . In order to proceed further, we assume that, since the vector population has a much faster time scale than the host population, the vector population is at a quasi-steady-state equilibrium, given by finding solutions of the equations for S_v and φ_v in (2) that are constant functions of t , but may depend on $S(t)$ and $\varphi(t)$. Thus, we assume

$$\frac{S_v}{N_v} = \frac{\mu}{\beta_v \frac{\varphi}{N} + \mu}$$

Since $\varphi \leq N$, we have

$$\frac{S_v}{N_v} \geq \frac{\mu}{\beta_v + \mu},$$

and thus

$$\log \frac{S_0}{S_\infty} \geq \left[\frac{\mu}{\mu + \beta_v} \mathcal{R}_v + \mathcal{R}_d \right] \left[1 - \frac{S_\infty}{N} \right]. \tag{14}$$

Combining (3) and (14), we have the final size estimates

$$\left[\frac{\mu}{\mu + \beta_v} \mathcal{R}_v + \mathcal{R}_d \right] \left[1 - \frac{S_\infty}{N} \right] \leq \log \frac{S_0}{S_\infty} \leq \mathcal{R}_0 \left[1 - \frac{S_\infty}{N} \right] \tag{15}$$

Numerical simulations indicate that $\log(S_0/S_\infty)$ is close to $\mathcal{R}_0[1 - S_\infty/N]$.

4. Discussion

We have examined an age of infection vector-transmission epidemic model that may be applied to dengue fever, chikungunya virus, and Zika virus outbreaks. We have obtained expressions for the reproduction number and ways of estimating the initial exponential growth rate, so that the reproduction number may be estimated from parameters that can be estimated. There are no exact analytic solutions for final size relation, but we have a sharp upper bound for the epidemic size.

While Zika and chikungunya virus have only one serotype in humans, dengue virus has four serotypes, with potential cross-immunity between strains. The models we have examined do not include the effect of multiple serotypes.

In spite of these shortcomings, our models can be used to simulate the effects of different control strategies, including mosquito control, reduction of contact with mosquitoes, and avoidance of sexual contact (for Zika). It might be worthwhile to formulate and analyze a Zika model with hosts divided into males and females, but at present it is unlikely that such a more detailed model would provide better information about the development of the epidemic.

It should be pointed out that control measures which decrease the mosquito population will decrease the rate of bites of humans because of the balance relation (1), and will thus decrease the reproduction number. However, measures that protect some humans from being bitten will only redistribute bites to other humans and thus introduce heterogeneity of bites and require an adjustment to the model to include two classes of humans with different rates of being bitten. It is not clear what effect this might have on the epidemic final size; it may even increase the number of infections. This suggests that control strategies aimed at decreasing the number of mosquitoes may be much more effective than measures protecting against being bitten. However, it is possible that if the supply of human victims is insufficient, mosquitoes may shift some of their bites to animals. This would destroy the balance equation, and would lead to a need to model vector disease transmission with more than one host species.

From a mathematical perspective, we point out that for vector disease transmission models there is a problem in the calculation of the reproduction number using the next generation matrix approach. If there is no direct transmission, the usual next generation matrix approach gives a square root in the reproduction number because it views the transition from host to vector to host as two generations. It is common, but by no means universal, to remove this square root from the reproduction number. A model with both direct and vector disease transmission such as (2) indicates that removal of the

square root is logically sound, and that care is needed in the calculation of the reproduction number for a vector transmission model.

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