NATURAL RESOURCE MODELING
Volume 25, Number 1, February 2012

MATHEMATICAL MODELING OF VIRAL ZOONOSES IN WILDLIFE

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ABSTRACT. Zoonoses are a worldwide public health concern, accounting for approximately 75% of human infectious diseases. In addition, zoonoses adversely affect agricultural production and wildlife. We review some mathematical models developed for the study of viral zoonoses in wildlife and identify areas where further modeling efforts are needed.

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Accepted 17th June 2011.

1. Introduction. Recently emergent and re-emergent infectious diseases pose a worldwide public health concern. Taylor et al. [2001] estimated that 75% of human infectious diseases originate from an animal reservoir, many caused by viruses. Human diseases originating from a nonhuman animal reservoir are referred to as zoonoses. Some recent emerging and re-emerging viral zoonoses include human immunodeficiency virus (HIV), Ebola virus, SARS coronavirus, rabies virus, avian influenza viruses (AIV), Nipah virus, Hendra virus, hantaviruses, and West Nile virus. The two strains of HIV, HIV-1, and HIV-2, evolved from two simian immunodeficiency viruses (SIV) carried by the chimpanzee and Sooty mangabey, respectively (Bengis et al. [2004]). Outbreaks of Ebola virus in humans have been associated with disease in chimpanzees, and the 2003 SARS outbreak originated from the masked palm civet (Bengis et al. [2004]). The source of Nipah and Hendra viral outbreaks have been traced to bats, whereas hantaviruses are carried by wild rodents, primarily rats and mice (Bengis et al. [2004]), and West Nile virus and avian influenza viruses are bird-borne pathogens.

Pathogens of wildlife spill over into humans, into domestic animals and into wild animals. Zoonoses have a negative impact on human health, agricultural production, and wildlife conservation (Chomel et al. [2007]). In this review, we concentrate on mathematical modeling techniques that have been applied to the study of viral pathogens in wildlife with a potential spill over to humans (see Figure 1). Some of the risk factors associated with the emergence of zoonotic diseases and spill over into humans include human encroachment, population expansion, wildlife trade and translocation, consumption of exotic food, migratory movements, and ecotourism (Daszak et al. [2000], Wolfe et al. [2005], Chomel et al. [2007]).

To prevent and control the spread of a zoonotic pathogen, it is essential to understand the mechanisms that lead to the persistence of a pathogen in its animal reservoir, the spread of a pathogen from an animal reservoir to humans (i.e., host-jumping) and the evolution of new diseases. Mathematical models of infectious diseases in wildlife have been used to increase our understanding of these mechanisms and to test hypotheses about effective methods for prevention and control of infectious diseases in wildlife and humans. The collection of work in the books edited by Grenfell and Dobson [1995] and Hudson et al. [2002] summarizes some of these modeling efforts. Our goals are to provide

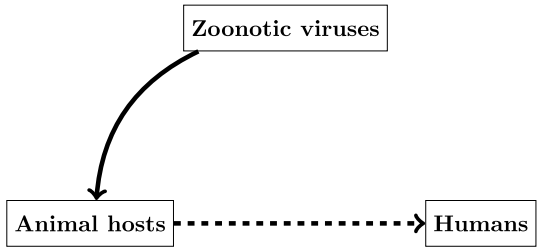

FIGURE 1. Zoonotic viruses infect animal hosts and spill over into humans.

a review of some of the mathematical modeling frameworks developed for the study of viral zoonoses in wildlife and to provide references for more detailed analyses. A recent survey of 442 modeling studies of zoonotic pathogens by Lloyd-Smith et al. [2009] found few dynamical models that account for multi-host pathogens, multiple pathogens, within-host pathogen dynamics in zoonotic transmission and pathogen evolution. In this review, we highlight these gaps and others in the modeling process that need to be filled to address important questions about viral zoonoses in wildlife. We examine some of the factors governing viral maintenance and transmission in the primary animal reservoir, how these factors have been accounted for in mathematical models and where additional modeling efforts are needed.

2. Maintenance and transmission in reservoir populations. Four stages of infection are identified from initiation to maintenance and transmission of a viral pathogen in a reservoir host: (1) contact or exposure, (2) cellular entry, (3) viral replication, assembly and release, and (4) transmission (see Figure 2). When the disease is maintained in the reservoir population, the stages are cyclic (1) $\rightarrow$ (2) $\rightarrow$ (3) $\rightarrow$ (4) $\rightarrow$ (1). A viral infection begins with contact or exposure of an animal host with a particular pathogen. At the first stage, environmental conditions including climate, seasonality, anthropogenic disturbances, landscape, and resources (i.e., habitat, food, water) may individually or collectively determine whether there is contact between host and pathogen (Altizer et al. [2006], Previtali et al. [2010]). In addition, the host's intrinsic characteristics, its population and social structure, mobility, behavior, and susceptibility may modulate the extent of its exposure. In the second stage, the within-host and cellular level, the virus must

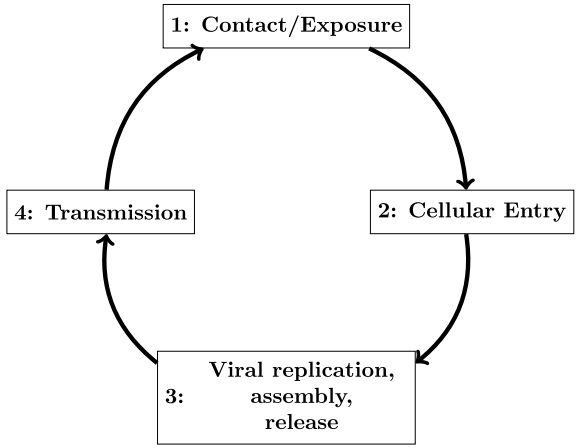

FIGURE 2. Four stages that lead to disease transmission and maintenance in an animal reservoir.

overcome physical barriers of the host, and must be compatible with cell receptors to gain entry into a target cell. After viral entry, the third stage, viral replication depends on host and viral genetics as well as host factors, such as the immune response, prior exposure, nutritional status, co-infection, age, sex, and reproductive status. Establishment of an infection in one host does not necessarily mean transmission to another host, as it may be a dead-end host. Transmission, the fourth stage of infection, depends on viral load, mode of viral shedding, host factors, and the community intra- and inter-host ecological interactions. These latter interactions are also affected by the spatial environment and anthropogenic factors.

Various modeling approaches are discussed in this review that have been applied to the study of maintenance and transmission of viral zoonoses among reservoir populations. Mathematical models and techniques developed for spread of disease in humans often apply to wildlife populations but there are key differences. For example, the wildlife reservoir has adapted to the specific viral infection while this is not the case for humans. In addition, environmental effects and anthropogenic disturbances have a much greater impact on diseases in wildlife than in humans. Mathematical models developed for diseases of wildlife often

concentrate on the population level, omitting steps (2) and (3) (Grenfell and Dobson [1995], Hudson et al. [2002]). Preventive and control measures (e.g., vaccination or culling) are often studied in terms of stages (1) and (4), whereas the effectiveness of treatment strategies (e.g., drug treatment) are studied within stages (2) and (3). In Section 3, we summarize some of the mathematical modeling efforts for stages (1) and (4), and models for stages (2) and (3) in Section 4.

Although the within-host and population dynamics are often modeled separately, host-pathogen interactions at the within-host level can influence the dynamics of the system at the population level in a number of ways. The pathogen may alter the host by changing its reproductive, movement or social behavior (Murray et al. [1986], Murray and Seward [1992], Klein et al. [2004], van Gils et al. [2007]). A pathogen may shorten the host lifespan, e.g., H5N1 influenza virus in chickens (Chen et al. [2006]). A better understanding of the behavior of the pathogen within-host will lead to better models and more accurate parameterization for host-pathogen interactions on a population or evolutionary level (Mideo et al. [2008]). For instance, knowledge of within-host biology tells us if we need to address time since infection or changes in immunity, persistently infectious individuals versus short-term infection resulting in recovery and possibly immunity. Host biology may tell us that infectivity is age-dependent or that infection alters behavior, e.g., hantavirus infection in male rodents increases aggression (Klein et al. [2004]), rabies infection in foxes increases erratic movement (Murray and Seward [1992], Murray et al. [1986]), low pathogenic avian influenza infection in swans delays migration (van Gils et al. [2007]). Host or pathogen biology may differ in space or time (seasonality) and the environment may play a significant role in the contact process, especially in an animal reservoir, e.g., spatial overlap of habitats leading to spill over of hantavirus infection in rodents (Allen et al. [2009]). Multiple hosts may amplify or dilute the pathogen effects or multiple pathogen co-infection may decrease the effectiveness of the immune response. That is, increased biodiversity in bird species reduces spillover of West Nile virus in humans (Swaddle and Calos [2008]), reduced species diversity increases infection prevalence of Sin Nombre virus in deer mice (Dizney and Ruedas [2009]), micro- and macro-parasitic co-infection induces antagonistic immune responses (Fenton et al. [2008]). In summary, the within-host biology leads to a

particular choice of model at the population level, such as an SI model with susceptible and infectious stages or an SIR model with susceptible, infectious, recovered and immune stages. Alternately, an SI_1I_2 model with susceptible and two infectious stages could be applied if the infection modifies the behavior of some individuals, such as those in infectious stage 2 but not stage 1. These types of models are discussed in more detail in the following sections.

A variety of models have been applied to wildlife diseases, including mathematical and statistical models. We restrict this review to viral zoonoses and to mathematical models, that are either deterministic or stochastic. In Sections 3 and 4, models that have been developed at the population level and cellular level, respectively, are summarized.

3. Contact/exposure and transmission. Contact with an infectious host is the first event in a chain that leads to transmission in a wildlife population. The contact or exposure of a host to a pathogen is often built on the premise of homogenous mixing in epidemiological models. The most common epidemiological models are SIR models, which are the basis for many population-based disease models (e.g., Anderson and May [1992], Grenfell and Dobson [1995], Hethcote [2000], Hudson et al. [2002], Brauer et al. [2008], Keeling and Rohani [2008]). For wildlife populations, births and deaths, sex-specific behavior, and sickness-related behavior may affect exposure or transmission success. Spatial structure of the population accounts for contacts that may depend on spatial proximity or habitat heterogeneity. Environmental variability and anthropogenic disturbances are also important factors affecting successful transmission. Interactions within and between different species may lead to an amplification or a dilution effect, resulting in either spatial expansion or contraction of the disease (Schmidt and Ostfeld [2001], Keesing et al. [2006, 2010]).

3.1. Basic epizootic model. The basic epizootic model is known as an SIR model. The flow diagram of an SIR model, $S \to I \to R$, means a susceptible individual becomes infectious then recovers and is immune. The model is the same as the well-known SIR epidemic model, but the term "epizootic" is used in place of "epidemic" to emphasize that we are applying these models to outbreaks in animal

populations. The term epizootic refers to a single outbreak, whereas enzootic implies persistence of the disease in an animal population. If there is no immunity, then re-infection may occur and the model is known as an SIS model; whereas if immunity wanes, then the model is known as an SIRS model. The simplest type of model assumes homogeneous mixing. That is, all susceptible individuals are equally likely to become infectious depending on the number of contacts (c) per unit time of an infectious individual with other individuals in the population and the probability (q) that a contact results in an infection.

Under the assumption that a population mixes homogeneously with a total population size of N with $N = S + I + R$, one infectious individual will infect $cq(S/N)$ susceptible individuals per unit time. The rate of new infections in the entire population is thus $cq(S/N)I = \beta SI/N$, a rate that is referred to as standard incidence or frequency-dependent incidence. If the population density rather than population size is modeled, then the number of contacts per unit time may depend on population density $c(N)$. If $c(N) = \tilde{c}N$, then the rate is $\tilde{c}qSI = \beta SI$, which is referred to as mass action incidence or density-dependent incidence.

Estimating incidence rates for animal populations is generally difficult. Anderson and May [1992] used an experiment where susceptible mice were introduced into an infected population at a constant daily rate to estimate the transmission rate, and Mayberry et al. [2010] fitted domestic sheep and goats with GPS transmitters to monitor their contacts. But experiments like this are rare. More experimental data are needed to quantify contact rates in animals (Stallknecht [2007]).

Using standard incidence, neglecting births and deaths not due to disease, denoting the recovery rate as γ (assuming an exponential distribution for the infectious period), and disease-related death rate as α, the SIR model is a system of differential equations for a single outbreak over time:

$$\begin{aligned} \frac{dS}{dt} &= -\beta \frac{S}{N} I, \\ \frac{dI}{dt} &= \beta \frac{S}{N} I - \gamma I - \alpha I = I\left(\beta \frac{S}{N} - \gamma - \alpha\right), \\ \frac{dR}{dt} &= \gamma I, \end{aligned} \tag{1}$$

where $S(0) = S_0 > 0$, $I(0) = I_0 \geq 0$, and $R(0) = 0$. The variables S, I, and R represent the number of susceptible, infectious and recovered individuals, respectively.

The dynamics of the SIR model are well known (Anderson and May [1992], Hethcote [2000]). The threshold for a disease outbreak is known as the basic reproduction number,

$$\mathcal{R}_0 = \frac{\beta S_0/N}{\gamma + \alpha} \approx \frac{\beta}{\gamma + \alpha}, \tag{2}$$

under the assumption that $S_0 \approx N$. Here $1/(\gamma + \alpha)$ is the average infectious period, and $\mathcal{R}_0$ is the average number of secondary infections caused by one infectious individual introduced into an entirely susceptible population during an individuals' infectious period (Hethcote [2000]). If $\mathcal{R}_0 > 1$, then there is an outbreak, a rise in the number of infectious individuals (see Figure 3 (a)). For example, if the value of the transmission rate β is large or the length of the infectious period is long, the value of $\mathcal{R}_0$ is also large, resulting in a greater likelihood of an outbreak when one infectious individual is introduced. In the case of mass-action incidence, the basic reproduction number is

$$\mathcal{R}_0 = \frac{\beta S_0}{\gamma + \alpha} \approx \frac{\beta N}{\gamma + \alpha}, \tag{3}$$

assuming $S_0 \approx N$. Brauer [2008] considers models in which the contact rate depends more generally on the total population size or density, $\beta = \beta(N)$ and also gives expressions for the final size of the outbreak. See also references (Brauer [1990, 1991], Pugliese [1990, 1991], Thieme [1992], Zhou and Hethcote [1994], Allen and Cormier [1996]). In the case of density-dependent incidence, a threshold for pathogen invasion can be defined in terms of $N = N_T$ when $\mathcal{R}_0 = 1$ (Lloyd-Smith et al. [2005]). Pathogen invasion occurs if

$$N > N_T = \frac{\gamma + \alpha}{\beta}.$$

The SIS and SIRS models have the same basic reproduction number as the SIR model. In the SIS model, the recovery rate γI is in the equation dS/dt. In the SIRS model, there is a loss of immunity,

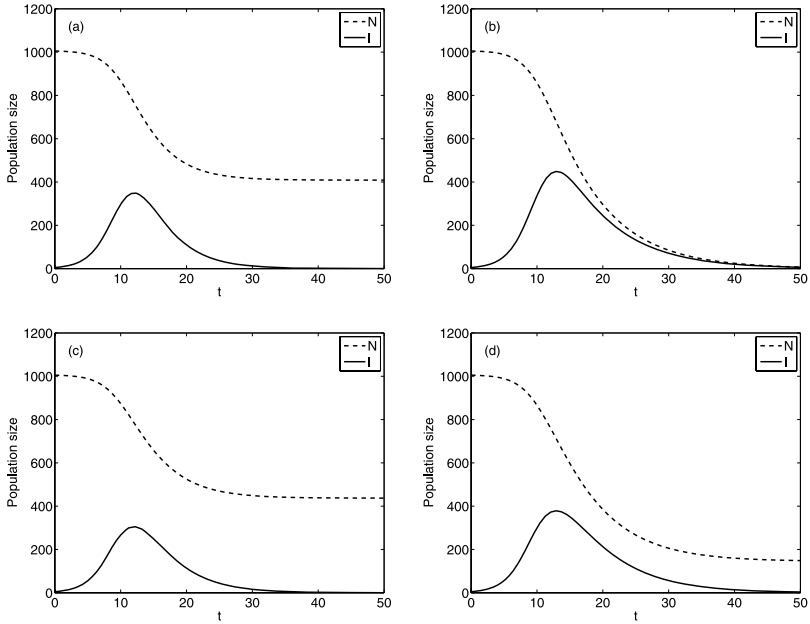

FIGURE 3. Parameters and initial conditions for the SIS and SIR models: $\gamma = 0.1, \alpha = 0.15, S_0 = 1000, I_0 = 5; \mathcal{R}_0 = 3$. (a) SIR model with standard incidence and disease fatalities reduces the total population size N; $\beta = 0.75$. (b) SIS model with standard incidence and disease fatalities results in population extinction; $\beta = 0.75$. (c) SIR model with mass action incidence and disease fatalities reduce the total population size N; $\beta = 7.5 \times 10^{-4}$; $N_T = 333$. (d) SIS model with mass action incidence and disease fatalities reduce the total population size N; $\beta = 7.5 \times 10^{-4}$; $N_T = 333$.

δR is subtracted from dR/dt and added to dS/dt. If $\mathcal{R}_0 > 1$ in the SIS and SIRS models with disease fatalities, then there is a single outbreak, which may lead to population extinction in the case of standard incidence. A model with standard incidence, disease fatalities and $\mathcal{R}_0 > 1$, will result in extinction of the entire population, $N(t) \to 0$ (see Appendix A and Figure 3 (b)). But with mass action incidence, the total population density is reduced but does not go to zero (Figure 3 (c) and (d)). If there are no disease fatalities, then the population size remains constant. Many animal reservoirs that maintain the disease in the wild have adapted to the pathogen so that there are few, if any,

disease-related mortalities; such is the case with hantavirus (Glass et al. [1998]). This is a distinct difference between the animal reservoir and the spill-over infection. Disease-related mortalities are a more common occurrence in spill over infections, where animal hosts have not adapted to the pathogen.

The primary reason for the difference between mass action and standard incidences with disease fatalities is that with standard incidence, the number of contacts remains the same regardless of the population size or density, whereas in mass action incidence the number of contacts decreases as the population density decreases. For a few systems where data are available, either standard or mass action incidence, have provided reasonable fits to observed data in wildlife. For example, standard incidence was fit to feline leukemia virus (FeLV) data from feral cats (Fromont et al. [1997]) and mass action incidence (plus transmission of the virus via the environment) was fit to avian influenza data from wild birds from the Camargue, France (Roche et al. [2009]). Estimates for the transmission rate for FeLV were obtained from the "time between the first contact with a contagious individual and the onset of infection" (Fromont et al. [1997], Pedersen et al. [1977]). The reciprocal of this value gives an estimate of β in the case of standard incidence ranging from 3.08 to 11.76 per year, with population densities ranging from 120 in rural settings to 1100 in urban settings (Fromont et al. [1997]). The contact rates for avian influenza, reported in Roche et al. [2009], were varied (with non transmission parameters kept fixed) to find the best fit of the model results to data. Contact rate was not calculated explicitly but the transmission rate was calculated. The value of N was in the region of 10^5, large enough to use a deterministic model, and was calculated from ornithological data. Other possible incidence rates are discussed by McCallum et al. [2001].

A method referred to as the next generation matrix method can be used to calculate $\mathcal{R}_0$ in a mathematical model (Diekmann and Heesterbeek [2000], Diekmann et al. [1990], van den Driessche and Watmough [2002, 2008]) (see Appendix B). Alternately, another threshold that is defined in terms of the next generation matrix is important in the control of specific groups of infectious individuals. This alternate threshold is known as the type reproduction number (Heesterbeek and Roberts [2007], Roberts and Heesterbeek [2003]) (see Appendix B). The type reproduction number and the basic reproduction number are the same

for this basic SIR model. There are also methods for calculation of $\mathcal{R}_0$ for periodic demographics or with seasonal variation in model parameters (Bacaer [2007], Bacaer and Guernaoui [2006], Wang and Zhao [2008]).

The concept of herd immunity comes from the SIR model and is important in control of infectious diseases. Herd immunity determines the proportion p of susceptible individuals that should be vaccinated or removed to prevent an outbreak. That is, the proportion p for herd immunity is found by solving $\mathcal{R}_0(1-p) < 1$, which yields

$$p > 1 - \frac{1}{\mathcal{R}_0}.$$

The minimal proportion to be vaccinated for herd immunity is $p = 1 - 1/\mathcal{R}_0$ assuming a homogeneously mixed population (Anderson and May [1992]). Due to the presence of $\mathcal{R}_0$ in this formula, the same limitations for p apply as for $\mathcal{R}_0$, namely that it relies on a large population size and assumes all individuals are initially susceptible.

The continuous-time SIS and SIR models serve as a point of departure for many other types of modeling formats, discrete-time and continuous-time, deterministic and stochastic SIS and SIR models (e.g., Allen [2010, 2008], Allen and van den Driessche [2008], Andersson and Britton [2000], Bailey [1990], Caswell [2001]). The basic stochastic SIS and SIR models include variability due to transmission, recovery and disease-related deaths. Stochastic SIS and SIR models can be used to predict the probability of an outbreak, the final size distribution of an epizootic, the expected duration of an epizootic or the limiting stationary or quasistationary probability distribution. For example, an approximation to the probability of an outbreak, PO, in either discrete-event, stochastic SIS or SIR models depends on the initial number of infected individuals, I_0, and on the basic reproduction number $\mathcal{R}_0$, as defined in (2) or (3):

$$PO \approx 1 - \left(\frac{1}{\mathcal{R}_0}\right)^{I_0}$$

given $\mathcal{R}_0 > 1$. This is a good approximation if N is large and I_0 is small (Allen [2008]). The probability of no outbreak, $(1 - PO) \approx$

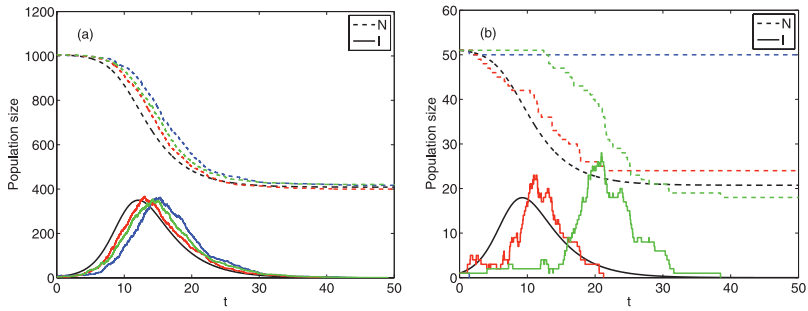

FIGURE 4. Three sample paths of a continuous-time, discrete-event, stochastic SIR model are graphed and compared to the deterministic SIR solution. Parameters and initial conditions for the SIR model with standard incidence and disease fatalities: $\gamma = 0.1$, $\alpha = 0.15$, $\beta = 0.75$, and $\mathcal{R}_0 = 3$. (a) $S_0 = 1000$, $I_0 = 5$, $PO \approx 0.996$. (b) $S_0 = 50$, $I_0 = 1$, $PO \approx 0.667$; in approximately one sample path out of three, there is no outbreak.

$(1/\mathcal{R}_0)^{I_0}$, decreases geometrically as I_0 increases. Figure 4 illustrates three stochastic realizations (or sample paths) of the continuous-time, discrete-event, stochastic SIR model with $S_0 = 1000$, $I_0 = 5$, and $PO = 0.996$ (compare with Figure 3 (a)) and with $S_0 = 50$, $I_0 = 1$, and $PO = 0.667$. Although there has been much theoretical research in stochastic SIR and SIS epidemic models, fewer stochastic models have been applied to zoonotic diseases and even fewer to viral zoonoses in wildlife populations. Thresholds in wildlife populations are more difficult to assess than in human or domestic animal populations due to lack of sufficient data (failed outbreaks are often not observed), possibility of alternative but unknown reservoirs and the differences in the types of thresholds (Lloyd-Smith et al. [2005]).

The basic SIR model (1) does not account for natural births and deaths, spatial heterogeneity, environmental variability, differences in susceptibility, co-infections and a multitude of other factors important in zoonotic diseases. Some of these factors will be examined as we consider the stages of infection.

3.2. Host factors. Inclusion of natural births and deaths in disease models enables the pathogen to infect new hosts and the disease to become enzootic. The population dynamics N, in the absence of

disease, are often assumed to have the form:

$$\frac{dN}{dt} = B(N) - D(N),$$

where $B(N)$ and $D(N)$ are density-dependent birth and death rates, respectively. If there is constant immigration or births, $B(N) = \Lambda$, and the death rate is proportional to the population size, $D(N) = mN$, then the disease-free population equilibrium is Λ/m. In an exponentially growing or declining population, $B(N) = bN$ and $D(N) = mN$, where $b > m$ or $b < m$, respectively. One of the most common assumptions for animal populations is logistic growth, where $B(N) - D(N) = r(1 - N/K)N$, $r = b - m > 0$ and $K > 0$; either the birth rate or death rate or both may be density-dependent. With logistic growth, the disease-free population equilibrium is the carrying capacity K.

An SIS model with standard incidence, density-dependent logistic deaths and disease-reduced fertility has the form:

$$\begin{aligned} \frac{dS}{dt} &= b[S + (1-f)I] - \left(m + \frac{rN}{K}\right) S - \beta \frac{S}{N} I + \gamma I, \\ \frac{dI}{dt} &= \beta \frac{S}{N} I - \left(\gamma + m + \alpha + \frac{rN}{K}\right) I, \end{aligned} \tag{4}$$

where $r = b - m > 0$ (Hethcote et al. [2005]). The density-dependent term affects only deaths. Infectious animals have reduced fertility by a factor f, $0 \leq f \leq 1$. Assuming $S(0) = S_0 \approx N = K$, the basic reproduction number for model (4) is

$$\mathcal{R}_0 = \frac{\beta}{b + \gamma + \alpha}.$$

The reduction in fertility does not affect the basic reproduction number. Hethcote et al. [2005] show that with standard incidence and $\mathcal{R}_0 \leq 1$, the disease cannot persist, $\lim_{t\to\infty} I(t) = 0$. However, if $\mathcal{R}_0 > 1$, either the population reaches an enzootic equilibrium with the population reduced in density or the population does not survive.

For mass-action incidence in model (4), the basic reproduction number depends on K, Namely, $\mathcal{R}_0 = \beta K/(b + \gamma + \alpha)$. When $\mathcal{R}_0 = 1$ a

critical carrying capacity can be defined, $K_T = (b + \gamma + \alpha)/\beta$, the minimal density needed for an outbreak. In stochastic epizootic models, there is also a concept of "critical community size." This concept is not as well-defined as the population threshold N_T or K_T. It was first introduced by Bartlett [1957] in connection with measles outbreaks. The disease does not persist if the community size is too small. Only through introduction of new infectious individuals will there be another outbreak. Unlike the estimate for the probability of an outbreak, there is no distinct threshold for critical community size in stochastic models. Persistence of wildlife disease between epizootics depends on the length of the tail of the preceding outbreak, the number of animals that did not become infected and the rate the susceptible pool is replenished (Lloyd-Smith et al. [2005]).

For a pathogen that is maintained in a reservoir host, it will often be the case that $\mathcal{R}_0 > 1$. If the pathogen has little effect on the mortality of the reservoir host, such as in the case of hantaviruses, then it is more important to monitor the prevalence of infection I/N than to compute $\mathcal{R}_0$. When infection prevalence increases in the reservoir, then humans are more likely to come in contact with the infected reservoir population. Thus, it is infection prevalence rather than $\mathcal{R}_0$ that is a determinant of risk in human infection. Infection prevalence may differ from animal abundance in that there may be a lag between abundance and infection (Davis et al. [2005], Adler et al. [2008]).

Differences in reproductive behavior, or behavior due to age or sex, vertical transmission, heterogeneity in host response and time since infection may impact the disease dynamics and deserve further study, particularly in wildlife disease modeling (Busenberg and Cooke [1993], Woolhouse et al. [1997], Galvani and May [2005], Allen et al. [2006], Klein and Calisher [2007], Adler et al. [2008], Banerjee et al. [2008], Keeling and Rohani [2008], Laverty and Adler [2009]). Reproductive differences between species can be introduced through the birth rates, that is, births can occur at a constant rate through the year, as is often modeled for human populations (Anderson and May [1992]), or as a seasonal pulse, which is often more probable in animal populations (Keeling and Rohani [2008]). The former case will provide (assuming no vertical transmission) a constant stream of new susceptibles into the population, whereas seasonal births will provide an influx of new susceptibles at a given time each year. The implications can be a

sudden change in the $\mathcal{R}_0$ value for the population with a corresponding change in the level of vaccination required for herd immunity. Behavioral differences in the sexes where male rodents' aggressive behavior when infected with hantavirus (Klein and Calisher [2007], Klein et al. [2004]) and vertical transmission when infected with arenavirus were modeled in (Allen et al. [2006], Banerjee et al. [2008]). Analyses of the models revealed distinct thresholds that depend on these sexual differences. Age structure or age since infection can be accounted for in models through either discrete or continuous ages and through multiple infectious stages indicating time since infection (Keeling and Rohani [2008]). Models with juveniles and adults whose behavioral differences may affect the disease dynamics have been considered in wildlife diseases, e.g., spread of rabies (Suppo et al. [2000]) but data are limited on age-structure or times since infection in wildlife populations. Addressing the heterogeneity in the host population has not been well studied but it clearly has implications for the maintenance and spread of viral pathogens. The best illustration of the importance of heterogeneity in host response to pathogens is the incidence of superspreaders (Woolhouse et al. [1997], Galvani and May [2005]), in which 20% of a host population contributes to 80% of transmission (20/80 rule). Vertical transmission, virus spread from mother to offspring, has been included in models by assuming infectious females give birth to infectious offspring with a given probability (Busenberg and Cooke [1993]).

An SIS model with density-dependent deaths $m(N)$, vertical transmission $\bar{b} \leq b$ (all newborns from infectious parents are infectious) and mass action incidence has the form:

$$\frac{dS}{dt} = S(b - m(N) - \beta I) + \gamma I,$$
$$\frac{dI}{dt} = I(\bar{b} - m(N) - \alpha - \gamma + \beta S).$$

The basic reproduction number with vertical transmission is

$$\mathcal{R}_0 = \frac{\beta K}{b + \gamma + \alpha} + \frac{\bar{b}}{b + \gamma + \alpha},$$

where $m(K) = b$. The two terms in $\mathcal{R}_0$ are due to horizontal (direct contact) transmission and vertical transmission of the disease. Vertical transmission provides another avenue for the disease to persist, which may be an evolutionary advantage for the pathogen.

3.3. Spatial and environmental factors. The geographic spread of pathogens in wildlife populations has been modeled in a variety of ways (e.g., Abramson et al. [2003], Allen et al. [2002], Anderson and May [1986], Ding et al. [2007], Hess [1996], Hess et al. [2002], Lewis et al. [2006], Maidana and Yang [2009], Murray [1993], Murray and Seward [1992], Ruan and Wu [2009], Suppo et al. [2000], Watts et al. [2009]). A model for the spatial spread of fox rabies in Murray [1993] employs partial differential equations. Susceptible and infectious foxes are modeled in a one-dimensional spatial domain. Infectious foxes are introduced in a small spatial region $[a_1, a_2] \subset \mathbb{R}$. The model is referred to as a system of reaction-diffusion equations:

$$\frac{\partial S}{\partial t} = -\beta SI,$$

$$\frac{\partial I}{\partial t} = \beta SI - \alpha I + D\frac{\partial^2 I}{\partial x^2},$$

where $S(x,0) = S_0 > 0, x \in \mathbb{R}, I(x,0) = I_0, x \in [a_1, a_2]$ for $-\infty < a_1 < a_2 < \infty$ and zero elsewhere. Mass action incidence is assumed and S and I are the susceptible and infectious population densities. In particular,

$$\int_{\mathbb{R}} I(x,t)\,dx$$

is the total number of infected foxes at time t. The equation for immune animals is omitted because it is assumed that infected foxes do not recover. Thus, the model is of SI type with $N = S + I$. Parameter α is the disease-related death rate and D is the diffusion coefficient.

The diffusion approximation implies that movement of infectious foxes is random; animals have no preference for any particular direction. In the absence of movement, $D = 0$, the model simplifies to the

well-known SI model. The threshold for disease outbreak is

$$\mathcal{R}_0 = \frac{\beta S_0}{\alpha}.$$

In the spatial model, with $D > 0$, a traveling wave of infection can be shown to exist if $\mathcal{R}_0 > 1$ with spreading speed given by (Murray et al. [1986], Murray [1993]):

$$2[D(\beta S_0 - \alpha)]^{1/2}.$$

In a more realistic rabies model, Murray [1993] and Murray et al. [1986] separated the types of rabies cases into nonfurious and furious types, denoted here by I and F, respectively. Animals with furious rabies as opposed to nonfurious rabies are more aggressive and may attack anything that moves; they become confused and wander randomly (Murray et al. [1986]). In their model, it is assumed that rabies is spread via animals with the furious type. Animals become infected with rabies, stage I, then may progress to the furious type, F. Including births and deaths in a logistic type growth function, the model takes the following form:

$$\begin{aligned}
\frac{\partial S}{\partial t} &= rS\left(1 - \frac{N}{K}\right) - \beta FS, \\
\frac{\partial I}{\partial t} &= -I\left(m + r\frac{N}{K}\right) + \beta FS - \sigma I, \\
\frac{\partial F}{\partial t} &= -F\left(m + r\frac{N}{K}\right) + \sigma I - \alpha F + D\frac{\partial^2 F}{\partial x^2},
\end{aligned} \tag{5}$$

where $r = b - m$, b and m are the density-independent birth and death rates, respectively, and $N = S + I + F$ is the total population density. All animals are born susceptible, but all animals are subject to density-independent and density-dependent deaths. In the absence of disease, the population grows logistically to carrying capacity K. Nonfurious foxes progress to the furious type at a rate σ. The rabid animals (furious rabies) have an additional disease-related mortality

rate α. The basic reproduction number for model (5) is

$$\mathcal{R}_0 = \frac{\beta\sigma K}{(b+\sigma)(b+\alpha)}.$$

For this model, there also exist traveling wave solutions, provided $\mathcal{R}_0 > 1$. With parameter values for rabies in foxes, Murray [1993] calculated a spreading speed of 51 km/year. Reaction-diffusion models of the type (5) have been applied to the spread of hantaviruses and West Nile virus (Abramson et al. [2003], Lewis et al. [2006], Maidana and Yang [2009]). Reaction-diffusion models can offer some tractability, allowing $\mathcal{R}_0$ to be calculated. However, this tractability does come at a cost. These models assume that dispersal is short range, which cannot always be justified.

In addition to simple reaction-diffusion models, other types of reaction-diffusion models include biased or directed motion and other types of spatial settings, such as spatially discrete locations or patches (e.g., Nisbet and Gurney [1982], Hess [1996], Swinton et al. [1998], Suppo et al. [2000], Allen et al. [2002, 2009], Arino et al. [2007], Ding et al. [2007], Foley et al. [1999], Gudelj et al. [2004], McCormack and Allen [2007], Keeling and Rohani [2008]). For example, in the case of rabies, baits laden with vaccine were deposited in strategic locations in Canada, the United States and Europe with the goal of stopping the spread of rabies in wildlife reservoirs, foxes, coyotes and raccoons; this has been modeled in (Allen et al. [2002], Childs et al. [2007], Coyne et al. [1989], Ding et al. [2007], Murray and Seward [1992], Smith and Cheeseman [2002], Suppo et al. [2000], Tilman and Kareiva [1997]). Childs et al. [2007] and Coyne et al. [1989] fit an SEIR model to spatial data on a raccoon rabies epizootic that occurred during the 1970s on the east coast of the United States. They found epizootic periods of 4–5 years and although recurrent epidemics declined in size, the model agreed most closely with an assumption of little or no immunity (Childs et al. [2007]). They also used the model to evaluate culling versus vaccination as control measures for raccoon rabies and found that the most cost effective strategy involves culling over 32% of the raccoons or yearly vaccination of up to 99% of the population (Coyne et al. [1989]). Smith and Cheeseman [2002] found that culling was more effective for disease elimination than vaccination for control of fox

rabies in Europe. Such types of studies on disease spread, vaccination coverage and other methods for control of zoonotic diseases are immensely valuable for prevention of human infection and conservation of wildlife.

Another study of a viral disease of wildlife that successfully applied a metapopulation model was an outbreak of phocine distemper virus (PDV) in harbour seals (Swinton et al. [1998]). Although PDV is not a viral zoonoses, the mathematical methods employed are useful to the study of viral zoonoses and the study is also important for conservation purposes. A stochastic patch SEIR model was applied to data on an outbreak in 1988 of PDV in the harbour seal in the North Sea (Swinton et al. [1998]). Harbour seals have contact with each other when on land (the patches are called haulouts). The force of infection for patch i was assumed to have a form equivalent to standard incidence, $\lambda_i = \beta_i I_i / N_i$ but also depended on nearest neighbor patches or location of haulouts:

$$\lambda_i = \beta \left[(1-\rho)\frac{I_i}{N_i} + \rho \frac{\sum_{j=i-1,i,i+1} I_j}{\sum_{j=i-1,i,i+1} N_j} \right],$$

where ρ is the relative frequency of between-haulout mixing. Numerical investigations conducted on extinction times of the infection as a function of population size $N = \sum_j N_j$ and number of patches showed that the critical community size is on the order of 10^8, a value much greater than the North Sea population of harbour seals (10^6) (Swinton et al. [1998]). Stochastic fade-out was observed. The model showed that it would be highly unlikely for the disease to persist in the population due to high transmission rates within subpopulations and a small annual birth rate (Swinton et al. [1998]).

Environmental factors such as seasonality, precipitation, humidity, vegetation and anthropogenic disturbances impact diseases in wildlife much more than diseases in humans (e.g., Altizer et al. [2006], Breban et al. [2010], Glass et al. [2000, 1998], Goodin et al. [2006], Hawley and Altizer [2011], Hazel et al. [2000], Hess et al. [2002], Pretorius et al. [1997], Previtali et al. [2010], Sauvage et al. [2007, 2003], Wesley et al. [2010], Wolf et al. [2006]). For example, in a study of cowpox virus in wild rodent reservoirs, seroconversion varied seasonally (Hazel et al.

[2000]). Epizootics of Rift Valley fever virus have been associated with heavy rainfall (Pretorius et al. [1997]). Human-disturbed landscape and increased precipitation are associated with hantavirus infection in rodent reservoirs and high risk for humans (Glass et al. [2000], Goodin et al. [2006], Previtali et al. [2010]). Persistence of the viral pathogen in the environment, outside the host, depends on temperature and humidity. Models for hantavirus with direct transmission and indirect transmission via the environment were considered in (Sauvage et al. [2003, 2007], Wesley et al. [2010], Wolf et al. [2006]). Indirect transmission provides a means for the pathogen to persist when direct transmission is low. Long-distance migration in birds may impact disease susceptibility due to compromised immune function during migration (Owen and Moore [2006, 2008], Weber and Stilianakis [2007]). A few studies have investigated migratory behavior of infected birds (Owen et al. [2006], van Gils et al. [2007]) but these have not been mathematically modeled.

Much of the modeling work on spatial effects or the impact of climate change on viral zoonoses has been computationally intensive. A computational model for spread of H5N1 avian influenza among birds was developed based on phylogenetic data of virus isolates, migratory bird pathways and trade in poultry and wild birds (Kilpatrick et al. [2006]). The model predicts global spread of H5N1, based on the location of H5N1 introductions in various countries. Remote sensing data on landscape and rainfall patterns have been applied to hantaviruses in rodents indicating significant relationships between geography, rainfall and disease in the reservoir (Glass et al. [1998, 2000], Goodin et al. [2006]). Satellite imagery of vegetation and data on precipitation and host and pathogen presence can be coupled to form risk maps (e.g., Glass et al. [1998, 2000], Goodin et al. [2006], Hess et al. [2002]). A review article by Clements and Pfeiffer [2010] summarizes some of the contributions of geographical information systems (GIS), remote sensing (RS) and spatially explicit modeling to human risk and intervention strategies with respect to rabies, West Nile virus, avian influenza and other emerging viral zoonoses. Mathematical models coupled with data from GIS and RS are "powerful and cost-effective tools" for assessing alternative control strategies (Clements and Pfeiffer [2010]). The importance of space in animal disease ecology has been demonstrated

theoretically but as noted by Steinberg and Karieva in reference to spatial ecology (Steinberg and Kareiva [1997], p. 318):

> ...we know "in theory" that space can make a huge difference, but we do not know how often "in fact" it does make a difference. ... Collecting spatially structured data, much less conducting "spatial experiments," is costly.

3.4. Multiple species. Multiple species are often involved in viral zoonoses (Woolhouse et al. [2001]). West Nile virus involves numerous species of birds, with as many as 300 species known to be infected (Wonham et al. [2006]). Reservoir competence and disease susceptibility are known to vary widely within birds (Kilpatrick et al. [2007]). The reservoir for Nipah and Hendra viruses is fruit bats that transmit the viruses to pigs and horses, respectively (Daniels et al. [2007]). The dog is the major reservoir for rabies throughout the world but wildlife reservoirs for rabies include foxes, coyotes, jackals, skunks, raccoons, insectivorous bats and yellow mongooses (Hemachudha and Rupprecht [2005]). Depending on reservoir competence, biodiversity effects can be amplified or diluted (Schmidt and Ostfeld [2001], Dobson [2004], Keesing et al. [2006, 2010]).

A mathematical model with n species consisting of n SIR equations with mass-action incidence has the form:

$$
\begin{aligned}
\frac{dS_j}{dt} &= \Lambda_j - S_j\left(m_j + \sum_{k=1}^{n} \beta_{jk} I_k\right), \\
\frac{dI_j}{dt} &= -m_j I_j + S_j \sum_{k=1}^{n} \beta_{jk} I_k - (\gamma_j + \alpha_j) I_j, \\
\frac{dR_j}{dt} &= \gamma_j I_j - m_j R_j,
\end{aligned}
\tag{6}
$$

where $j = 1, \ldots, n$ (Dobson [2004], Keeling and Rohani [2008], McCormack and Allen [2007]). The parameter Λ_j is an immigration/birth rate for species j, m_j is the natural mortality rate and α_j is the disease-related mortality rate. The contact rate of an infectious animal of species I_k with a susceptible animal of species

S_j is β_{jk}. The initial conditions are $S_j(0) > 0$, $I_j(0) \geq 0$, $R_j(0) = 0$ with the total population for species j, $N_j = S_j + I_j + R_j$, a solution of

$$\frac{dN_j}{dt} = \Lambda_j - m_j N_j - \alpha_j I_j.$$

Species j disease-free state is $N_j = \Lambda_j/m_j = K_j$. With immigration, disease cannot drive any of the populations N_j to extinction, even in the case of standard incidence rate: $\beta_{jk} S_j I_k/N_j$. From the inequality, $0 \leq I_j \leq N_j$, it follows that $dN_j/dt \geq \Lambda_j - N_j(m_j + \alpha_j)$.

The basic reproduction number $\mathcal{R}_0$ for model (6) is the spectral radius of an $n \times n$ matrix $M, \mathcal{R}_0 = \rho(M)$, where $M = [\mathcal{R}_{jk}]$ and

$$\mathcal{R}_{jk} = \frac{K_j \beta_{jk}}{m_k + \gamma_k + \alpha_k},$$

with $S_j(0) \approx K_j$. The magnitude of the entries $\mathcal{R}_{jk}$ in matrix M depend on the contact rate between an infectious animal of species k and a susceptible animal of species j, β_{jk}, the density of susceptible species j, K_j, and the sum of the mortality and recovery rates of the infectious species k, $m_k + \gamma_k + \alpha_k$. For standard incidence, the entries $\mathcal{R}_{jk}$ do not depend on K_j. In human diseases, a matrix known as the WAIFW matrix (who acquires infection from whom) (Anderson and May [1992]) is often used to determine the contacts among different groups. Matrix M plays a similar role. Depending on the magnitude of the entries $\mathcal{R}_{jk}$ the basic reproduction $\mathcal{R}_0$ may either decrease or increase with multiple hosts, resulting in either an amplification effect or a dilution effect, respectively (Dobson [2004], McCormack and Allen [2007]). To eradicate infection in a wildlife reservoir, $\mathcal{R}_0$ needs to be reduced below one. This may be accomplished through direct control of the reservoir population or possibly through one or more spill over species, especially if that species has an amplifying effect. Due to the large number of parameters, estimates of $\mathcal{R}_0$ with multiple hosts is difficult. Alternative measures such as infection prevalence I_j/N_j may be more easily estimated from data and potentially more relevant for wildlife diseases (e.g., Adler et al. [2008], Davis et al. [2005]).

The interspecies relationships may be more complex than simply pathogen transmission; for example, there may be competition for

resources or predator–prey interactions (e.g., Anderson and May [1979a, 1979b], Han et al. [2001], van den Driessche and Zeeman [2004]). The presence of infectious disease may change the competitive hierarchy or the predator–prey relationships in unexpected ways, such as causing oscillations in competing populations or reducing oscillations in predator–prey systems (Hilker and Schmitz [2008], van den Driessche and Zeeman [2004]).

3.5. Multiple pathogens. Multiple infections are a frequent occurrence in human and animal diseases (e.g., Feng and Velasco-Hernandez [1997], Glavits et al. [2005], Telfer et al. [2010]). A pre-existing pathogen infection may impact the course of a viral infection. For example, an already activated immune response may suppress amplification of a new infection. Alternatively, multiple viral infections in a single host may lead to new viral strains, as in the case of influenza A virus (Sharp et al. [1997], Suarez et al. [2004]). In some cases, the effects of co-infection may be of greater magnitude than the effects associated with the host or the environment (Telfer et al. [2010]).

A model with n directly transmitted pathogen infections illustrates some of the complexity in models with multiple pathogens. The population density in a single host population infected with pathogen j is denoted as I_j. An SIR model with mass action incidence and multiple infections but without co-infections has the form:

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - S\left(m + \sum_{j=1}^{n} \beta_j I_j\right), \\
\frac{dI_j}{dt} &= I_j\left(\beta_j S - m - \gamma_j - \alpha_j\right), \quad j = 1, 2, \ldots, n, \\
\frac{dR}{dt} &= \sum_{j=1}^{n} \gamma_j I_j - mR,
\end{aligned}
\tag{7}
$$

where $S(0) = S_0 > 0$, $I_j(0) \geq 0$, $R(0) = 0$ and $N = S + \sum_{j=1}^{n} I_j + R$. The parameter m is the natural mortality rate, Λ is the immigration/birth rate and α_j is the disease-related mortality rate.

A model with co-infection by two pathogens, j and k, denoted I_{jk}, would include transmission from I_j to I_k and from I_k to I_j.

For model (7), the total population is a solution of the differential equation

$$\frac{dN}{dt} = \Lambda - mN - \sum_{j=1}^{n} \alpha_j I_j.$$

The disease-free state is $N = \Lambda/m = K$. A pathogen reproduction number can be defined for each pathogen j:

$$\mathcal{R}_j = \frac{\beta_j K}{m + \gamma_j + \alpha_j}. \tag{8}$$

Here, it is also assumed that $S_0 \approx N$. With standard incidence the pathogen reproduction number is

$$\mathcal{R}_j = \frac{\beta_j}{m + \gamma_j + \alpha_j}. \tag{9}$$

Disease cannot drive the population to extinction because of the immigration into the population.

Bremermann and Thieme [1989] analyzed system (7) for mass action incidence with the assumption of density-dependent births, $\Lambda = Nf(N)$, where f is a strictly decreasing function of N, $f(0) > m$ and $f(N) < m$ for N large. In this case, a unique disease-free state for N is the solution $K > 0$ satisfying $f(K) = b$. The pathogen reproduction number is given by (8). It is also the case for this model that disease does not drive the population to extinction.

The basic reproduction number for model (7) is

$$\mathcal{R}_0 = \max_j \{\mathcal{R}_j\}, \tag{10}$$

where the pathogen reproduction number is defined in (8) or (9) for mass action or standard incidence, respectively. No pathogen persists in the population if $\mathcal{R}_0 < 1$ (applying techniques from Bremermann and Thieme [1989]). A competitive exclusion result holds if $\mathcal{R}_0 > 1$.

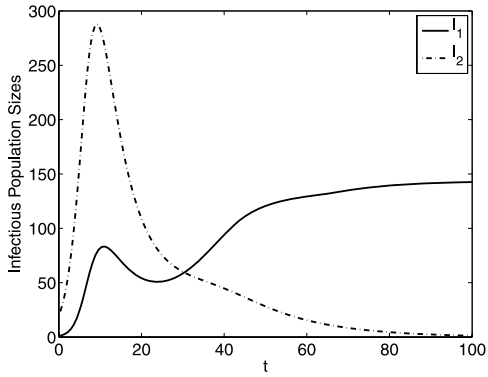

FIGURE 5. Parameters and initial conditions for the SIR model with two pathogens and standard incidence: $\Lambda = 50$, $m = 0.05$, $\beta_1 = 1$, $\beta_2 = 0.75$, $\gamma_i = 0.2\alpha_i = 0.01$ for $i = 1, 2$, $S(0) = 1000$, $I_1(0) = 1$, $I_2(0) = 20$ and $R(0) = 0; \mathcal{R}_1 = 3.85$ and $\mathcal{R}_2 = 2.89$. Strain 1 is competitively dominant.

Suppose pathogen 1 has the largest reproduction number, $\mathcal{R}_0 = \mathcal{R}_1 > 1$ and $\mathcal{R}_j < \mathcal{R}_1, j = 2, \ldots, n$. Then pathogen 1 is the only persistent pathogen, outcompeting all other pathogens (see Figure 5 for standard incidence and $\Lambda =$ constant) (Bremermann and Thieme [1989]).

This latter result about the maximal pathogen reproduction number (10) has led to much speculation about the evolution of virulence (Dieckmann et al. [2002]). The parameter α_j is a measure of pathogen virulence. The preceding result implies that it is to the pathogen's advantage to evolve to reduced virulence, that is, to evolve so that α_j is small and $\mathcal{R}_j$ is large (Bremermann and Thieme [1989], Levin and Pimentel [1981]). A well-known natural experiment of myxoma virus in rabbits supports this hypothesis (Fenner and Ratcliffe [1965], Fenner and Myers [1978], Levin and Pimentel [1981]). The European rabbit, introduced into Australia in the mid 1800s, rapidly increased to very high densities causing a serious problem to agriculture. To control the rabbit population, a lethal strain of myxoma virus was introduced in the mid 1950s. The initial mortality rate in infected rabbits was estimated at 99.8% (Fenner and Myers [1978], Levin and Pimentel [1981]). But over time, the mortality decreased, the virulence level of the virus decreased in the rabbit population. The relationship between reduced virulence and disease persistence is not as

simple as a decrease in pathogen reproduction number with virulence, α_j (see e.g., Ackleh and Allen [2003, 2005], Anderson and May [1992], Bremermann and Thieme [1989], Day [2002], Day and Burns [2003], May and Nowak [1994, 1995], Pugliese [2002]). The parameters in the definition of $\mathcal{R}_j$ are generally not independent; for example, transmission may be correlated with virulence (Anderson and May [1992], Bremermann and Thieme [1989]).

Co-infection and superinfection are two pathways whereby a single host can be multiply infected with several viral strains or pathogens. Co-infection of a host with several strains may lead to viral recombination and a new strain that is more virulent. This is one of the major concerns with avian influenza (Suarez et al. [2004]). Superinfection occurs when pathogens can invade one another sequentially. With co-infection, superinfection, stochastic effects or density-dependent births instead of deaths, the competitive exclusion principle no longer holds (see e.g., Ackleh and Allen [2003, 2005], Adler and Losada [2002], Allen et al. [2003], Castillo-Chavez and Velasco-Hernandez [1998], Esteva and Vargas [2003], May and Nowak [1995], Mosquera and Adler [1998], Nowak and May [1994], Nowak and Sigmund [2002], Pugliese [2002]). In these latter cases, other factors in combination with the infection determine the outcome of the pathogen competition. In addition, calculation of thresholds becomes more complex and explicit expressions may not be possible. Only a few longitudinal co-infection studies have been conducted in natural nonhuman animal populations (e.g., Telfer et al. [2008, 2010]).

4. Cellular entry and viral replication. A virus-cell model is similar to an SIR model in that uninfected and infected target cells as well as free virus particles or virions are modeled. However, this model does not account for many factors that influence the success of a viral entry, replication and release. Factors that affect viral infection include the host immune response, host and viral genetics and activity along nonimmune signaling pathways (e.g., cell-death, metabolism) that correlate with productive infection. Some of these factors will be mentioned briefly in the following sections.

4.1. Basic virus-cell model. Let V denote virions that enter a healthy target cell T changing this target cell into an infected one

I, where the virus is capable of replication and release. We refer to this model as a TIV model, where there are two types of target cells, healthy and infected, and the virus particles or virions. This model has been extensively investigated with respect to human infectious diseases, in particular HIV-1 (e.g., Nowak and May [2000], Perelson and Nelson [1999]). The TIV model is a system of three differential equations,

$$\begin{aligned} \frac{dT}{dt} &= \lambda - \beta VT - \delta_T T, \\ \frac{dI}{dt} &= \beta VT - \delta_I I, \\ \frac{dV}{dt} &= \pi I - cV - \beta_1 VT, \end{aligned} \tag{11}$$

where $T(0) = T_0 > 0$, $I(0) = I_0 \geq 0$ and $V(0) = V_0 > 0$. The expression βVT represents rate of viral entry into a host cell; λ is a constant reproductive rate of target cells; δ_T, δ_I and c are death rates of healthy target cells, infected target cells and virions, respectively. The death rate of infected target cells exceeds that of healthy cells, $\delta_I > \delta_T$. The parameter π represents rate of reproduction of virions from one infected cell and is sometimes written as $\pi = N\delta_I$, where N is known as the burst size, $N \geq 2$. Sometimes the expression βVT is divided by total number of cells, $T + I$, so that the incidence rate is standard (see e.g., Gourley et al. [2008]). In the absence of infection, the disease-free equilibrium target cell population is $\bar{T} = \lambda/\delta_T$. The loss of virions because of entry into a target cell is often not accounted for in this model, namely, $-\beta_1 VT$, in the equation for dV/dt, because this term is small compared to the viral clearance rate, cV. Generally, $\beta_1 \geq \beta$, since one or more virion may be associated with infection of a target cell. Tuckwell and Le Corfec [1998] and De Leenheer and Smith [2003] assume $\beta_1 = \beta$.

The basic reproduction number for model (11), computed from the next generation matrix approach (Appendix B), with next generation

matrix

$$M = \begin{bmatrix} 0 & \dfrac{\beta \bar{T}}{c + \beta_1 \bar{T}} \\ N & 0 \end{bmatrix},$$

is given by

$$\mathcal{R}_0 = \rho(M) = \sqrt{\frac{\beta N \bar{T}}{c + \beta_1 \bar{T}}} \tag{12}$$

when $T_0 \approx \bar{T}$. In the case of standard incidence, $\mathcal{R}_0 = \sqrt{\beta N/(c + \beta_1 \bar{T})}$. When controlling either the virus or the infected cells but not both, the type reproduction number is $\mathcal{T} = (\mathcal{R}_0)^2$, the square of the basic reproduction number (Yuan and Allen [2011]) (see Appendix B). It is this latter expression that is often reported in the literature (e.g., Perelson and Nelson [1999], Nowak and May [2000]). The infection at the within-host level may be controlled through reduction of the burst size proportionally by $1 - p$, e.g., through drugs that cause infected cells to produce uninfected virions (Perelson and Nelson [1999]). To ensure $\mathcal{R}_0 < 1$ requires that the proportion $p > 1 - 1/\mathcal{T}$. If the term $-\beta_1 VT$ is omitted in dV/dt, then a simpler expression for the basic reproduction number is

$$\mathcal{R}_0 = \sqrt{\frac{\beta N \bar{T}}{c}}. \tag{13}$$

The TIV model (11) has been mathematically analyzed by De Leenheer and Smith [2003] in two cases: $\beta_1 = \beta$ and $\beta_1 = 0$. It has been shown in both cases that $\mathcal{R}_0 < 1$ implies global asymptotic stability of the disease-free equilibrium $\bar{T}$ (De Leenheer and Smith [2003]). In addition, if $\mathcal{R}_0 > 1$, there exists a unique chronic disease equilibrium:

$$(T_c, I_c, V_c) = \left(T_c, \frac{\lambda}{\delta_I} \left[1 - \frac{T_c}{\bar{T}} \right], \frac{\lambda}{\beta T_c} \left[1 - \frac{T_c}{\bar{T}} \right] \right), \tag{14}$$

with $T_c = c/(\beta N)$ if $\beta_1 = 0$ and $T_c = c/[\beta(N-1)]$ if $\beta_1 = \beta$. Note that the healthy T cell population is reduced as well as the total number of

T cells at the chronic disease equilibrium; $T_c + I_c < \bar{T}$ due to the fact that $\delta_I > \delta_T$. Furthermore, if $\beta_1 = 0$, or if $\beta_1 = \beta$ and $\beta\lambda < \delta_T\delta_I$, then the chronic disease equilibrium is globally asymptotically stable (De Leenheer and Smith [2003]). Although the $\mathcal{R}_0$ in (De Leenheer and Smith [2003]) differs from the one given in (12), the threshold value $\mathcal{R}_0 = 1$ is the same.

The basic TIV model has been extended to include some of the immune system components e.g., dendritic cells, macrophages, helper T cells, cytotoxic T lymphocytes and antibodies (Asachenkov et al. [1994], Marchuk [1997], Nowak and May [2000], Wodarz [2007], Lee et al. [2009]). Because these mathematical models are useful for interpreting patient data and testing hypotheses, they have been primarily applied to human diseases, HIV-1, hepatitis B and C viruses, lymphocytic choriomeninigitis virus, influenza virus and cytomegalovirus (Asachenkov et al. [1994], Lee et al. [2009], Marchuk [1997], Nowak and May [2000], Perelson [2002], Perelson and Nelson [1999], Wodarz [2007]). The virus and intracellular dynamics are probably one of the most neglected modeling areas for viral zoonoses (Pulliam [2008], Lloyd-Smith et al. [2009]).

4.2. Host immune response. The host immune response is responsible for eliminating the source of infection, the infected cells and the virions from a host. The immune system is very complex, involving many types of molecules, cells and chemicals (e.g., Murphy et al. [2008], Perelson [2002]). Two important cellular components of the adaptive immune response are B cells and T cells. The B cells are responsible for generation of antibody molecules and T cells are responsible for production of cytokines and killing of infected cells. In response to a viral pathogen, B cells are activated to produce antibodies, molecules specific to a particular virus particle. Antibodies bind to a specific virus particle so that it can be recognized and cleared by multiple mechanisms, including by macrophages, which can then present antigen to T cells. Natural killer cells also are activated by receptors on the surface of infected cells. They bind to these receptors and release chemicals inside the cell that may either kill the infected cell or cause the infected cell to stop replication of the virus particle. Helper T cells assist in both B cell and cytotoxic T lymphocyte (CTL) activation.

In a simplified version of the immune response, Wodarz [2007] includes the actions of antibodies A and CTLs C to the TIV model (11):

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - \beta VT - \delta_T T,\\
\frac{dI}{dt} &= \beta VT - \delta_I I - \sigma_C IC,\\
\frac{dV}{dt} &= \pi I - cV - \sigma_A VA,\\
\frac{dA}{dt} &= \rho_A VA - \delta_A A,\\
\frac{dC}{dt} &= \rho_C IC - \delta_C C,
\end{aligned} \tag{15}$$

where $T(0) > 0$, $I(0) \geq 0$, $V(0) \geq 0$, $A(0) \geq 0$, and $C(0) \geq 0$. In this new model, antibodies are activated by the virus $\rho_A VA$ and CTLs are activated by infected cells $\rho_C IC$. Antibodies play an important role in long-term immunization, so that the death rate of antibodies is relatively small, $\delta_A \ll 1$. Infected cells are killed by CTLs, $\sigma_C IC$, and the virus is bound to antibodies $\sigma_A VA$. For this model, the basic reproduction number is given by (13). The presence of A and C reduces the viral load and number of infected cells. Further studies are needed to understand the dynamics of model (15) and to consider alternate formulations for activation of A and C in animal reservoirs.

Because model (15) does not include the activity of the innate immune response prior to antibody production and CTL activity, there may be delays prior to activation (Eikenberry et al. [2009], Lee et al. [2009]). In long-term infections, the immune response adapts to the persistent infection, caused by a down-regulation of the immune response (Schönrich et al. [2008]). When a virus jumps to a naive host, the immune response may be very strong. For example, in some viral infections, the CTL response can lead to tissue damage and if severe enough, host death (Wodarz [2007]). Wodarz [2007] refers to this latter type of response as CTL-induced pathology. In addition, the immunological response and infection length are influenced by current infections and infection history (Telfer et al. [2008]). Pedersen and Fenton

[2007] emphasize the importance of understanding the community ecology at the level of the within-host, that is, a tri-trophic level interaction among the immune system, pathogen community and their respective target cells. The differences in the immune response to a viral pathogen by a reservoir as opposed to a spill over species needs further investigation. These differences in responses are key to understanding host-switching and cross-species pathogen transmission (Childs et al. [2007], Hochberg and Holt [1990], Parrish et al. [2008], Pedersen and Davies [2009], Pulliam [2008], Schönrich et al. [2008]). Mathematical models with multiple pathogens are just beginning to explore the role of the within-host immune response on the population dynamics (Fenton [2008], Fenton et al. [2008], Hawley and Altizer [2011], Pugliese and Gandolfi [2008]).

4.3. Viral quasispecies. The viral genetic variation has been included in the basic TIV model into what is referred to as viral quasispecies models (Bull et al. [2005], Lauring and Andino [2010], Nowak and May [2000]). Eigen [1971] introduced the concept of quasispecies in 1971 to describe the origin of life and more recently, this concept has been applied to RNA viruses (Holmes [2010], Lauring and Andino [2010], Más et al. [2010]). Regardless if one uses the concept of quasispecies to describe intra-host variation of RNA viruses or population theories, it is well supported that RNA viruses have a high mutation rate and lack error-correcting mechanisms. This lack of error correction results in a greater diversity and distribution of the viral genetics that may be selected upon within the host following a successful infection. Insight into the mechanism in which viruses adapt to new hosts is critical since many new viral zoonoses are RNA viruses, such as hantaviruses, avian influenza viruses, Nipah virus and SARS CoV. Hence, modeling of this phenotype of RNA viruses can shed light on how to predict which viruses in wildlife have intrinsic genetic character that would permit spill over into other species and amplification.

A simple mathematical model for viral quasispecies assumes the possibility of n viral strains (Bull et al. [2005], Nowak and May [2000]). Mutation occurs during replication within an infected cell and leads to production of a mutant type. Assuming the master viral sequence is

type 1, then the probability of a mutation from genotype 1 to j is q_{j1}. In general, q_{ij} is the mutation from genotype j to i, $j \neq i$ and q_{ii} is the probability that genotype i does not mutate. A simple model for viral quasispecies has the following form (Nowak and May [2000]):

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - \delta_T T - T\sum_{i=1}^{n} \beta_i V_i,\\
\frac{dI_i}{dt} &= T\sum_{j=1}^{n} q_{ij}\beta_j V_j - \delta_i I_i, \quad i = 1, \ldots, n,\\
\frac{dV_i}{dt} &= \pi_i I_i - c_i V_i,
\end{aligned}$$

where $Q = [q_{ij}]$ is an $n \times n$ mutation matrix, $\pi_i = N_i\delta_i$ and N_i is the burst size for viral strain i. Initial conditions are $T(0) > 0$, $I_i(0) \geq 0$, and $V_i(0) \geq 0$. Assuming there is no back mutation; that is, strain j mutates to i, where $i \geq j$ but there is no mutation from i to j, then matrix Q is a lower triangular matrix:

$$Q = \begin{bmatrix}
q_{11} & 0 & 0 & \cdots & 0\\
q_{21} & q_{22} & 0 & \cdots & 0\\
q_{31} & q_{32} & q_{33} & \cdots & 0\\
\vdots & \vdots & \vdots & \ddots & \vdots\\
q_{n1} & q_{n2} & q_{n3} & \cdots & q_{nn}
\end{bmatrix}.$$

The entries q_{ij} are probabilities with the property that the column sum is equal to one. For example, if there are only two strains, then

$$Q = \begin{bmatrix}
q_{11} & 0\\
1 - q_{11} & 1
\end{bmatrix}.$$

In the absence of mutation, $Q = \mathcal{I}$ an identity matrix, the basic reproduction number is

$$\mathcal{R}_0 = \max_i\{\mathcal{R}_i\}$$

where $\mathcal{R}_i = \sqrt{\beta_i N_i \bar{T}/c_i}$ is the strain reproduction number and $\bar{T} = \lambda/\delta_T$. A competitive exclusion result applies to this model, similar to the result for multiple pathogens (see (10)). If $\mathcal{R}_0 > 1$ and $\mathcal{R}_1 = \mathcal{R}_0 > \mathcal{R}_j, j \neq 1$, then strain 1, the virus with the greatest strain reproduction number outcompetes all other virus strains and persists (De Leenheer and Pilyugin [2008]). If all strain reproduction numbers are less than one, that is, if $\mathcal{R}_0 < 1$, then all strains die out. With mutation, $Q \neq \mathcal{I}$, and $\mathcal{R}_0 > 1$, more than one strain persists (De Leenheer and Pilyugin [2008]).

Interesting questions arise about quasispecies when studying control of RNA viruses. Ribavirin is a drug used as an antiviral therapy, which acts as a mutagenic agent for some RNA viruses (Chung et al. [2007], Graci et al. [2008], Grand-Pérez et al. [2002]). To eradicate an RNA virus, ribavirin therapy is given to patients in the hope that it will lead to a nonviable pathogen referred to as lethal mutagenesis (Chung et al. [2007], Graci et al. [2008]). In theory, as the mutation rates increase, the dominant strain changes to another strain (an error catastrophe) or results in complete eradication of all strains (extinction catastrophe) (Bull et al. [2005]).

A new approach suggested by Grenfell et al. [2004] combines epidemiology and evolutionary biology, and is applicable to rapidly evolving RNA viruses. Using a two-tiered approach, Koelle et al. [2010] model the epidemiological dynamics as the first tier via a stochastic $S_i I_i R_i$ model for each antigenic variant, then the genetic sequence evolution as the second tier to model production of new antigenic variants. The modeling simulations can be related to phylogenetic diagrams of virus lineages (e.g., influenza A and B) (Koelle et al. [2010]).

5. Summary. Gaps exist in modeling of wildlife viral zoonoses that need further investigation to move the field forward. Models that can evaluate the genomic trajectory of particular RNA viruses in reservoir host species are essential to understanding how viral zoonoses are maintained in nature. Additionally, models that incorporate selective pressures (e.g., resources such as food and water, predators, breeding cycles), infection history and the heterogeneity in an animal's ability to maintain and amplify a pathogen can be used to probe how viruses are maintained in their reservoirs and to determine what drives spill over

into new nonreservoir species. There is a need for increased surveillance of wildlife diseases and inclusion of this data in model formulation and analysis. Difficulties encountered due to case acquisition and underreporting, and lack of existing wildlife surveillance infrastructure and validated diagnostic tests need to be overcome (Stallknecht [2007]). Modeling is crucial given that the successful spill over event is rare, and can help drive hypothesis testing that can capture such events in controlled experimental or field settings. With respect to immunological pressures, many unanswered questions need to be addressed with models. For example, what are the mechanisms of the immune response in the wildlife host that lead to a persistent infection or to the possibility of a superspreader? How and why does it differ in the spill over dead-end host that either dies or has no productive infection? How does the immune response differ when a host is infected with a single versus multiple pathogens? What effects do seasonality or climate change have on the immune response and disease susceptibility? What are the drivers of host-switching events that lead to emergence of new disease? Formulation and analysis of more detailed within-host models to existing population level model structures will be necessary to accurately evaluate and predict risk of infection and development of disease in animal populations.

Our objective in this review is to emphasize the role of mathematical models in the study of viral zoonoses. The models described are mathematical, deterministic and stochastic, and are therefore limited in scope. We did not discuss statistical models or statistical techniques that are valuable in the study of viral zoonoses and that are especially important in fitting models to data. We mentioned briefly some of the computationally intensive models that use information about geography, landscape and environment to identify factors associated with high prevalence of disease in wildlife or to model disease spread. The list of references provides some additional sources for more details.

Deterministic and stochastic mathematical models are powerful and cost-effective tools. When used in conjunction with laboratory and field data and geographic information and remote sensing tools, they lead to a better understanding of the four stages of infection and transmission (Figure 2). Developing new models that cross disciplinary boundaries (integrating stages (1), (2), (3), and (4)), accurately describing the dynamics that take place within the wildlife reservoir and between

hosts and generating new hypotheses about viral evolution will help address some unanswered questions in the study of viral zoonoses in wildlife and spur new research in this area.

Acknowledgments. This work was assisted through participation in Mathematical Modeling of Virus Zoonoses Investigative Workshop at the National Institute for Mathematical and Biological Synthesis, sponsored by the National Science Foundation, the U.S. Department of Homeland Security and the U.S. Department of Agriculture through NSF Award #EF-0832858, with additional support from The University of Tennessee, Knoxville. The research of LJSA and CBJ is partially supported by a grant from the Fogarty International Center #R01TW006986-02 under the NIH NSF Ecology of Infectious Diseases initiative. The research of VLB is partially supported by a grant from the National Science Foundation DEB-0917853. The research of PvdD is partially supported by MITACS and NSERC. We thank the reviewers for their helpful suggestions.

Appendix A

The SIS model with standard incidence, disease fatalities and no natural births and deaths can be expressed as a function of the proportion of infectious individuals. This leads to a differential equation for $i = I/N$, where $0 \leq i \leq 1$,

$$\frac{di}{dt} = i[\beta - \gamma - \alpha - (\beta - \alpha)i].$$

Analysis of the preceding autonomous differential equation shows that if $\beta \leq \gamma + \alpha$, then $i(t) \to 0$. But if $\beta > \gamma + \alpha$, then $i(t) \to i^* = 1 - \gamma/(\beta - \alpha) \in (0, 1)$. The differential equation for the total population size can be expressed as

$$\frac{dN}{dt} = -\alpha i N. \tag{A1}$$

Hence, if $i(t) \to i^*$, then $N(t) \to 0$.

The SIRS model with standard incidence, disease fatalities, no natural births and deaths and temporary immunity δ, can be expressed in

terms of the proportion of susceptible or infectious individuals, where $s + i + r = 1$,

$$\frac{ds}{dt} = -\beta si + \delta(1 - i - s) + \alpha is,$$
$$\frac{di}{dt} = i[\beta s - \gamma - \alpha + \alpha i].$$

The preceding system can be easily shown to have a unique locally stable positive equilibrium $(s^*,\ i^*)$, $s^*,\ i^* \in (0,\ 1)$ iff $\beta > \gamma + \alpha$; the equilibrium $s = 1$ and $i = 0$ is a saddle point. Application of Dulac's criteria with Dulac function $B = 1/(si)$ shows there are no periodic solutions. Hence, if $\beta > \gamma + \alpha$, then $(s(t),\ i(t)) \to (s^*,\ i^*)$; whereas if $\beta \leq \gamma + \alpha$, $(s(t),\ i(t)) \to (1,\ 0)$. But if $i(t) \to i^* > 0$, the total population size is a solution of (A1), which implies $N(t) \to 0$.

Appendix B

The next generation matrix approach is used to define the basic reproduction number. It is assumed that the population has a stable disease-free equilibrium in the absence of disease. Only variables that represent infected individuals are considered. If $\vec{I} = (I_1, \ldots, I_n)^T$ denotes the vector of infected individuals, then linearizing the system of differential equations about the disease-free equilibrium yields $d\vec{I}/dt = J\vec{I}$, where $J = F - V$. Matrix F represents the rate of acquisition of new infections and matrix V represents the rate of recovery and transitions between infected classes. Some sufficient conditions guarantee that the basic reproduction number is the spectral radius of the next generation matrix (van den Driessche and Watmough [2002, 2008]). If these conditions are satisfied, then the next generation matrix, defined as $M = FV^{-1}$, gives

$$\mathcal{R}_0 = \rho(M).$$

The type reproduction number is defined in terms of the next generation matrix M. Only those variables in the vector of infected individuals $\vec{I}$ that are to be controlled are considered. For example, to eliminate disease spread by controlling I_1, let $e^T = (1,\ 0, \ldots,\ 0)$,

$P = (p_{ij})$, $p_{11} = 1$ and $p_{ij} = 0$, $i, j \neq 1, 1$. In the first generation, the number of infections of type 1 is $e^T Me = m_{11}$. In the second generation, the number of infections of type 1 is $e^T M[(\mathcal{I} - P)M]e$, where $\mathcal{I}$ is the identity matrix of order n. Therefore, in generation j, the number of infections of type 1 is $e^T M[(\mathcal{I} - P)M]^{j-1}e$. In general, the type reproduction for control of host type 1 is

$$\begin{aligned}\mathcal{T}_1 &= e^T M \sum_{k=0}^{\infty} [(\mathcal{I} - P)M]^k e \\ &= e^T M[\mathcal{I} - (\mathcal{I} - P)M]^{-1} e\end{aligned}$$

provided $\rho((\mathcal{I} - P)M) < 1$ and M is irreducible (Heesterbeek and Roberts [2007], Roberts and Heesterbeek [2003]). If all infected individuals $I_1, \ldots, I_n$ are to be controlled, then P, e and e^T are replaced by the identity matrix, and the spectral radius of the resulting matrix is taken. In this case the type reproduction number is the same as the basic reproduction number $\mathcal{T} = \rho(M) = \mathcal{R}_0$.

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