Chapter 12
Dengue Fever and the Zika Virus

12.1 Dengue Fever

While there have been cases of probable dengue fever more than 1000 years ago, the first recognized dengue epidemics occurred in Asia, Africa, and North America in the 1780s. There have been frequent outbreaks since then, 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.

Dengue, a re-emerging vector-borne disease, is caused by members of the genus *Flavivirus* in the family *Flaviviridae* with four active antigenically distinct serotypes, DENV-1, DENV-2, DENV-3, and DENV-4 [15]. The pathogenicity of dengue can range from asymptomatic, mild dengue fever (DF), to dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) [15, 23]. Although infection with a dengue serotype does not usually protect against other serotypes, it is believed that secondary infections with a heterologous serotype increase the probability of DHF and DSS [10, 22]. According to the World Health Organization, 40% of the global population is at risk for dengue infection with an estimate of 50–100 million infections yearly including 500,000 cases of DHF. It has been estimated that about 22,000 deaths, mostly children under 15 years of age, can be attributed to DHF [46]. In the United States, approximately 5% or more of the Key West population in Florida was exposed to dengue during the 2009–2010 outbreak [11] while the Hawaii Department of Health reported 190 cases

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during the 2015 outbreak on Oahu, the first outbreak since 2011. Since dengue is not endemic in Hawaii, health authorities have suggested that the recent outbreak may have been started by infected visitors [25]. Dengue is highly prevalent and endemic in Southeast Asia, which has experienced a 70% increase in cases since 2004 [29]; Mexico, also an endemic country, reported over a million cases of DF and more than 17,000 cases of DHF [21, 33] during the 2002 outbreak. Dengue is transmitted primarily by the vector *Ae. aegypti*, which is now found in most countries in the tropics [24, 37]. The secondary vector, *Ae. albopictus*, has a range reaching farther north than *Ae. aegypti* with eggs better adapted to subfreezing temperatures [26, 33]. Differences in susceptibility and transmission of dengue infection [3, 27, 42] raise the possibility that some serotypes are either more successful at invading a host population, or more pathogenic, or both [30]. DENV-2 is the most associated with dengue outbreaks involving DHF and DSS cases [32, 38, 48], followed by DENV-1 and DENV-3 viruses [4, 24, 32]. While infection with any of the four dengue serotypes could lead to DHF, the rapid displacement of DENV-2 American by DENV-2 Asian genotype has been linked to major outbreaks with DHF cases in Cuba, Jamaica, Venezuela, Colombia, Brazil, Peru, and Mexico [31, 32, 38, 39, 41, 48]. A possible mechanism involved in the dispersal and persistence of DENV-2 in nature is vertical transmission (transovarial transmission) via *Ae. aegypti*. Advances in molecular biology have been used to show that vertical transmission involving *Ae. aegypti* and *Ae. albopictus* is possible in captivity and in the wild [3, 8, 12, 20, 34, 40]. Thus, assessing transmission dynamics and pathogenicity between the DENV-2 American and Asian genotypes' differences is one of the priorities associated with the study of the epidemiology of dengue. In short, dengue has an increasing recurrent presence putting a larger percentage of the global population at risk of dengue infection, a situation that has become the norm due to the growth of travel and tourism between endemic and non-endemic regions.

The potential role of vertical transmission in dengue endemic regions or in fluctuating environments has been explored in [1, 18, 36]. The role of host movement has also been explored in the context of dengue [2] in a formulation that does not account for the effective population size.

The model (6.2) in Chapter 6 is a generic model for vector-transmitted diseases. For any specific disease, it is necessary to modify this model to incorporate properties of the disease not included in the generic model.

Suppose we assume that the mosquito population is in equilibrium, so that the mosquito birth rate is $\beta_v N_v$. We assume also vertical transmission for mosquitoes. The birth rate of mosquitoes is $\mu_v N_v$, of which $\mu_v I_v$ are born to infective mother mosquitoes, and we assume that a fraction q of these are born infective. Then a model describing the dynamics of DENV-2 is given by the following system of differential equations:

$$
\begin{aligned}
S_h' &= \mu_h N_h - \beta_h S_h \frac{I_v}{N_v} - \mu_h S_h \\
E_h' &= \beta_h S_h \frac{I_v}{N_v} - (\eta_h + \mu_h) E_h \\
I_h' &= \eta_h E_h - (\gamma + \mu_h) I_h \\
S_v' &= \mu_v (N_v - q I_v) - \beta_v S_v \frac{I_h}{N_h} - \mu_v S_v \\
E_v' &= \beta_v S_v \frac{I_h}{N_h} - (\eta_v + \mu_v) E_v \\
I_v' &= q \mu_v I_v + \eta_v E_v - \mu_v I_v.
\end{aligned}
\tag{12.1}
$$

This model is the same as the basic vector transmission model (6.2) in Chapter 6 except that the birth rate of susceptible hosts is now $\mu_h N_h$ and vertical transmission of hosts is added. In the absence of selection, that is, differences in birth and death rate and in the absence of vertical transmission, the model (12.1) turns out to be equivalent to a model considered by Chowell et al. in [13]. Model (12.1) is well defined supporting a sharp threshold property, namely, the disease dies out if the basic reproduction number $\mathscr{R}_0$ is less than unity and persists whenever $\mathscr{R}_0 > 1$.

12.1.1 Calculation of the Basic Reproduction Number

We calculate the basic reproduction number for the model (12.1) in two stages, as we did for the model (6.2) in Sect. 6.2.

In the first stage, an infective mosquito infects humans at a rate $\beta N_h / N_v$ for a time $1/\mu_v$, producing $\beta N_h / N_v \mu_v$ infected humans per mosquito.

In the second stage, an infective human infects mosquitoes, at a rate $\beta_v N_v / N_h$ for a time $1/(\mu_h + \gamma)$. This produces $\beta_v N_v / N_h (\gamma + \mu_h)$ infected mosquitoes, of whom a fraction $\eta_v / (\eta_v + \mu_v)$ proceeds to become infective.

The net result of these two stages is

$$
\mathscr{R}_v = \frac{\beta_v N_v}{N_h} \frac{1}{\mu_h + \gamma} \frac{\eta_v}{\eta_v + \mu_v} \frac{\eta_h}{\eta_h + \mu_h} \frac{1}{\mu_v} = \beta_h \beta_v \frac{1}{\mu_h + \gamma} \frac{\eta_v}{\eta_v + \mu_v} \frac{\eta_h}{\eta_h + \mu_h} \frac{1}{\mu_v}
\tag{12.2}
$$

infected vectors. In addition, an infective mosquito produces

$$
\mathscr{R}_d = q \mu_v
\tag{12.3}
$$

infective mosquitoes through vertical transmission, giving a total basic reproduction number

$$\begin{aligned}\mathscr{R}_0 &= \mathscr{R}_v + \mathscr{R}_d \\ &= \beta_h \beta_v \frac{1}{\mu_h + \gamma} \frac{\eta_v}{\eta_v + \mu_v} \frac{\eta_h}{\eta_h + \mu_h} \frac{1}{\mu_v} + q\mu_v.\end{aligned} \tag{12.4}$$

We could also calculate the basic reproduction number by using the next generation matrix approach [45]. If we interpret only human infections as new infections and consider vector infections as transitions, we would obtain the same result.

12.2 A Model with Asymptomatic Infectives

Many cases of dengue are very mild and may not be reported. We can incorporate this in a model by assuming that a fraction p of exposed members become infective while the remainder of the exposed class go to an asymptomatic stage with lower infectivity and possibly more rapid recovery. We have already described a model with such transitions in influenza models in Sect. 9.2. We consider a model including this structure, namely

$$\begin{aligned}S_h' &= \mu_h N_h - \beta_h S_h \frac{I_v}{N_v} - \mu_h S_h \\ E_h' &= \beta_h S_h \frac{I_v}{N_v} - (\eta_h + \mu_h) E_h \\ I_h' &= p\eta_h E_h - (\gamma + \mu_h) I_h \\ A_h' &= (1-p)\eta_h E_h - (\kappa + \mu_h) A_h \\ S_v' &= \mu_v (N_v - q I_v) - \beta_v S_v \frac{I_h + \delta A_h}{N_h} - \mu_v S_v \\ E_v' &= \beta_v S_v \frac{I_h + \delta A_h}{N_h} - (\eta_v + \mu_v) E_v \\ I_v' &= q\mu_v + \eta_v E_v - \mu_v I_v.\end{aligned} \tag{12.5}$$

Here, δ is the infectivity reduction factor for asymptomatics, and κ is the recovery rate for asymptomatics.

12.2.1 Calculation of the Basic Reproduction Number

We calculate the basic reproduction number for the model (12.5) in two stages, as we did for the model (12.1) in the previous section.

In the first stage, an infective mosquito infects humans at a rate $\beta N_h/N_v$ for a time $1/\mu_v$, producing $\beta N_h/N_v\mu_v$ infected humans per mosquito. A fraction $\eta_h/(\eta_h+\mu_h)$ of these proceed to an infective stage, with

$$p\beta_h \frac{N_h}{\mu_v N_v}\frac{\eta_h}{\eta_h+\mu_h}$$

going to I_h and

$$(1-p)\beta_h \frac{N_h}{\mu_v N_v}\frac{\eta_h}{\eta_h+\mu_h}$$

going to A_h. In the second stage, an infective human infects mosquitoes, at a rate $\beta_v N_v/N_h$ for a time $1/(\mu_h+\gamma)$. An asymptomatic infects mosquitoes at a rate $\delta\beta_v N_v/N_h$ for a time $1/(\mu_h+\kappa)$. A fraction $\eta_v/(\eta_v+\mu_v)$ of each of these groups develop into infective mosquitoes. Thus, the second stage produces

$$\beta_v \frac{N_v}{N_h}\frac{\eta_v}{\eta_v+\mu_v}\left[\frac{p}{\mu_h+\gamma}+\frac{\delta(1-p)}{\mu_h+\kappa}\right]$$

infected mosquitoes.

The net result of these two stages is

$$\mathscr{R}_v = \beta_h \frac{N_h}{\mu_v N_v}\frac{\eta_h}{\eta_h+\mu_h}\beta_v \frac{N_v}{N_h}\frac{\eta_v}{\eta_v+\mu_v}\left[\frac{p}{\mu_h+\gamma}+\frac{\delta(1-p)}{\mu_h+\kappa}\right] \tag{12.6}$$

infected mosquitoes. In addition, an infective mosquito produces

$$\mathscr{R}_d = q\mu_v \tag{12.7}$$

infective mosquitoes through vertical transmission, giving a total basic reproduction number

$$\mathscr{R}_0 = \mathscr{R}_v + \mathscr{R}_d. \tag{12.8}$$

Again, we could also calculate the basic reproduction number by using the next generation matrix approach [45]. If we interpret only human infections as new infections and consider vector infections as transitions, we would obtain the same result, but if we interpreted both human and vector infections we would obtain a different version of the basic reproduction number

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

12.3 The Zika Virus

The Zika virus, a mosquito borne arbovirus, was first identified in Uganda in 1947. Similar to the dengue and chikungunya viruses, Zika is primarily spread by the mosquito, *Aedes aegypti*. Recent outbreaks of Zika disease have occurred in Yap Island in the Pacific in 2007 [16] and in French Polynesia in 2013–2014 [28]. Since 2015, Zika has spread through much of South America, Central America, and the Caribbean, where the *Aedes aegypti* species is endemic, recently reaching pandemic levels in 2016. While the reasons for the explosive spread of the disease in the Americas are still unclear, the rapid urbanization in countries with under-developed infrastructure for surveillance and vector control probably plays a role.

Zika disease is usually asymptomatic, and typically is mild even with a clinical presentation. Its symptoms are similar to those of dengue and chikungunya virus infections. However, the disease has been linked to an apparent increased risk of the neurological disorder Guillain–Barré syndrome, and also to neonate microcephaly. The latter is of particular concern, because pregnant women may not even know they have been infected, and the damage to their unborn infants may result in subsequent lifelong disabilities. There is currently no vaccine or specific treatment for Zika infection, leaving control of the vector populations and avoidance through the use of mosquito repellents as the only means to control the spread of the disease.

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. Estimation of the basic reproduction number is particularly difficult for Zika because of the difficulty in estimating the relative importance of transmission through vectors and direct transmission through sexual contact. A vaccine is being developed for the Zika virus, and analysis of the question of whether this vaccine can control an outbreak is contained in [44].

12.4 A Model with Vector and Direct Transmission

We approach the question of formulating a model for the Zika virus by beginning with the basic vector transmission model (6.2) and adding direct host to host transmission. We add to the model (6.2) a term $\alpha S_h \frac{I_h}{N_h}$ describing a rate α of movement from S to E. Also, we consider a single outbreak model, and omit demographic terms and vertical transmission in the host population.

This leads to the following model [9]:

$$S_h' = -\beta_h S_h \frac{I_v}{N_v} - \alpha S_h \frac{I_h}{N_h}$$

$$E_h' = \beta_h S_h \frac{I_v}{N_v} + \alpha S_h \frac{I_h}{N_h} - \eta_h E_h$$

$$
\begin{aligned}
I_h' &= \eta_h E_h - \gamma I_h \qquad (12.9)\\
S_v' &= \mu_v N_v - \mu_v S_v - \beta_v S_v \frac{I_h}{N_h}\\
E_v' &= \beta_v S_v \frac{I_h}{N_h} - (\mu_v + \eta_v) E_v\\
I_v' &= \eta_v E_v - \mu_v I_v.
\end{aligned}
$$

The rate α is an average over the human population; if transmission is possible only from male to female this is incorporated into α.

To calculate the basic reproduction number $\mathscr{R}_0$, we use the same direct approach as that used in Section 6.2. If there is sexual transmission, this operates independent of the host–vector interaction, and produces α cases in unit time for a time $1/\gamma$, adding a simple term α/γ to the reproduction number

$$
\mathscr{R}_0 = \beta_h \beta_v \frac{\eta_v}{\mu_v \gamma (\mu_v + \eta_v)} + \frac{\alpha}{\gamma}. \qquad (12.10)
$$

We define

$$
\mathscr{R}_v = \beta_h \beta_v \frac{\eta_v}{\mu_v \gamma (\mu_v + \eta_v)}, \qquad (12.11)
$$

the vector transmission reproduction number, and

$$
\mathscr{R}_d = \frac{\alpha}{\gamma}, \qquad (12.12)
$$

the direct transmission reproduction number, so that

$$
\mathscr{R}_0 = \mathscr{R}_v + \mathscr{R}_d.
$$

If we use the next generation matrix approach, using the same approach as that used in Sect. 12.1.1, we form the matrix product $K_L = FV^{-1}$ with

$$
F = \begin{bmatrix} 0 & \alpha & 0 & \beta_h \frac{N_h}{N_v} \\ 0 & 0 & 0 & 0 \\ 0 & \beta_v \frac{N_v}{N_h} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \eta_h & 0 & 0 & 0 \\ -\eta_h & \gamma & 0 & 0 \\ 0 & 0 & \mu_v + \eta_v & 0 \\ 0 & 0 & -\eta_v & \mu_v \end{bmatrix}.
$$

Then the next generation matrix with large domain is

$$
K_L = \begin{bmatrix} \frac{\alpha}{\gamma} & \frac{\alpha}{\gamma} & \beta_h \frac{N_h}{N_v} \frac{\eta_v}{\mu_v(\mu_v+\eta_v)} & \beta_h \frac{N_h}{N_v} \frac{1}{\mu_v} \\ 0 & 0 & 0 & 0 \\ \beta_v \frac{N_v}{N_h} \frac{1}{\gamma} & \beta_v \frac{N_v}{N_h} \frac{1}{\gamma} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}.
$$

The next generation matrix K is the 2×2 matrix

$$K = \begin{bmatrix} \frac{\alpha}{\gamma} & \beta_h \frac{N_h}{N_v} \frac{\eta_v}{\mu_v(\mu_v+\eta_v)} \\ \beta_v \frac{N_v}{N_h} \frac{1}{\gamma} & 0 \end{bmatrix}.$$

The positive eigenvalue of this matrix is

$$\begin{aligned} \lambda &= \frac{\alpha}{2\gamma} + \frac{1}{2}\sqrt{\frac{\alpha^2}{\gamma^2} + 4\mathscr{R}_v} \\ &= \frac{1}{2}\left[\mathscr{R}_d + \sqrt{\mathscr{R}_d^2 + 4\mathscr{R}_v}\right]. \end{aligned}$$

We may calculate that $\lambda = 1$ if and only if

$$\mathscr{R}_v + \mathscr{R}_d = 1.$$

We now have two potential expressions for the basic reproduction number, namely $\mathscr{R}_v + \mathscr{R}_d$, with $\mathscr{R}_v$ and $\mathscr{R}_d$ given by (12.11) and (12.12) respectively, and

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

Different expressions are possible for the next generation matrix and these may lead to different expressions for the basic reproduction number. This is shown in [14].

The expression $\mathscr{R}_v + \mathscr{R}_d$ appears to us to be a more natural form than $\mathscr{R}^*$, and we choose to use this for the basic reproduction number. It can be obtained from the following expression for the next generation matrix. We consider only human infections as new infections, and take

$$F = \begin{bmatrix} 0 & \alpha & 0 & \beta_h \frac{N_h}{N_v} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \eta_h & 0 & 0 & 0 \\ -\eta_h & \gamma & 0 & 0 \\ 0 & -\beta_v \frac{N_v}{N_h} & \mu_v + \eta_v & 0 \\ 0 & 0 & -\eta_v & \mu_v \end{bmatrix}.$$

Then

$$V^{-1} = \begin{bmatrix} \frac{1}{\eta_h} & 0 & 0 & 0 \\ [2pt]\frac{1}{\gamma} & \frac{1}{\gamma} & 0 & 0 \\ \beta_v \frac{N_v}{N_h} \frac{1}{\gamma(\mu_v+\eta_v)} & \beta_v \frac{N_v}{N_h} \frac{\eta_v}{\gamma(\mu_v+\eta_v)} & \frac{1}{\mu_v+\eta_v} & 0 \\ \beta_v \frac{N_v}{N_h} \frac{\eta_v}{\mu_v\gamma(\mu_v+\eta_v)} & \beta_v \frac{N_v}{N_h} \frac{\eta_v}{\mu_v\gamma(\mu_v+\eta_v)} & \frac{\eta_v}{\mu_v(\mu_v+\eta_v)} & \frac{1}{\mu} \end{bmatrix}.$$

Since only the first row of F has non-zero entries, the same is true of FV^{-1}, and from this we can deduce that the only non-zero eigenvalue of FV^{-1} is the entry in the first row, first column of FV^{-1}, and this is

$$\frac{\alpha}{\gamma} + \beta_h \beta_v \frac{\eta_v}{\mu_v \gamma(\mu_v + \eta_v)} = \mathscr{R}_d + \mathscr{R}_v = \mathscr{R}_0.$$

If we use this somewhat unorthodox approach to the next generation matrix for the model (6.2), we obtain the form $\mathscr{R}_v$, with no square root, for the reproduction number. We now have two viable expressions for the basic reproduction number, namely $\mathscr{R}^*$ and $\mathscr{R}_0$, both derived from a next generation matrix approach but with different separations. We have chosen to use $\mathscr{R}_0$ for the basic reproduction number because it is more readily interpreted as a number of secondary infections. Other sources, including [19], use $\mathscr{R}^*$. In studying data for epidemic models that include vector transmission it is absolutely vital to specify exactly which form is being used for the basic reproduction number.

12.4.1 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 (12.9) about the disease-free equilibrium $S = N_h$, $E_h = I_h = 0$, $S_v = N_v$, $E_v = I_v = 0$. If we let $y = N_h - S$, $z = N_v - S_v$, we obtain the linearization

$$\begin{aligned}
y' &= \beta_h N_h \frac{I_v}{N_v} + \alpha I_h \\
E_h' &= \beta_h N_h \frac{I_v}{N_v} + \alpha I_h - \eta_h E_h \\
I_h' &= \eta_h E_h - \gamma I_h \\
z' &= -\mu_v z + \beta_v N_v \frac{I_h}{N_h} \\
E_v &= \beta_v N_v \frac{I_h}{N_h} - (\mu_v + \eta_v) E_v \\
I_v' &= \eta_v E_v - \mu_v I_v.
\end{aligned} \tag{12.13}$$

The corresponding characteristic equation is

$$det \begin{bmatrix}
-\lambda & 0 & \alpha & 0 & 0 & \beta_h \frac{N_h}{N_v} \\
0 & -(\lambda + \eta_h) & \alpha & 0 & 0 & \beta_h \frac{N_h}{N_v} \\
0 & \eta_h & -(\lambda + \gamma) & 0 & 0 & 0 \\
0 & 0 & \beta_v \frac{N_v}{N_h} & -(\lambda + \mu_v) & 0 & 0 \\
0 & 0 & \beta_v \frac{N_v}{N_h} & 0 & -(\lambda + \mu_v + \eta_v) & 0 \\
0 & 0 & 0 & 0 & \eta_v & -(\lambda + \mu_v)
\end{bmatrix} = 0.$$

We can reduce this equation to a product of two factors and a fourth degree polynomial equation

$$\lambda(\lambda+\mu_v)det\begin{bmatrix} -(\lambda+\eta_h) & \alpha & 0 & \beta_h\frac{N_h}{N_v} \\ \eta_h & -(\lambda+\gamma) & 0 & 0 \\ 0 & \beta_v\frac{N_v}{N_h} & -(\lambda+\mu_v+\eta_v) & 0 \\ 0 & 0 & \eta_v & -(\lambda+\mu_v) \end{bmatrix} = 0.$$

The initial exponential growth rate is the largest root of this fourth degree equation, which reduces to

$$\begin{aligned} g(\lambda) =&(\lambda+\eta_h)(\lambda+\gamma)(\lambda+\mu_v+\eta_v)(\lambda+\mu_v)-\beta_h\beta_v\eta_v\eta_v \\ &-\eta_h\alpha(\lambda+\mu_v)(\lambda+\mu_v+\eta_v)=0. \end{aligned} \tag{12.14}$$

The largest root of this equation is the initial exponential growth rate, and this may be measured experimentally. If the measured value is ρ, then from (12.14) we obtain

$$\begin{aligned} (\rho+\eta_h)(\rho+\gamma)(\rho+\mu_v+\eta_v)(\rho+\mu_v)-\beta_h\beta_v\eta_h\eta_v \\ -\eta_h\alpha(\rho+\mu+v)(\rho+\mu_v+\eta_v)=0. \end{aligned} \tag{12.15}$$

From (12.15) we can see that $\rho = 0$ corresponds to $\mathscr{R}_0 = 1$, confirming that our calculated value of $\mathscr{R}_0$ has the proper threshold behavior.

Equation (12.15) determines the value of $\beta_h\beta_v$, and we may then calculate $\mathscr{R}_0$, provided we know the value of α. However, this presents a major problem. In [19] 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. 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.

What would be required would be another quantity which can be determined experimentally and can be expressed in terms of the model parameters. In the absence of further information, all we can accomplish is to estimate reproduction numbers for various choices of α and $\beta_h\beta_v$ that satisfy (12.15). We use the parameter values [43] 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.

$$\kappa = 1/7 \quad \gamma = 1/5 \quad \eta_v = 1/9.5 \quad \mu_v = 1/13,$$

Table 12.1 Reproduction number values

α	$\beta_h\beta_v$	$\mathscr{R}_d$	$\mathscr{R}_v$	$\mathscr{R}_0$	$\mathscr{R}^*$	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

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

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

To satisfy this equation, we must have $0 \le \alpha \le 0.413$. We then calculate $\mathscr{R}_0$ and $\mathscr{R}^*$ for several values of α in this range, assuming population sizes of 1000 humans and 4000 mosquitoes. We obtain the results summarized in Table 12.1.

We observe that $\mathscr{R}^*$ is not very sensitive to changes in the direct contact rate while $\mathscr{R}_0$ is quite sensitive to changes in α. We have also shown the results of simulations of the model (12.9) 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.

12.5 A Second Zika Virus Model

A model for the Zika virus with somewhat more detail than the model (12.9) has been described in [19]. This model includes the assumption that many Zika cases are asymptomatic, and has two infectious stages acute and convalescent. The model takes the form

$$\begin{aligned}
S_h' &= -abS_h\frac{I_v}{N_h} - \beta S_h\frac{\kappa E_h + I_{h1} + \tau I_{h2}}{N_h}\\
E_h' &= \theta\left[abS_h\frac{I_v}{N_h} + \beta S_h\frac{\kappa E_h + I_{h1} + \tau I_{h2}}{N_h}\right] - \nu_h E_h\\
I_{h1}' &= \nu_h E_h - \gamma_{h1} I_{h1}\\
I_{h2}' &= \gamma_{h1} - \gamma_{h2} I_{h2}\\
A_h' &= (1-\theta)\left[bS_h\frac{I_v}{N_h} + \beta S_h\frac{\kappa E_h + I_{h1} + \tau I_{h2}}{N_h}\right] - \gamma_h A_h\\
R_h' &= \gamma_{h2} + \gamma_h A_h\\
S_v' &= \mu_v N_v - \mu_v S_v - ac\frac{S_v\eta A_h + I_{h1}}{N_h}\\
E_v' &= acS_v\frac{\eta A_h + I_{h1}}{N_h} - (\mu_v + \nu_v)E_v\\
I_v' &= \nu_v E_v - \mu_v I_v.
\end{aligned} \tag{12.16}$$

Table 12.2 Model parameters

Parameter	Description	Value
a	Mosquito biting rate	0.5
b	Transmission probability, vector to human	0.4
c	Transmission probability, human to vector	0.5
η	Transmission probability, asymptomatic humans to vector	0.1
β	Transmission probability, human to human	0.1
κ	Relative transmission probability, exposed to infective	0.6
τ	Relative transmission probability, convalescent to asymptomatic	0.3
θ	Proportion of symptomatic infections	18
m	Ratio of mosquitoes to humans	5
$1/\nu_h$	Human incubation period (days)	5
$1/\nu_v$	Mosquito incubation period (days)	10
$1/\gamma_{h1}$	Acute phase duration (days)	5
$1/\gamma_{h2}$	Convalescent period duration (days)	20
$1/\gamma_h$	Asymptomatic infection duration (days)	7
$1/\mu_v$	Mosquito lifetime (days)	14

The reproduction numbers for this model are

$$\mathscr{R}_d = \frac{\beta\kappa\theta}{\nu_h} + \frac{\beta\theta}{\gamma_{h1}} + \frac{\beta\tau\theta}{\gamma_{h2}}, \quad \mathscr{R}_v = \left(\frac{a^2 b\eta c\theta}{\nu_h\mu_v} + \frac{a^2 bc\theta}{\gamma_{h1}\mu_v}\right)\frac{\eta_v}{\eta_v + \mu_v}.$$

Parameter values were chosen to fit vector transmission data for Brazil, El Salvador, and Colombia up to February 2016. For direct (sexual) transmission of infection, parameters were chosen with an assumed probability of transmission of infection per sexual contact, but this assumption might be questionable (Table 12.2).

With these parameter values, this model yielded estimates of

$$\mathscr{R}_d = 0.136, \quad \mathscr{R}_v = 3.842,$$

so that

$$\mathscr{R}_0 = 3.973, \quad \mathscr{R}^* = 2.055.$$

However, there are indications that the number of cases of Zika due to sexual contacts may be considerably higher. Perhaps, the value of β should be larger.

12.6 Project: A Dengue Model with Two Patches

When dengue fever invades a location, it tends to move from one patch to another. To describe this, we consider a model for DENV-2 in two separate patches, with movement between the patches. The single patch model (12.1) is the building block for the two-patch model. Within each patch, in the absence of host mobility, dengue dynamics are modeled via the system (12.1). We consider an epidemic model in two patches, one of which has a significantly larger contact rate, with short term travel between the two patches. The total population resident in each patch is constant. We follow a Lagrangian perspective, that is, we keep track of each individual's place of residence at all times [6, 17]. It is assumed that vectors do not move between patches since the vectors *Ae. aegypti* and *Ae. albopictus* do not travel more than few tens of meters over their lifetime [2, 47]; moving 400–600 meters at most [7, 35], respectively. In short, we neglect vector dispersal.

Thus we consider two patches, with total resident population sizes N_1 and N_2 respectively, each population being divided into susceptibles, infectives, and removed members. S_i and I_i denote the number of susceptibles and infectives respectively who are residents in Patch i, regardless of the patch in which they are present.

The host residents of Patch 1, population size $N_{h,1}$, spends, on average, p_{11} proportion of its time in their own Patch 1 and p_{12} proportion of its time visiting Patch 2. Residents of Patch 2, population of size $N_{h,2}$, spend p_{22} proportion of their time in Patch 2 while spending $p_{21} = 1 - p_{22}$ visiting Patch 1. Thus, at time t, the *effective population* in Patch 1 is $p_{11}N_{h,1} + p_{21}N_{h,2}$ and the *effective population* in Patch 2 is $p_{12}N_{h,1} + p_{22}N_{h,2}$. The susceptible population of Patch 1 ($S_{h,1}$) could be infected by a vector in either Patch 1 ($I_{v,1}$) or Patch 2 by ($I_{v,2}$), depending on which patch they are located in at the time of infection. Thus, the dynamics of the susceptible population in Patch 1 are given by

$$\dot{S}_{h,1} = \mu_h N_{h,1} - \beta_h S_{h,1} \sum_{j=1}^{2} a_j p_{1j} \frac{I_{v,j}}{p_{1j}N_{h,1} + p_{2j}N_{h,2}} - \mu_h S_{h,1}. \tag{12.17}$$

The *effective infectious* population in Patch 1 is $p_{11}I_{h,1} + p_{21}I_{h,2}$ and, consequently, the proportion of infectious individuals in Patch 1, is

$$\frac{p_{11}I_{h,1} + p_{21}I_{h,2}}{p_{11}N_{h,1} + p_{21}N_{h,2}}.$$

The dynamics of susceptible mosquitoes in Patch 1 are modeled as follows:

$$\dot{S}_{v,i} = \mu_v(N_{v,i} - qI_{v,i}) - \beta_v S_{v,1} \frac{p_{11}I_{h,1} + p_{21}I_{h,2}}{p_{11}N_{h,1} + p_{21}N_{h,2}} - \mu_v S_{v,1}. \tag{12.18}$$

Question 1 Show that the dynamics of DENV-2, with the host moving between patches, is given by the system

$$\begin{aligned}
S'_{h,i} &= \mu_h N_{h,i} - \beta_h S_{h,i} \sum_{j=1}^{2} a_j p_{ij} \frac{I_{v,j}}{p_{1j}N_{h,1} + p_{2j}N_{h,2}} - \mu_h S_{h,i} \\
E'_{h,i} &= \beta_h S_{h,i} \sum_{j=1}^{2} a_j p_{ij} \frac{I_{v,j}}{p_{1j}N_{h,1} + p_{2j}N_{h,2}} - (\mu_h + \eta_h) E_{h,i} \\
I'_{h,i} &= \eta_h E_{h,i} - (\mu_h + \gamma_i) I_{h,i} \\
S'_{v,i} &= q\mu_v (N_{v,i} - q I_{v,i}) - \beta_v S_{v,i} \frac{\sum_{j=1}^{2} p_{ji} I_{h,j}}{\sum_{k=1}^{2} p_{ki} N_{h,k}} - \mu_v S_{v,i} \\
E'_{v,i} &= \beta_v S_{v,i} \frac{\sum_{j=1}^{2} p_{ji} I_{h,j}}{\sum_{k=1}^{2} p_{ki} N_{h,k}} - (\mu_v + \eta_v) E_{v,i} \\
I'_{v,i} &= \eta_v E_{h,i} + (1-q)\mu_v I_{v,i}, \quad i = 1, 2.
\end{aligned} \tag{12.19}$$

Question 2 Determine the basic reproduction number of the model (12.19).

Question 3 Obtain a pair of final size relations for the model (12.19).

The results of this project, together with appropriate data, can be used to estimate the spread of dengue from one community to another [5].

12.7 Exercises

1.* Use the next generation matrix to calculate the basic reproduction number of the model (12.1).
2.* Use the next generation matrix to calculate the basic reproduction number of the model (12.5).
3. If $\mathscr{R}_v$ and $\mathscr{R}_d$ are two non-negative numbers, show that $\frac{1}{2}\left[\mathscr{R}_d + \sqrt{\mathscr{R}_d^2 + 4\mathscr{R}_v}\right]$ is equal to 1 if and only if $\mathscr{R}_d + \mathscr{R}_v = 1$.

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