# Chapter 14
# A Comparative Analysis of Models for West Nile Virus

M.J. Wonham and M.A. Lewis

**Abstract** This chapter describes the steps needed to formulate, analyze and apply epidemiological models to vector-borne diseases. Our models focus on West Nile (WN) virus, an emerging infectious disease in North America, first identified in Africa. We begin by introducing a minimalist model for WN dynamics to illustrate the processes of model formulation, analysis, and application. We then revisit the question of model formulation to examine how two major biological assumptions affect the model structure and therefore its predictions. Next, we briefly compare these different model structures in an introductory exercise of model parameterization, validation, and comparison. Finally, we address model applications in more detail with two examples of how the model output can usefully be connected to public health applications.

## 14.1 Introduction: Epidemiological Modeling

Investigating and controlling infectious diseases is a complex enterprise that has long been assisted by mathematical modeling (e.g., [2, 23]). In now classic examples, key insights into the dynamics of malaria, influenza, measles, and other infectious diseases have emerged from epidemiological modeling [26, 33, 39]. Today, emerging and re-emerging infectious diseases such as HIV/AIDS, SARS, feline immunodeficiency virus, hoof and mouth, and plant fungi and viruses pose major challenges in public health, wildlife, and agricultural management realms. The increase in outbreak frequency of these diseases demands a rapid and effective management response [9–11, 14, 16, 18].

Centre for Mathematical Biology, Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, AB, Canada T6G 2G1 mwonham@ualberta.ca mlewis@math.ualberta.ca

Happily, there are many well-developed mathematical tools for effectively studying disease dynamics. There remain, however, continuing and exciting challenges in both formulating and analyzing biologically relevant disease models.

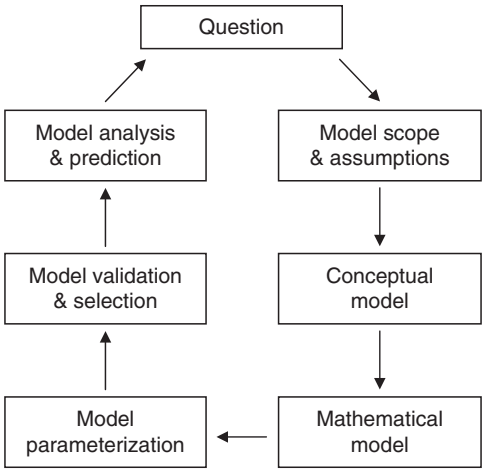


**Fig. 14.1** Cartoon of the model development process from an initial question through model formulation and analysis to the generation of further questions

Developing and applying a disease model, as indeed any model, typically follows a series of steps (Fig. 14.1). An initial disease observation prompts questions such as how fast the disease will spread, or how best the outbreak can be controlled. From the initial question, we first define the scope and assumptions of the problem and develop a conceptual hypothesis (1), This is then formulated as a mathematical expression (2), which is parameterized (3), validated and compared (4), analysed (5), and finally applied and used to generate predictions (6), In this view, mathematical modeling follows the familiar scientific method. The model is essentially a formalization of a hypothesis that must be defined (steps 1–2) and tested (steps 3–4) before being used to answer questions or generate predictions (steps 5–6).

If we are lucky, the model's predictions shed light on the original question. They will also likely generate new questions and hypotheses to be addressed by further data collection and a subsequent return to modeling. In this chicken-and-egg fashion, our understanding of disease dynamics develops as empirical study informs modeling which in turn informs further empirical investigation.

The focus of this chapter is primarily on the steps of model formulation (steps 1–2) and model application (step 6) for infectious diseases. Model

parameterization, validation, and comparison (steps 3–4) would readily fill another chapter, so we will restrict ourselves to a brief introduction to these important topics and provide references to more detailed resources. The mathematical analysis (step 5) of disease models in general is well treated in this book and elsewhere, so we will keep this aspect to a relative minimum.

We will focus our discussion on one particular type of epidemiological models, the well-studied $S - I$ or Susceptible-Infectious models. These compartmental models, descended from the work of [26], use the dynamics of interactions between $S$ and $I$ individuals to model the rate of emergence of new infectious individuals.

Many excellent texts introduce the philosophy and tools of mathematical modeling in infectious disease systems. For a general presentation of mathematical modeling in biological systems, we find those by [8, 20, 27, 35] particularly helpful. For modeling infectious diseases in particular, [2, 6, 12], provide excellent overviews and detailed examples. For the philosophy and methodology of model selection using maximum likelihood, we refer to [7, 25].

## 14.2 Case Study: West Nile Virus

Our model formulation and application center around the example of West Nile virus (WN), an emerging infectious disease in North America. WN was first identified in Uganda in 1947, and is widespread in Africa, the Middle East, and Western Asia. Occasional European outbreaks are introduced by migrating birds [21, 38]. In North America, the first recorded epidemic was detected in New York State in 1999 and spread rapidly across the continent. The unprecedented level of bird, horse, and human mortality was attributed to a highly virulent emerging strain of the virus [1, 36].

WN is characterized as an arboviral encephalitis, a designation that refers to its mosquito (arthropod) vector, its viral pathogenic agent, and its encephalitic symptoms. The disease amplifies in a transmission cycle between vector mosquitoes and reservoir-host birds, and is secondarily transmitted to mammals including humans [4, 19, 37]. The North American outbreak has been exceptionally well documented at mosquito, bird, and human levels, making it a prime candidate for mathematical analysis.

We will begin by introducing a minimalist model for WN dynamics to illustrate the processes of model formulation, analysis, and application. We will then revisit the question of model formulation to examine how two major biological assumptions affect the model structure and therefore its predictions.

Next, we will briefly compare these different model structures in an introductory exercise of model parameterization, validation, and comparison. Finally, we will address model applications in more detail with two examples of how the model output can usefully be connected to public health applications.

## 14.3 Minimalist Model

### *14.3.1 The Question*

It is not often we see a dead bird outdoors in an urban setting. If we had lived in New York City in the summer of 1999, however, we would have been astonished by the unusually high number of dead crows, blue jays, and other birds found in backyards and parks. Later that year, we would have learned that the cause of death was a newly introduced disease, West Nile virus, that was carried by mosquitoes and was killing birds and humans [1, 28]. With those initial reports, we might have begun to ask any number of important questions. How would the disease affect bird populations? How infectious would it be in humans? How fast would it spread from New York to other locations? Would it spread to other animals as well? Was it carried by all mosquito species? Did they transmit it in every bite? How could the disease be controlled? Would mosquito spraying help? Would culling the bird population help?

Some of these questions would best be addressed in field and laboratory studies, others with mathematical modeling, and yet others with both approaches. For now, we will focus on the key question of how best to control a WN outbreak, and take advantage of empirical studies to inform and test our mathematical modeling.

### *14.3.2 Model Scope and Scale*

To formulate a WN disease model , we must make some decisions about its scope and scale. Specifically, we need to think about the model's goals and complexity, and about how to represent time, space, population structure, and natural variation.

In terms first of model goals, are we interested in a more strategic model that simplifies the system to its barest essentials, or a more tactical model with comparatively more detail and complexity [29]? Model choice influences the kind of analysis we can conduct: generally speaking, a simpler model will be more amenable to analytical or more general analysis, whereas a more complex model will be restricted to numerical, or more specific case

study analysis. Thus, the strategic approach may provide more qualitative insight into the basic properties of a system, whereas the tactical approach may provide better predictive ability for given species in a given location. Choosing a strategic philosophy is useful at this stage for studying general WN dynamics and control; later we might be interested in a more tactical model of local dynamics in a particular location. Our choice of a strategic or bare bones approach will help inform the remaining decisions about the model scale and scope.

Second, how should we model time and space? Mosquito and bird population dynamics exhibit an annual cycle, so we might consider a discrete-time model with yearly increments. But since we saw a very rapid disease increase in New York City within one summer, it might be interesting to focus on the shorter-term dynamics of a single season. This would allow us to ignore bird vital dynamics, and would require a model mosquito population that reproduces throughout the season. We thus choose a continuous time model that can be formulated as a system of ordinary differential equations (ODEs). For a more detailed discussion of continuous vs. discrete time models of WN virus, see [31]. Since our focal question is not explicitly spatial, we will consider only the changes in populations over time, giving us a nonspatial model. For some spatial approaches to modeling WN, see [30, 32].

Third, how should we represent the mosquito and bird populations? We could treat them in an individual-based framework, in age or stage classes, or as a homogeneous population. In the interests of strategy, we will think of them simply as homogeneous populations of identical individuals that can be represented by a single equation for all ages and stages. (We will revisit this choice in Sect. 14.5.) WN has been reported thus far from ∼60 mosquito species and ∼280 bird species in North America. Again for strategy, we will model only a single generic mosquito and a single generic bird species, acknowledging that this limits our ability to address broader scale ecological questions in WN dynamics (e.g., [14, 17]). Furthermore, since mammals (including humans) appear not to transmit the disease back to the mosquito population, they are considered secondary hosts [4, 19, 24, 37], so the fundamental disease dynamics do not depend on them. Our model will therefore represent only the mosquito and bird populations.

Finally, are we interested in a stochastic model that can capture the natural variation in model parameters such as birth, death, and infection rates? Or are we interested in a more deterministic model that forsakes the vagaries of realism in favour of clearer, but simplified, analytical results? Given our strategic focus, we will develop a deterministic model. (In the interests of interpreting and applying the model output, however, we will examine the effects of stochastic variation on model predictions in Sect.14.4.3.)

### *14.3.3 Model Formulation*

We have now decided to develop a strategic, continuous-time, single-season, nonspatial, non age-structured deterministic model of WN dynamics. With our adjectives thus in place, we can begin to sketch out the model structure.

We have already chosen to use the well-established $S-I$ epidemiological modeling framework, in which bird and mosquito populations will be divided into classes of susceptible and infectious individuals. We thus have four classes representing the densities of susceptible birds ($S_B$), infectious birds ($I_B$), susceptible mosquitoes ($S_M$), and infectious mosquitoes ($I_M$) (Fig. 14.2a). Susceptible birds can become infectious when they are bitten by an infectious mosquito; susceptible mosquitoes can become infectious when they bite an infectious bird. For the bird lifecycle, which is one to two orders of magnitude longer than the single season represented by the model, birth and death rates can reasonably be omitted. The mosquito lifecycle, which has length of order one month, is represented by birth and death rates. Since birds die from WN infection, but mosquitoes do not, we include a disease-death rate for birds. This model (Fig. 14.2a) can be expressed as a system of four ordinary differential equations,

$$\begin{aligned}
\underbrace{\frac{dS_B}{dt}}_{\substack{\text{Susceptible}\\ \text{birds}}} &= - \underbrace{\alpha_B\beta_B\frac{S_B}{N_B}I_M}_{\text{disease transmission}} \\
\underbrace{\frac{dI_B}{dt}}_{\substack{\text{Infectious}\\ \text{birds}}} &= \underbrace{\alpha_B\beta_B\frac{S_B}{N_B}I_M}_{\text{disease transmission}} - \underbrace{\delta_B I_B}_{\substack{\text{death from}\\ \text{disease}}} \\
\underbrace{\frac{dS_M}{dt}}_{\substack{\text{Susceptible}\\ \text{mosquitoes}}} &= \underbrace{b_M N_M}_{\text{birth}} - \underbrace{\alpha_M\beta_B\frac{I_B}{N_B}S_M}_{\text{disease transmission}} - \underbrace{d_M S_M}_{\text{death}} \\
\underbrace{\frac{dI_M}{dt}}_{\substack{\text{Infectious}\\ \text{mosquitoes}}} &= \underbrace{\alpha_M\beta_B\frac{I_B}{N_B}S_M}_{\text{disease transmission}} - \underbrace{d_M I_M}_{\text{death}}
\end{aligned} \tag{14.1}$$

where the total bird population density $N_B = S_B + I_B$ and the total adult female mosquito population density $N_M = S_M + I_M$. At the disease-free equilibrium (DFE), where all individuals are susceptible, the bird and mosquito population densities are denoted $N_B^*$ and $N_M^*$, respectively. We assume that, at the DFE, the mosquito population is constant so the birth and death

rates are balanced and $b_M = d_M$. The model variables and parameters are further defined in Tables 14.1 and 14.2. The disease-transmission dynamics used in this model are known as frequency-dependent. In the Sect. 14.4, we define this term more fully and compare the effects of modeling different transmission dynamics.

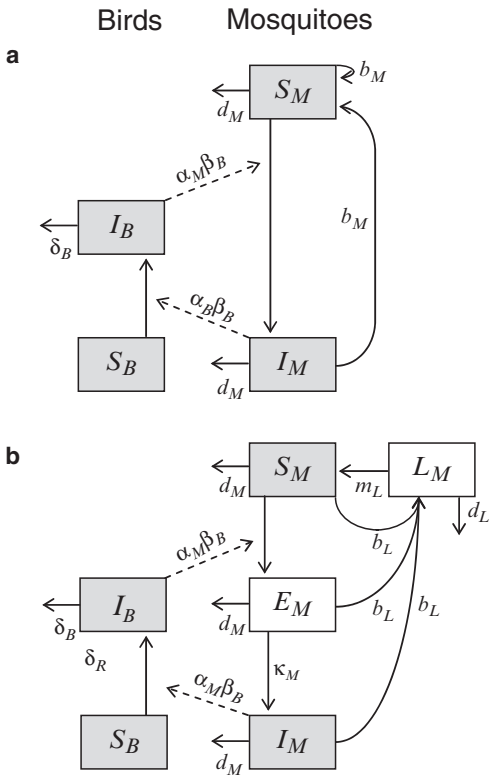


**Fig. 14.2** Conceptual model for West Nile disease dynamics in mosquitoes and birds for (**a**) the minimalist model with only four population classes (14.1) and (**b**) a slightly more biologically complex and realistic model with two added mosquito compartments (14.9). Vital and epidemiological dynamics indicated with solid lines and transmission dynamics with dashed lines. Variables and parameters are defined in Tables 14.1 and 14.2. Adapted from [43] Fig. 1

### *14.3.4 Model Analysis*

One of the most powerful tools developed for analyzing and interpreting epidemic models is the disease basic reproduction number, $\mathcal{R}_0$ [2, 15, 22, 23]. Conceptually, $\mathcal{R}_0$ is defined as the average number of secondary infections caused by the introduction of a typical infective individual into an otherwise entirely susceptible population [2, 22]. Mathematically, $\mathcal{R}_0$ is defined as the spectral radius of the next generation matrix for new infections [13, 42].

The reproduction number serves as an invasion threshold for predicting disease outbreaks and evaluating control strategies. Quantitatively, it has a threshold value of one. When $\mathcal{R}_0 < 1$, the DFE is locally stable and the introduction of a small number of infectious individuals will not lead to a disease outbreak. When $\mathcal{R}_0 > 1$ the DFE is unstable and an outbreak will occur. The analytical expression for $\mathcal{R}_0$ is also very useful, since it indicates which elements of the disease system can be manipulated to reduce the chance of an outbreak.

To obtain $\mathcal{R}_0$ for model (14.1), we follow [42] in using vector notation to rewrite the equations in which infections appears as the difference between $f_j$, the rate of appearance of new infectives in class $j$, and $v_j$, the rate of transfer of individuals into and out of class $j$ by all other processes. New infectives arise in $I_B$ and $I_M$ only, giving

$$\frac{d}{dt}\begin{bmatrix} I_B \\ I_M \end{bmatrix} = f - v = \begin{bmatrix} \alpha_B \beta_B \frac{S_B}{N_B} I_M \\ \alpha_M \beta_B \frac{I_B}{N_B} S_M \end{bmatrix} - \begin{bmatrix} \delta_B I_B \\ d_M I_M \end{bmatrix}. \tag{14.2}$$

The corresponding Jacobian matrices, $F$ and $V$, describe the linearization of this reduced system about the DFE (where $S_M = N_M^*$ and $S_B = N_B^*$),

$$F = \begin{bmatrix} 0 & \alpha_B \beta_B \\ \alpha_M \beta_B \frac{N_M^*}{N_B^*} & 0 \end{bmatrix}, V = \begin{bmatrix} \delta_B & 0 \\ 0 & d_M \end{bmatrix}, \tag{14.3}$$

giving the next generation matrix,

$$FV^{-1} = \begin{bmatrix} 0 & \frac{\alpha_B \beta_B}{d_M} \\ \frac{\alpha_M \beta_B N_M^*}{\delta_B N_B^*} & 0 \end{bmatrix}. \tag{14.4}$$

The spectral radius, or spectral bound, of $FV^{-1}$ is the reproduction number,

$$\mathcal{R}_0 = \underbrace{\sqrt{\frac{\alpha_B \beta_B}{d_M}}}_{\substack{\text{mosquito} \\ \text{to bird}}} \underbrace{\sqrt{\frac{\alpha_M \beta_B N_M^*}{\delta_B N_B^*}}}_{\substack{\text{bird to} \\ \text{mosquito}}}. \tag{14.5}$$

The $\mathcal{R}_0$ expression in (14.5) consists of two elements under the square root sign. The first represents the number of secondary bird infections caused by one infected mosquito. The second represents the number of secondary mosquito infections caused by one infected bird. Taking the square root gives the geometric mean of these two terms, which can be interpreted as $\mathcal{R}_0$ for the addition of an average infectious individual, whether mosquito or bird, to an otherwise susceptible system [41].

### *14.3.5 Model Application*

The minimalist WN model (14.1) is a neat, simple, compact model for the disease dynamics in mosquitoes and birds. What we do not know is if this model is any good at capturing empirically observed WN dynamics. This important question will be addressed in the processes of model parameterization, validation, and comparison, to which we will return in Sect. 14.6. For simplicity of presentation, however, we will first consider how this model – assuming it is a good one – might be applied.

Given our model, what is the best strategy for controlling a WN outbreak? In the expression for $\mathcal{R}_0$ (14.5), we can find the answer. The goal for reducing the chance of a WN outbreak is to reduce $\mathcal{R}_0$, which can be accomplished by reducing the mosquito density at the DFE, $N_M^*$. In contrast, reducing the bird density $N_B^*$ will increase $\mathcal{R}_0$ and therefore increase the chance of outbreak. What is the explanation for this puzzling result? Although it seems counterintuitive at first, we can see that reducing the bird density means the remaining individuals are bitten more often by hungry mosquitoes. In this way, the disease transmission is concentrated through a few highly-bitten birds that are more likely to become infected, and to re-infect the mosquitoes.

By looking more closely at the $\mathcal{R}_0$ expression, we can determine how much control is needed. Here the ratio of mosquitoes to birds at the DFE, $n_m^* = N_M^*/N_B^*$, is the crucial feature. Setting $\mathcal{R}_0$ to its critical value of one and rearranging the expression gives the threshold ratio of mosquito to bird densities,

$$\hat{n}_m^* = d_M \delta_B / \alpha_B \alpha_M \beta_B^2 \tag{14.6}$$

above which an outbreak can occur. Reducing the relative mosquito density below this level will prevent an outbreak. The mechanics of applying this strategy are described in more detail in Sect. 14.7. The structure and control implications of $\mathcal{R}_0$ that we see here follow directly from the assumption in

model (14.1) of frequency-dependence disease transmission. In the next section, we will see how the results differ when different transmission dynamics are assumed.

## 14.4 Biological Assumptions 1: When does the Disease-Transmission Term Matter?

The disease-transmission term in our WN mode represents the contact dynamics between mosquitoes and birds, which depend on the biting rate by a mosquito. The term used to describe the biting rate in an $S-I$ model typically takes one of two forms, frequency dependence or mass action [2, 3, 34].

### *14.4.1 Frequency Dependence*

The commonly used frequency dependent transmission, shown in (14.1), follows [2] in assuming that the mosquito biting rate is saturated, and not limited by bird density. In other words, the biting rate by an individual mosquito is constant across bird densities (Fig. 14.3a), and the biting rate experienced by an individual bird increases with mosquito density (Fig. 14.3b). Under this assumption, the biting rate by a mosquito is taken to be the maximal rate allowed by the gonotrophic cycle, or, the minimum time required between blood meals for a female to produce and lay eggs, or, the maximum possible number of bites per day made by a single mosquito. This biting rate $\beta_B$ has unit time$^{-1}$.

These biological assumptions are captured in the mathematical formulation of frequency dependence, in which the proportional bird densities appear in (14.1). Near the disease-free equilibrium, where both populations are almost entirely susceptible (i.e., $S_M^* = N_M^*$, $S_B^* = N_B^*$, and $I_M$ and $I_B$ are very small) the mosquito-to-bird transmission rate $\beta_B I_M S_B/N_B$ depends only on the biting rate, while the bird-to-mosquito transmission rate $\beta_B S_M I_B/N_B$ depends on the biting rate and also on the ratio of mosquito to bird densities (as well as on the disease transmission probabilities $\alpha_M$ and $\alpha_B$ which for simplicity are not shown here).

### *14.4.2 Mass Action*

Another common disease transmission term is mass action (e.g., [3, 34]). Mass action differs from frequency dependence in assuming that the mosquito

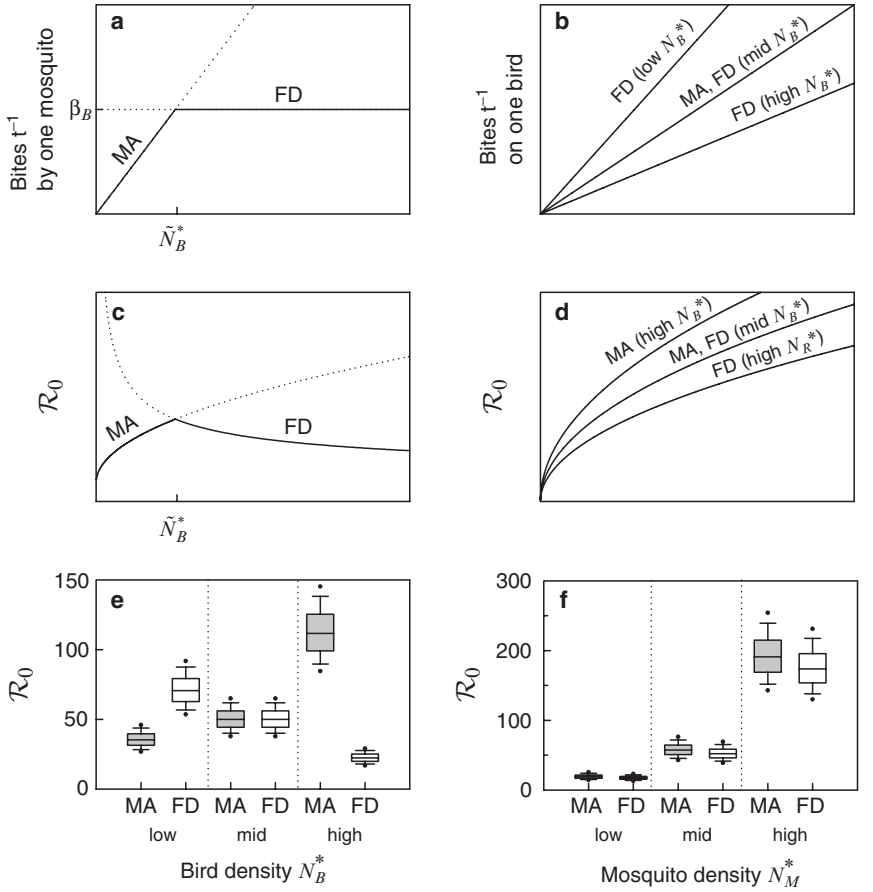


**Fig. 14.3** Different disease-transmission terms in the West Nile model assume different biting rates (**a**–**b**) and lead to qualitatively different reproduction numbers, $\mathcal{R}_0$ (**c**–**d**) with different numerical values (**e**–**f**). Biting rates are shown as (**a**) the number of bites per day by a single mosquito as a function of bird density, and (**b**) the number of bites per day on a single bird as a function of mosquito density, for the two disease-transmission terms, frequency dependence FD and mass action MA. The maximum biting rate $\beta_B$ is reached at the bird density denoted $\tilde{N}_B^*$. The bird densities over which each transmission term applies are indicated by the *solid lines*; using a term at an inappropriate bird density in the *dotted line* regions will give misleadingly high or low $\mathcal{R}_0$ estimates (**a,c**). The reproduction number $\mathcal{R}_0$ is shown as a function of (**c**) bird density and (**d**) mosquito density. At mid bird densities ($N_B^* = \tilde{N}_B^*$), the biting rates (**a,b**) and the $\mathcal{R}_0$ (**c,d**) of MA and FD coincide. At higher bird densities ($N_B^* > \tilde{N}_B^*$), the biting rate (**a,b**) and the $\mathcal{R}_0$ (**c,d**) of FD lie below that of MA, whereas at lower bird densities ($N_B^* < \tilde{N}_B^*$), they lie above ($\mathcal{R}_0$ for this latter scenario not shown in **d**). For numerical $\mathcal{R}_0$ estimates, *vertical dotted lines* separate regions of (**e**) low ($N_B^* < \tilde{N}_B^*$), medium ($N_B^* = \tilde{N}_B^*$), and high ($N_B^* > \tilde{N}_B^*$) bird densities, and (**f**) low, medium, and high mosquito densities. Sample population densities chosen to illustrate these different regions of $\mathcal{R}_0$, expressed as number km$^{-2}$, are (**a**) $N_M^* = 1{,}000$, $\tilde{N}_B^* = 100$, and $N_B^* = 50$ (low), 100 (mid), and 500 (high), and (**b**) $\tilde{N}_B^* = 500$, $N_B^* = 550$, and $N_M^* = 100$ (low), 550 (mid), and 5,500 (high). Parameter values as in Table 14.2. *Boxes* show median and 25th and 75th percentiles, *bars* show 10th and 90th percentiles, and *dots* show 5th and 95th percentiles. Adapted from [43] Fig. 2–3

biting rate is limited by the densities of both mosquitoes and birds (Fig. 14.3a,b). Mass action is a biologically sensible assumption only up to some threshold bird density, denoted $\tilde{N}_B^*$. We can understand this limit by examining the disease transmission terms, which are written as $\beta'_B I_M S_B$ (mosquito to bird) and $\beta'_B S_M I_B$ (bird to mosquito), again omitting the terms $\alpha_M$ and $\alpha_B$ for clarity. The biting parameter $\beta'_B = \beta_B/\tilde{N}_B^*$ has units time$^{-1}$ density$^{-1}$, and can be thought of as the number of bites per day made by a single mosquito, per unit density of birds. Above $\tilde{N}_B^*$, the mosquito biting rate in units bites time$^{-1}$, $\beta'_B N_B^*$, would exceed $\beta_B$, and therefore by definition would exceed the physiological capacity of the mosquito (Fig. 14.3a).

Replacing the frequency-dependence transmission in model (14.1) with mass action transmission gives a different reproduction number, namely

$$\mathcal{R}_0 = \underbrace{\sqrt{\frac{\alpha_B \beta'_B}{d_M}}}_{\substack{\text{mosquito} \\ \text{to bird}}} \underbrace{\sqrt{\frac{\alpha_M \beta'_B N_M^* N_B^*}{\delta_B}}}_{\substack{\text{bird to} \\ \text{mosquito}}}. \tag{14.7}$$

In this case (14.7), $\mathcal{R}_0$ is sensitive not to the ratio, but to the absolute densities of mosquitoes and birds. Thus, the model predicts that reducing either mosquito or bird density will reduce $\mathcal{R}_0$ and reduce the chance of disease outbreak (Fig. 14.3c,d). In terms of the bird population, this prediction is opposite to that of frequency dependence. Setting $\mathcal{R}_0 = 1$ gives the mosquito density threshold for WN outbreak under mass action,

$$\hat{N}_M^* = d_M \delta_B / \alpha_B \alpha_M (\beta'_B)^2 N_B^*. \tag{14.8}$$

When the bird density at the DFE is $N_B^* = \tilde{N}_B^*$, the biting rates under mass action and frequency dependence coincide (Fig. 14.3a–b) and the $\mathcal{R}_0$ values are equal (Fig. 14.3c–d). At lower bird densities where $N_B^* < \tilde{N}_B^*$, the biting rate and $\mathcal{R}_0$ of frequency dependence are artificially high, whereas at higher densities where $N_B^* > \tilde{N}_B^*$, it is those of mass action that are artificially high (Fig. 14.3a,c). This is because the frequency-dependent formulation assumes the maximal mosquito biting rate even when the bird density is very low, and the mass action formulation assumes an impossibly high biting rate when the bird density is very high.

We can see the same dynamics when we examine biting rates and $\mathcal{R}_0$ with respect to mosquito density. As expected, the $\mathcal{R}_0$ curves for both transmission terms coincide when $N_B^* = \tilde{N}_B^*$ (Fig. 14.3d, middle curve). At higher bird densities ($N_B^* > \tilde{N}_B^*$) the curve for frequency dependence is lower, but the curve for mass action is higher because the maximal mosquito biting rate is exceeded (Fig. 14.3d). In the opposite case of $N_B^* < \tilde{N}_B^*$, the relative positions of the two curves are reversed (not shown).

### *14.4.3 Numerical Values of $\mathcal{R}_0$*

The analytical results obtained above illustrate how the choice of disease-transmission term can change $\mathcal{R}_0$, thus altering the model's control implications. Do these alterations translate into significant differences in the numerical estimates of $\mathcal{R}_0$? To address this question, we generated quantitative $\mathcal{R}_0$ estimates that incorporated the underlying variation in the constituent model parameters (Table 14.2, Fig. 14.3e–f). For details of this parameter estimation and resampling see [43]; an introduction to these methods is given in [5]. At low bird density where mass action applies, the $\mathcal{R}_0$ of frequency dependence can be significantly too high (Fig. 14.3e). At the threshold bird density $\tilde{N}_B^*$, where both mass action and frequency dependence apply, the $\mathcal{R}_0$ value is the same. At higher bird density where frequency dependence applies, the $\mathcal{R}_0$ of mass action is significantly too high (Fig. 14.3e). Similar comparisons can be made for low, medium, and high mosquito densities (Fig. 14.3f). These numerical results show that, for these parameter values, a transmission term misapplied at an inappropriate host or mosquito population density can significantly over- or underestimate $\mathcal{R}_0$. For the remainder of the chapter, we will use the model formulation with frequency-dependent transmission terms, as in (14.1).

## 14.5 Biological Assumptions 2: When do Added Model Classes Matter?

The minimalist model (14.1) contains the fewest possible classes for bird and mosquito populations. For mosquitoes in particular, this is a considerable oversimplification of the lifecycle and epidemiology. What is the effect on the model output of incorporating additional biologically realistic classes? We will consider two candidate mosquito classes, and find that one influences $\mathcal{R}_0$ whereas the other does not.

The mosquito lifecycle includes larval and pupal stages, which may represent up to a quarter of the mosquito lifespan. Their inclusion might therefore be expected to slow down the model dynamics. These pre-adult stages can be added to the model as a combined Larval compartment $L_M$, with associated birth rate $b_L$ and maturation rate $m_L$ (Fig. 14.2b).

Empirical studies of infected mosquitoes show that they undergo a viral incubation period during which they are infected, but not infectious. Only when the virus reaches a sufficiently high concentration, and is disseminated out of the gut and into the salivary glands, is the insect capable of transmitting the disease. This incubation period lasts some 7–12 days and can be modeled as an exposed compartment, $E_M$, with associated incubation rate

$\kappa_M$ (Fig. 14.2b). These two compartments can be incorporated into the model's mathematical structure as follows:

$$\begin{aligned}
\underbrace{\frac{dS_B}{dt}}_{\substack{\text{Susceptible}\\ \text{birds}}} &= - \underbrace{\alpha_B \beta_B I_M \frac{S_B}{N_B}}_{\text{disease transmission}} \\
\underbrace{\frac{dI_B}{dt}}_{\substack{\text{Infectious}\\ \text{birds}}} &= \underbrace{\alpha_B \beta_B I_M \frac{S_B}{N_B}}_{\text{disease transmission}} - \underbrace{\delta_B I_B}_{\substack{\text{death from}\\ \text{disease}}} \\
\underbrace{\frac{dL_M}{dt}}_{\substack{\text{Larval}\\ \text{mosquitoes}}} &= \underbrace{b_L \left(S_M + E_M + I_M\right)}_{\text{birth}} - \underbrace{m_L L_M}_{\text{maturation}} - \underbrace{d_L L_M}_{\text{death}} \\
\underbrace{\frac{dS_M}{dt}}_{\substack{\text{Susceptible}\\ \text{mosquitoes}}} &= - \underbrace{\alpha_M \beta_B S_M \frac{I_B}{N_B}}_{\text{disease transmission}} + \underbrace{m_L L_M}_{\text{maturation}} - \underbrace{d_M S_M}_{\text{death}} \\
\underbrace{\frac{dE_M}{dt}}_{\substack{\text{Exposed}\\ \text{mosquitoes}}} &= \underbrace{\alpha_M \beta_B S_M \frac{I_B}{N_B}}_{\text{disease transmission}} - \underbrace{\kappa_M E_M}_{\substack{\text{disease}\\ \text{incubation}}} - \underbrace{d_M E_M}_{\text{death}} \\
\underbrace{\frac{dI_M}{dt}}_{\substack{\text{Infectious}\\ \text{mosquitoes}}} &= \underbrace{\kappa_M E_M}_{\substack{\text{disease}\\ \text{incubation}}} - \underbrace{d_M I_M}_{\text{death}}
\end{aligned} \tag{14.9}$$

where the total female mosquito density $N_M = (L_M + S_M + E_M + I_M)$. For this model, the assumption of a constant mosquito population at the DFE is met by the parameter constraint that $b_L = d_M(m_L + d_L)/m_L$.

Following a similar $\mathcal{R}_0$ analysis as that given above (14.2–14.5), we obtain

$$\mathcal{R}_0 = \sqrt{\frac{\alpha_B \beta_B \phi_M}{d_M} \frac{\alpha_M \beta_B \frac{N_M^*}{N_B^*}}{\delta_M}}, \tag{14.10}$$

where $\phi_M$ is the proportion of exposed mosquitoes surviving the exposed period to become infectious, $\phi_M = \kappa_M / (\kappa_M + d_M)$. As before, setting $\mathcal{R}_0 = 1$ returns the critical relative mosquito density above which the virus will invade a constant population of susceptible individuals,

$$n_m^* = d_M \delta_B / \alpha_B \alpha_M \beta_B^2 \phi_M. \tag{14.11}$$

By inspecting this $\mathcal{R}_0$ expression (14.10), we can see that the added exposed class alters $\mathcal{R}_0$, reducing it by the fraction $\sqrt{\phi_M}$. In contrast, the added larval class does not influence $\mathcal{R}_0$. We can understand this curious result by recalling the definition of $\mathcal{R}_0$, which applies only to the linearized system around the DFE, and is calculated using only the equations for infected individuals. Recall too that $\mathcal{R}_0$ is simply a ratio and has no time scale, so that although adding a larval compartment may delay the system's dynamics (see Sect. 14.6), it does not affect the average number of secondary infections caused by the introduction of an infectious individual into an otherwise susceptible population – the definition of $\mathcal{R}_0$. The following section shows how both the larval and exposed mosquito compartments can influence the model's numerical outbreak simulations.

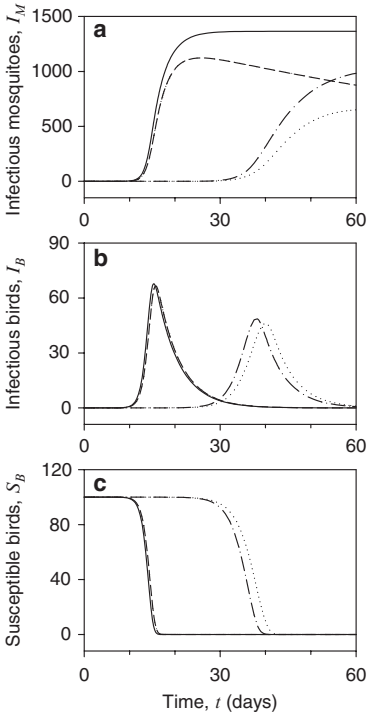


**Fig. 14.4** Numerical model simulations showing the densities of (**a**) infectious mosquitoes, (**b**) infectious birds, and (**c**) susceptible birds over time for the minimalist West Nile virus model (*solid line*) and extensions with a larval mosquito class (*dashed line*), an exposed mosquito class (*dash-dot line*), and both exposed and larval classes (*dotted line*). Simulations run for 60 days with initial susceptible densities $N_M^* = 1{,}500$ and $N_B^* = 100$, and a disease inoculum of $I_M(0) = 0.0001$

## 14.6 Model Parameterization, Validation, and Comparison

In the terms of the scientific method, formulating a model is the formal equivalent of proposing a conceptual hypothesis. Applying a model without testing it (as we did in Sect. 14.3) is like using a hypothesis to make predictions before the hypothesis has been tested. As with hypotheses, evaluating one model is good, but testing and comparing multiple models is even better [7, 25]. The science of model testing – which includes parameterization, validation, and multi-model comparison – is a highly developed statistical enterprise with multiple approaches. One key approach is that of maximum likelihood, which tests the relative abilities of multiple models to fit an independent dataset. This is a widely used and powerful method, but the details are beyond the scope of this chapter and readers are referred to central references such as [7, 25] for further guidance.

Instead, we will take a brief look at how model parameterization can be tackled, and then used for qualitative model comparison. From the two WN models we have formulated, (14.1) and (14.9), we can generate four candidate model structures for this disease: the minimalist model (14.1), two models of intermediate complexity based on model (14.1) with either the larval or the exposed mosquito class added, and the full model with both added classes (14.9). Running numerical solutions can help us compare the predictions of these four models.

Numerical simulation requires first that we obtain parameter values, which can be derived from literature reports of field and laboratory studies (Table 14.2). The more recent studies are readily found through Internet search engines; older studies, which are often gold mines of valuable data, may require a little more legwork and library time. Often, we can find only a mean and range of expected values for our parameters. The mean values give us deterministic model simulations, and the ranges can be used in stochastic simulations to evaluate the effects of natural variation and uncertainty in the estimates (e.g., [43]).

Figure 14.4 shows numerical simulations of all four WN model structures using the mean parameter values in Table 14.2. For a given set of initial conditions, we can predict the densities of infectious mosquitoes, infectious birds, and susceptible birds, over time following the introduction of a small infectious inoculum to an otherwise entirely susceptible population. From these simulations, we can see that the simplest model (14.1) has the fastest dynamics and the earliest outbreak, and the most complex model (14.9) has the slowest and latest (Fig. 14.4). Adding the larval class to model (14.1) makes only the slightest difference in the outbreak timing, but adding the exposed class to model (14.1) makes a substantial difference (Fig. 14.4).

This type of preliminary qualitative model assessment should best be followed by a rigorous quantitative comparison using maximum likelihood or other evaluative techniques to see which model best fits the observed, independent, outbreak data. Some of these methods are discussed for WN models by [43]; more extensive commentary and methodology of model validation and comparison are provided by [7, 25]. For the remaining model analyses in this chapter, we will use the full model with both larval and exposed mosquito classes (14.9).

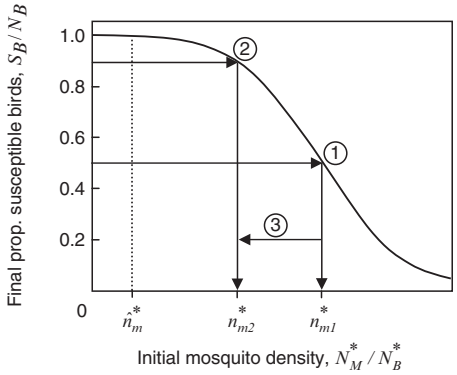


**Fig. 14.5** Connecting the WN model output to disease surveillance and control applications. The *curved line* shows the final proportion of surviving birds at the end of the season as a function of the initial mosquito-to-bird density at the beginning of the season. For a season with observed 50% bird mortality, the initial mosquito density can be inferred (1) For a future season with a target bird survival of 90%, the required initial mosquito density can be inferred in the same way (2) The ratio of these two initial mosquito densities (3) gives the relative reduction in the mosquito population required to obtain the target level of bird mortality. Adapted from [41] Fig. 3a

## 14.7 Model Application #1: WN Control

The model output from (14.9) presents a WN outbreak threshold in terms of the relative densities of mosquitoes and birds at the DFE (14.11). However, this ratio would be extremely difficult to estimate on the ground. Can the model output be better connected to real-life disease management? WN surveillance programs typically track the number of dead birds throughout a season, a datum that can be linked to the initial mosquito-to-bird ratio as follows. By running repeated numerical solutions starting from different initial population densities at the DFE, a relationship can be plotted between the

initial ratio of mosquito to bird densities, $n_m^*$, and the final disease-induced bird mortality at the end of the season (Fig. 14.5). For a given level of mortality observed at the end of the season, the initial value $n_m^*$ can be inferred. For future seasons, a target level of bird loss can be obtained by calculating the required relative reduction in the mosquito population (Fig. 14.5).

## 14.8 Model Application #2: Seasonal Mosquito Population

Our model is restricted to a single temperate North American season, during which we assume the mosquito population density remains constant. More realistically, however, the population will increase in spring and decline in fall (Fig. 14.6a). How will this variation affect the model predictions? There are a number of ways to tackle this question, from the simple to the complex and from the analytical to the numerical. We will take a simpler approach that will give us both analytical results and a useful graphical interpretation (Fig. 14.6).

To pursue this analysis, we will have to put $\mathcal{R}_0$ to one side and introduce a second major model analysis tool, the disease growth rate $\lambda$. Mathematically, $\lambda$ is the maximum real part of the eigenvalues of the ODE system linearized around the DFE. It has the threshold value $\lambda = 0$, above which a disease outbreak will occur and below which it will not. The parameters $\lambda$ and $\mathcal{R}_0$ are related, in that the same threshold mosquito density $\hat{n}_m^*$ corresponds to both $\mathcal{R}_0 = 1$ and $\lambda = 0$. An important difference between the two parameters is that $\mathcal{R}_0$ is a dimensionless ratio with no time scale, whereas $\lambda$ is a rate with unit time$^{-1}$. This feature is an advantage when we want to consider the effects of different mosquito levels over time.

Note that the disease reproduction number $\mathcal{R}_0$ and the disease growth rate $\lambda$ are connected by the disease generation time, $T_g$, the mean time interval between infection of a host individual and the secondary infections it causes, such that $\lambda = \log(\mathcal{R}_0)/T_g$.

Calculation of the disease growth rate is given in the Appendix. Its calculation introduces a slight change of notation that was partially introduced in (14.6) and will prove more convenient for what follows. Specifically, the ratio of the current mosquito density to the initial bird density, $N_M/N_{B^*}$, becomes $n_m$, the ratio at the DFE, $N_{M^*}/N_{B^*}$, becomes $n_m^*$, and the threshold ratio for disease outbreak with a constant mosquito density is $\hat{n}_m^*$.

Based on empirical observations, we will represent mosquito seasonality as a simple step function (Fig. 14.6a), giving the mean relative mosquito density over the season,

$$\bar{n}_m = \left(t_a n_m^a + t_b n_m^b\right) / \left(t_a + t_b\right), \tag{14.12}$$

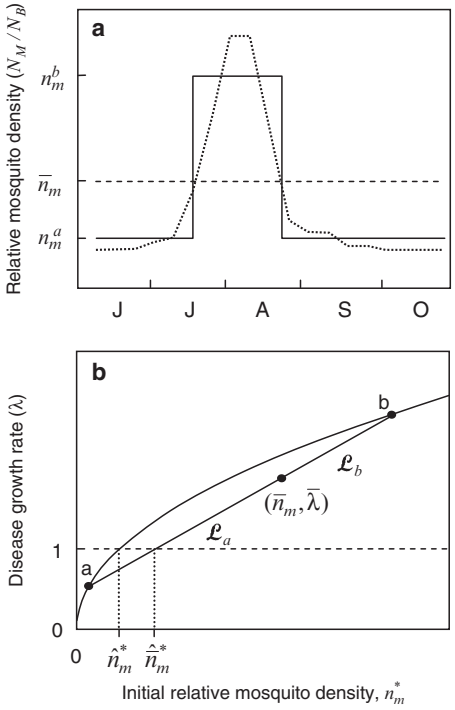


**Fig. 14.6** Applying the WN model to a seasonal mosquito population. (**a**) The observed mosquito population levels (from June to October in Boston, USA; data from [40] Fig. 1 replotted here on a linear scale) shown with the dotted line can be represented crudely as a step function from $n_m^a$ to $n_m^b$ to $n_m^a$ (*solid line*). Multiplying by the time spent at levels $a$ and $b$, periods $t_a$ and $t_b$ respectively, gives the mean mosquito density over the season, $\bar{n}_m$ (*dashed line*). (**b**) For a constant population, the relationship between the disease growth rate $\lambda$ and the initial mosquito density $n_m^*$ is shown with the curved line. WN outbreak occurs when $\lambda > 0$, i.e., when $n_m^* > \hat{n}_m^*$. For variable mosquito density, the linear relationship between the average growth rate $\bar{\lambda}$ and the average initial disease-free mosquito density $\bar{n}_m^*$ is given by the straight line $L = L_a + L_b$ that connects points a $(n_m^a,\lambda_a)$ and b $(n_m^b,\lambda_b)$. A WN outbreak occurs when $\bar{\lambda} > 0$, i.e., when $\bar{n}_m^* > \hat{\bar{n}}_m^*$. For a given season, the point $(\bar{n}_m^*, \bar{\lambda})$ may be calculated from (14.12)–(14.13), or may be obtained graphically as the point along $L$ where the ratio between line segments $L_a{:}L_b = t_a{:}t_b$. As long as the lower population density $n_m^a < \hat{n}_m^*$, the threshold mosquito density for disease outbreak will be higher for a seasonal than for a constant mosquito density. Adapted from [41] Fig. 3b–c

where $t_a$ and $t_b$ refer to the total time spent at population levels $n_m^a$ and $n_m^b$, respectively (Fig. 14.6a). The mean disease growth rate is then given by

$$\bar{\lambda} = (t_a\lambda_a + t_b\lambda_b) / (t_a + t_b), \tag{14.13}$$

where $\lambda_a$ and $\lambda_b$ are the largest eigenvalues of the Jacobian matrix $J$ evaluated at $n_m^a$ and $n_m^b$, respectively (Fig. 14.6b; see Appendix for details). This gives a mean geometric growth rate for infective mosquitoes over the season of $e^{\bar{\lambda}(t_a+t_b)} = e^{\lambda_a t_a} e^{\lambda_b t_b}$. Setting $\bar{\lambda} = 0$ in (14.11) gives the critical average mosquito level, $\hat{\bar{n}}_m^* > \hat{n}_m^*$, above which WN can invade a seasonally variable population and below which it cannot (Fig. 14.6b). Provided the lower of the two mosquito population levels, $n_m^a$, is below the threshold $\hat{n}_m^*$, disease-outbreak control requires only that the higher level, $n_m^b$, be reduced such that the average mosquito density $\bar{n}_m^* < \hat{\bar{n}}_m^*$. We therefore expect WN virus to be easier to control in more seasonal northern regions than in warmer southern regions where the population remains constant above $\hat{n}_m^*$ year-round.

## 14.9 Summary

In its simplest form, a model can be thought of as a "black box" which takes inputs, such as parameters and initial conditions, and produces outputs, such as disease thresholds, or outbreak levels over time. The conversion from inputs to outputs requires underlying hypotheses about the dynamical relationships between components. These hypotheses are then translated into equations, whose subsequent analysis and simulation yield the model outputs.

As mathematicians we often focus on the details of the black box, fixing the set of model equations, and deriving sophisticated methods for determining the model outputs. This chapter suggests an alternative and complementary activity: analysis of the role of inputs (parameters) and hypotheses (formalized into model structure) in determining the model outputs. Such analyses employ a suite of different models, with uncertain parameters and variable structure. The effects of the parameter uncertainty and model structure on the model outputs (such as predictions of $\mathcal{R}_0$) are then deduced.

We believe that this kind of comparative analysis approach is key for scientists wishing to interface biology with mathematical models, particularly in the area of epidemiology. The goal of this chapter is to demonstrate both the methods and the usefulness of the comparative analysis approach.

Our series of models describes the cross-infection of West Nile virus between birds and mosquitoes. The primary mathematical tool is the basic reproduction number $\mathcal{R}_0$, which is derived from mathematical epidemiology as the spectral radius of the next generation operator [42]. We calculate how $\mathcal{R}_0$ changes with differences in the disease transmission term (frequency

dependence versus mass action, Sect. 14.4), with additional model classes (larval and exposed mosquito classes, Sect. 14.5) and with uncertain and variable parameters (Sect. 14.6). Finally, we make two applications of the model, one to WN virus control (Sect. 14.7) and one to outbreaks in seasonal environments (Sect. 14.8).

The calculation of $\mathcal{R}_0$ for the frequency-dependent and mass-action transmission term models shows a striking dependence of the model predictions on model structure. Although both transmission term models have a sound theoretical basis, they yield starkly contrasting predictions as to the effect of bird density on WN virus. When bird densities are low, the frequency-dependent model predicts remaining birds receive more bites and become local hot spots for disease transmission, with each bird having a high probability of becoming infected and passing on the virus. By way of contrast, the mass-action model predicts the disease will die out in regions of low bird density. Thus, while the mass-action model predicts that bird control would be effective in controlling WN, the frequency-dependent model predicts that it would be counterproductive (see [31] for further discussion).

The calculation of $\mathcal{R}_0$ for models with larval and exposed mosquito classes shows how the added complexity of a more realistic model does not always translate into refined model predictions. Here an additional larval class has no effect on the basic reproduction number, and hence on whether an outbreak will occur. Interestingly, the additional larval class does actually change the time-dependent dynamics if an outbreak actually occurs (Fig. 14.4). By way of contrast, the additional exposed class means that some infected mosquitoes may be removed before ever making it to the infective state. As our intuition would lead us to believe, this yields a reduced $\mathcal{R}_0$.

Our experience shows that parameterization of epidemiological models is a substantial task, requiring great familiarity with the biological literature. For example, the parameters shown in Fig. 14.2 (taken from [43]) originally came from 25 different sources, each of which had to be carefully read before the parameter could be extracted. However, as shown in Fig. 14.3, careful model parameterization allows us to incorporate the uncertainty of parameter values into ranges of predictions for $\mathcal{R}_0$, following the methods of [5]. In the case of WN virus models, variation in $\mathcal{R}_0$ arising from model structure was larger than variation arising from parameter uncertainty.

Finally, once a model is tested, via parameterization, validation and multimodel comparison, it is possible to make applications to different epidemiological scenarios. How can a disease be controlled? How is control managed in a seasonal mosquito population? These applications sometime require model extensions (Fig. 14.6) and unique perspective on model outputs (Fig. 14.5). However, it is the applications that allow us to move the science forward and, more often than not, the applications also lead to a new generation of models that promise to keep mathematicians employed for considerable time to come.

## References


1. Anderson J., Andreadis T.G., Vossbrink C., Tirrell S., Wakem E., French R., Germendia A. & Van Kruiningen H. (1999) Isolation of West Nile virus from mosquitoes, crows, and a Cooper's hawk in Connecticut. *Science*, 286, 2331–2333.
2. Anderson R.M. & May (1991) *Infectious Diseases of Humans*. Oxford University Press, Oxford.
3. Begon M., Bennett M., Bowers R.G., French N.P., Hazel S.M. & Turner J. (2002) A clarification of transmission terms in host-microparasite models: numbers, densities and areas. *Epidemiology and Infection*, 129, 147–153.
4. Bernard K.A., Maffei J.G., Jones S.A., Kauffman E.B., Ebel G.D., Dupuis A.P., Jr, Ngo K.A., Nicholas D.C., Young D.M., Shi P.-Y., Kulasekera V.L., Eidson M., White D.J., Stone W.B., Team N.S.W.N.V.S. & Kramer L.D. (2001) West Nile virus infection in birds and mosquitoes, New York State, 2000. *Emerging Infectious Diseases*, 7, 679–685.
5. Blower S.M. & Dowlatabadi H. (1994) Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example. *International Statistical Review*, 62, 229–243.
6. Brauer F. & Castillo-Chavez C. (2001) *Mathematical Models in Population Biology and Epidemiology*. Springer, Berlin Heidelberg New York.
7. Burnham K.P. & Anderson D. (2002) *Model Selection and Multi-model Inference*. Springer, Berlin Heidelberg New York.
8. Case T.J. (1999) *An Illustrated Guide to Theoretical Ecology*. Oxford University Press, Oxford.
9. Castillo-Chavez C., with Blower S., van den Driessche P., Kirschner D. & Yakubu A.-A. (2002) *Mathematical Approaches for Emerging and Reemerging Infectious Diseases: An Introduction*. Springer, Berlin Heidelberg New York.
10. Chomel B.B. (2003) Control and prevention of emerging zoonoses. *Journal of Veterinary Medical Education*, 30, 145–147.
11. Daszak P. (2000) Emerging infectious diseases of wildlife - threats to biodiversity and human health. *Science*, 287, 1756–1756.
12. Diekmann O. & Heesterbeek H. (2000) *Mathematical Epidemiology of Infectious Diseases*. Wiley, New York.
13. Diekmann O., Heesterbeek J.A.P. & Metz J.A.J. (1990) On the Definition and the Computation of the Basic Reproduction Ratio $\mathcal{R}_0$ in Models for Infectious-Diseases in Heterogeneous Populations. *Journal of Mathematical Biology*, 28, 365–382.
14. Dobson A. (2004) Population dynamics of pathogens with multiple host species. *American Naturalist*, 164, S64–S78.
15. Dobson A. & Foufopoulos J. (2001) Emerging infectious pathogens of wildlife. *Philosophical Transactions of the Royal Society of London Series B*, 356, 1001–1012.
16. Enserink M. (2004) Emerging infectious diseases - a global fire brigade responds to disease outbreaks. *Science*, 303, 1605–1606.
17. Ezenwa V.O., Godsey M.S., King R.J. & Guptill S.C. (2006) Avian diversity and West Nile virus: testing associations between biodiversity and infectious disease risk. *Proceedings of the Royal Society of London Series B*, 273, 109–117.
18. Gubler D.J. (2002) The global emergence/resurgence of arboviral diseases as public health problems. *Archives of Medical Research*, 33, 330–342.
19. Gubler D.J., Campbell G.L., Nasci R., Komar N., Petersen L. & Roehrig J.T. (2000) West Nile virus in the United States: guidelines for detection, prevention, and control. *Viral Immunology*, 13, 469–475.
20. Haefner J. (1996) *Modeling Biological Systems: Principles and Applications*. Chapman & Hall, New York.
21. Hayes C.G. (1988) West Nile fever. In: Monath TP (ed.) *The Arboviruses: Epidemiology and Ecology V. 5* , CRC Press, Boca Raton, FL, pp. 59–88.

22. Heesterbeek H. (2002) A brief history of $\mathcal{R}_0$ and a recipe for its calculation. *Acta Biotheoretica*, 50, 189–204.
23. Hethcote H.W. (2000) The mathematics of infectious diseases. *SIAM Review*, 42, 599–653.
24. Higgs S., Schneider B.S., Vanlandingham D.L., Klingler K.A. & Gould E.A. (2005) Nonviremic transmission of West Nile virus. *Proceedings of the National Academy of Sciences of the United States of America*, 102, 8871–8874.
25. Hilborn R. & Mangel M. (1997) *The Ecological Detective: Confronting Models with Data*. Princeton University Press, Princeton, NJ.
26. Kermack W. & McKendrick A. (1927) A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society of London Series A*, 115, 700–721.
27. Kot M. (2001) *Elements of Mathematical Ecology*. Cambridge University Press, Cambridge.
28. Lanciotti R., Roehrig J., Deubel V., Smith J., Parker M., Steele K., Crise B., Volpe K., Crabtree M., Scherret J., Hall R., MacKenzie J., Cropp C., Panigrahy B., Ostlund E., Schmitt B., Malkinson M., Banet C., Weissman J., Komar N., Savage H., Stone W., McNamara T. & Gubler D. (1999) Origin of the West Nile virus responsible for an outbreak of encephalitis in the Northeastern United States. *Science*, 286, 2333–2337.
29. Levins D. (1968) *Evolution in a Changing Environment*. Princeton University Press, Princeton.
30. Lewis M.A., Rencławowicz J. & van den Driessche P. (2006a) Traveling waves and spread rates for a West Nile virus model. *Bulletin of Mathematical Biology*, 68, 3–23.
31. Lewis M.A., Rencławowicz J., van den Driessche P. & Wonham M.J. (2006b) A comparison of continuous and discrete time West Nile virus models. *Bulletin of Mathematical Biology*, 68, 491–509.
32. Liu R., Shuai J., Wu J. & Zhu H. (2006) Modeling spatial spread of West Nile virus and impact of directional dispersal of birds. *Mathematical Biosciences and Engineering*, 3, 145–160.
33. Macdonald G. (1957) *The Epidemiology and Control of Malaria*. Oxford University Press, Oxford.
34. McCallum H., Barlow N. & Hone J. (2001) How should pathogen transmission be modelled? *Trends in Ecology & Evolution*, 16, 295–300.
35. Murray J. (2002) *Mathematical Biology I: An Introduction, 3rd ed.* Springer, Berlin Heidelberg New York.
36. Petersen L.R. & Roehrig J.T. (2001) West Nile virus: a reemerging global pathogen. *Emerging Infectious Diseases*, 7, 611–614.
37. Peterson A.T., Komar N., Komar O., Navarro-Siguenza A., Robbins M.B. & Martinez-Meyer E. (2004) West Nile virus in the New World: potential impacts on bird species. *Bird Conservation International*, 14, 215–232.
38. Rappole J., Derrickson S.R. & Hubalek Z. (2000) Migratory birds and spread of West Nile virus in the Western hemisphere. *Emerging Infectious Diseases*, 6, 1–16.
39. Ross R. (1911) *The Prevention of Malaria*. Murray, London.
40. Spielman A. (2001) Structure and seasonality of Nearctic *Culex pipiens* populations. *Annals of the New York Academy of Sciences*, 951, 220–234.
41. van den Driessche P. & Watmough J. (2002) Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, 180, 29–48.
42. Wonham M.J., de-Camino-Beck T. & Lewis M.A. (2004) An epidemiological model for West Nile virus: invasion analysis and control applications. *Proceedings of the Royal Society of London Series B*, 271, 501–507.
43. Wonham M.J., Lewis M.A., Rencawowicz J. & van den Driessche P. (2006) Transmission assumptions generate conflicting predictions in host-vector disease models: a case study in West Nile virus. *Ecology Letters*, 9, 706–725.

## Appendix

We include this appendix to illustrate a different approach to calculating the disease growth rate, $\lambda$, for the full West Nile model (14.9). Although this exercise is somewhat redundant with the earlier $\mathcal{R}_0$ calculations, it provides an alternative and pedagogically useful perspective.

We use linear analysis to calculate the disease growth rate for the two-level mosquito population shown in Fig. 14.6a. To simplify the ODE system (14.9), we non-dimensionalise by scaling time $t$ with the quantity $1/\kappa$ by setting $\tau = \kappa t$, scaling all parameters to $\kappa$, and scaling the bird and mosquito densities by the initial bird density $N_B^*$. In the resulting dimensionless system (14.14), the two bird compartments $s_b$ and $i_b$ indicate the fraction of the initial bird density in susceptible and infected classes, with the total live bird density $0 \leq n_b = (s_b + i_b) \leq 1$. The four mosquito compartments $l_m$, $s_m$, $e_m$, and $i_m$, represent larval, susceptible, exposed, and infected females scaled to the initial bird density, with the total female mosquito population density $0 \leq n_m = (l_m + s_m + e_m + i_m)$. The rescaled system is:

$$\begin{aligned}
\tfrac{ds_b}{d\tau} &= -\alpha_b \beta_b i_m \tfrac{s_b}{n_b} \\
\tfrac{di_b}{d\tau} &= \alpha_b \beta_b i_m \tfrac{s_b}{n_b} - \delta_b i_b
\end{aligned}$$

$$\begin{aligned}
\tfrac{dl_m}{d\tau} &= b_l\,(s_m + e_m + i_m) - m_l l_m - d_l l_m \\
\tfrac{ds_m}{d\tau} &= -\alpha_m \beta_b s_m \tfrac{i_b}{n_b} + m_l l_m - d_m s_m \\
\tfrac{de_m}{d\tau} &= \alpha_m \beta_b s_m \tfrac{i_b}{n_b} - e_m - d_m e_m \\
\tfrac{di_m}{d\tau} &= e_m - d_m i_m
\end{aligned} \tag{14.14}$$

where the subscripts $b$ and $m$ indicate the dimensionless versions of the dimensional variables and parameters defined in Tables 14.1 and 14.2. As in the dimensional system, we ensure a constant mosquito population density by setting $b_l = d_m(m_l + d_l)/m_l$.

For the DFE for this system, $(s_b, i_b, l_m, s_m, e_m, i_m) = (1, 0, b_l n_m^*/(m_l + d_l), n_m^*, 0, 0)$, we define small perturbations in each variable, $(\tilde{s}_b, \tilde{i}_b, \tilde{l}_m, \tilde{s}_m, \tilde{e}_m, \tilde{i}_m)$. The corresponding Jacobian matrix, $J$, describes the linearization with respect to $(\tilde{i}_b, \tilde{l}_m, \tilde{s}_m, \tilde{e}_m, \tilde{i}_m)$:

$$J = \begin{bmatrix}
-\delta_b & 0 & 0 & 0 & \alpha_b\beta_b \\
0 & -m_l - d_l & b_l & b_l & b_l \\
-\alpha_m\beta_b n_m^* & m_l & -d_m & 0 & 0 \\
\alpha_m\beta_b n_m^* & 0 & 0 & -d_m - 1 & 0 \\
0 & 0 & 0 & 1 & -d_m
\end{bmatrix}. \tag{14.15}$$

(The term $\tilde{s}_b$ is not included because it decouples from the rest of the system; in other words, the $6 \times 6$ matrix that includes $\tilde{s}_b$ has an entire column of zeroes.) This yields the characteristic polynomial in $\lambda$:

$$0 = Det(J - \lambda I) = \lambda \left( \lambda + d_m + \frac{m_l b_l}{d_m} \right) (\lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3), \quad (14.16)$$

where $I$ is the $5 \times 5$ identity matrix and $a_1 > 0$, $a_2 > 0$. The zero root of the 5th order polynomial comes from the steady-state condition $b_l = d_m(m_l + d_l)/m_l$ that means the disease-free mosquito population is constant. For $a_3 > 0$, and $a_1 a_2 > a_3$, by the Roth–Hurwitz conditions, all roots of the cubic polynomial in $\lambda$ have negative real parts. Some algebra shows that $a_1 a_2 > a_3$, since

$$\begin{aligned} a_1 &= 1 + \delta_b + 2d_m \\ a_2 &= d_m^2 + 2\delta_b d_m + \delta_b + d_m \\ a_3 &= \delta_b d_m^2 - \alpha_b \alpha_m \beta_b^2 n_m^* + \delta_b d_m \end{aligned} \quad . \quad (14.17)$$

The disease outbreak threshold is thus when $a_3 = 0$ or equivalently, when zero is the largest eigenvalue of $J$. In biological terms this threshold may be thought of as a disease growth rate of zero, which corresponds directly to the reproduction number threshold, $\mathcal{R}_0 = 1$.

**Table 14.1** Variables for West Nile virus model. Subscripts $M$ and $m$ refer to mosquitoes and $B$ and $b$ to birds; capital letters refer to dimensional forms and lower case to nondimensional forms, which are rescaled to $N_B^*$. Dashes indicate term not used

| Meaning | Dimensional | Dimensionless |
|---|---|---|
| Mosquitoes | | |
| Larval female mosquito density | $L_M$ | $l_m$ |
| Susceptible adult female mosquito density | $S_M$ | $s_m$ |
| Exposed adult female mosquito density | $E_M$ | $e_m$ |
| Infectious adult female mosquito density | $I_M$ | $i_m$ |
| Total female mosquito density, $N_M = L_M + S_M + E_M + I_M$ | $N_M$ | $n_m$ |
| Total female mosquito density at the disease-free equilibrium | $N_M^*$ | $n_m^*$ |
| Threshold mosquito density for disease outbreak, given constant population | $\hat{N}_M^*$ | $\hat{n}_m^*$ |
| Average mosquito density across a season, given variable population | – | $\bar{n}_m$ |
| Average mosquito density at the disease-free equilibrium | – | $\bar{n}_m^*$ |
| Threshold average mosquito density for disease outbreak, given variable population | – | $\hat{\bar{n}}_m^*$ |
| Birds | | |
| Susceptible bird density | $S_B$ | $s_b$ |
| Infectious bird density | $I_B$ | $i_b$ |
| Total bird density $N_B = S_B + I_B$ | $N_B$ | $n_b$ |
| Bird density at which frequency dependent and mass action disease-transmission terms coincide, giving identical mosquito biting rates | $\tilde{N}_B$ | – |
| Total bird density at the disease-free equilibrium | $N_B^*$ | 1 |

**Table 14.2** Parameters and estimated values for the West Nile virus models. Subscripts $M$ and $m$ refer to mosquitoes (parameterized primarily for *Culex pipiens* spp.), and $B$ and $b$ to birds (parameterized primarily for American crows, *Corvus brachyrhynchos*). Capital-letter subscripts refer to dimensional parameters and lower-case letters to dimensionless forms; numerical estimates given for dimensional forms only. All rates are *per capita* per day. For details and sources of parameter estimates, see [43] Tables 2–3 and sources therein. Dashes indicate term not used in numerical calculations

| Meaning | Dimensional | Dimensionless | Mean | Range |
|---|---|---|---|---|
| Mosquitoes | | | | |
| Birth rate for model with no larval class | $b_M = d_M$ | $b_m$ | – | – |
| Birth rate for model with larval class | $b_L = d_M(m_L + d_L)/m_L$ | $b_l$ | – | – |
| Natural death rate, adults | $d_M$ | $d_m$ | 0.03 | 0.02–0.07 |
| Natural death rate, larvae | $d_L$ | $d_l$ | 0.02 | 0.01–0.06 |
| Maturation rate | $m_L$ | $m_l$ | 0.07 | 0.05–0.09 |
| Biting rate under frequency-dependence | $\beta_B$ | $\beta_b$ | 0.44 | 0.34–0.53 |
| Biting parameter under mass action | $\beta'_B = \beta_B \tilde{N}_B^*$ | – | – | – |
| Probability of virus transmission to mosquito, per infectious bite | $\alpha_M$ | $\alpha_m$ | 0.69 | 0.23–1.00 |
| Virus incubation rate | $\kappa_M$ | $\kappa_m$ | 0.10 | 0.09–0.12 |
| Proportion surviving viral incubation period | $\phi_M = \kappa_M/(d_M + \kappa_M)$ | $\phi_m$ | – | – |
| Birds | | | | |
| Probability of virus transmission to bird, per infectious bite | $\alpha_B$ | $\alpha_b$ | 0.74 | 0.27–1.00 |
| Death rate from virus | $\delta_B$ | $\delta_b$ | 0.20 | 0.17–0.25 |