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MODELS FOR AN ARENAVIRUS INFECTION IN A RODENT POPULATION: CONSEQUENCES OF HORIZONTAL, VERTICAL AND SEXUAL TRANSMISSION

Chandrani Banerjee†, Linda J. S. Allen† and Jorge Salazar-Bravo‡

†Department of Mathematics and Statistics
Texas Tech University, Lubbock, TX 79409-1042, USA

‡Department of Biological Sciences
Texas Tech University, Lubbock, TX 79409-1031, USA

Abstract. Arenaviruses are associated with rodent-transmitted diseases in humans. Five arenaviruses are known to cause human illness: Lassa virus, Junin virus, Machupo virus, Guanarito virus and Sabia virus. In this investigation, we model the spread of Machupo virus in its rodent host *Calomys callosus*. Machupo virus infection in humans is known as Bolivian hemorrhagic fever (BHF) which has a mortality rate of approximately 5-30% [31].

Machupo virus is transmitted among rodents through horizontal (direct contact), vertical (infected mother to offspring) and sexual transmission. The immune response differs among rodents infected with Machupo virus. Either rodents develop immunity and recover (immunocompetent) or they do not develop immunity and remain infected (immunotolerant). We formulate a general deterministic model for male and female rodents consisting of eight differential equations, four for females and four for males. The four states represent susceptible, immunocompetent, immunotolerant and recovered rodents, denoted as S, I^t, I^c and R, respectively. A unique disease-free equilibrium (DFE) is shown to exist and a basic reproduction number $\mathcal{R}_0$ is computed using the next generation matrix approach. The DFE is shown to be locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

Special cases of the general model are studied, where there is only one immune stage, either I^t or I^c. In the first model, SI^cR^c, it is assumed that all infected rodents are immunocompetent and recover. In the second model, SI^t, it is assumed that all infected rodents are immunotolerant. For each of these models, the basic reproduction numbers are computed and their relationship to the basic reproduction number of the general model determined. For the SI^t model, it is shown that bistability may occur, the DFE and an enzootic equilibrium, with all rodents infectious, are locally asymptotically stable for the same set of parameter values. A simplification of the SI^t model yields a third model, where the sexes are not differentiated, and therefore, there is no sexual transmission. For this third simplified model, the dynamics are completely analyzed. It is shown that there exists a DFE and possibly two additional equilibria, one of which is globally asymptotically stable for any given set of parameter values; bistability does not occur. Numerical examples illustrate the dynamics of the models. The biological implications of the results and future research goals are discussed in the conclusion.

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1. **Introduction.** Arenaviruses are a family of viruses, some of which are associated with rodent-transmitted diseases in humans. Each virus is associated with a particular rodent reservoir. The arenaviruses are divided into two groups: the New World and the Old World. Lassa virus is the only Old World virus known to cause human disease. New World viruses that cause human disease are Junin virus, Machupo virus, Guanarito virus and Sabia virus [27]. Our goal is to model the spread of Machupo virus in its rodent reservoir, identified as the vesper mouse, *Calomys callosus* [14, 15]. Machupo virus infection in humans is known as Bolivian hemorrhagic fever (BHF), named because it was first isolated during an outbreak in 1963 in San Joaquin, Bolivia, near the Machupo River [20, 25]. Cases of person-to-person spread are uncommon, but spread among nursing and laboratory staff and family of infected individuals has been reported [18]. The mortality rate for BHF is approximately 5-30% [31].

Little information is published about the ecology, immunology or natural history of the reservoir species *C. callosus*. Kuns [19] reported *C. callosus* as a pastoral species often located in grasslands and along forest edges around the town of San Joaquin. He also remarked on the commensalism of this species with humans, as many individuals were trapped in and around houses. Information about the natural history of *C. callosus* is based on several years of data from laboratory rearing of this species [17]. The report stated that breeding was continuous throughout the year. Sexual maturity was attained at about eight weeks, estrous cycle was six days and the gestation period was estimated as 21 days [17]. Average litter size was approximately six, with high weaning ratios [17]. Laboratory studies where *C. callosus* rodents from San Joaquin (of known age) were challenged with known quantities of viral loads showed a split response into two groups of phenotypes [34]. Either they were characterized by persistent viremia, little or no antibody production and reduced fertility in females (i.e., immunotolerant) or completely (or nearly so) cleared viremia, presented antibodies, did not shed virus and showed no reduced fertility (i.e., immunocompetent) [34].

Arenaviruses have three modes of transmission in rodents: horizontal transmission (direct contact), vertical transmission (infected mother to offspring) and sexual transmission. These modes of transmission differ from those of other rodent-borne zoonoses such as hantaviruses. In hantaviruses, the primary mode of transmission is horizontal. Although differing in modes of transmission, hantaviruses are similar to arenaviruses in many respects. Hantaviruses, like arenaviruses, are generally associated with a single rodent reservoir population, where the disease is maintained [10]. Continuous contamination of the environment by infectious urine shed by infected peridomestic rodents is the primary mode of infection in humans for both diseases [10]. In addition, hantavirus or arenavirus infection in humans is associated with increased densities of the rodent reservoir [10]. Hantavirus infection in humans results in either hemorrhagic fever with renal syndrome, common in Europe and Asia, or hantavirus pulmonary syndrome (HPS), common in the Americas [23]. HPS and BHF are both recognized as emerging diseases and as agents with bioterrorism potential.

Mathematical models have been developed and analyzed for the spread of hantaviruses in rodent populations [1, 2, 4, 5, 6, 21, 22, 28, 29, 35, 36], but few have been developed for arenaviruses [5, 7]. The models developed by Allen and colleagues [4, 6] for hantavirus included the dynamics of susceptible, exposed, infective and recovered (SEIR) male and female rodents. Both deterministic (ordinary differential

equations) and stochastic (stochastic differential equations) models were developed. Numerical examples and simulations were based on data for the hantavirus Bayou virus, present in the United States, whose reservoir host is the rice rat. Numerical simulations showed that environmental and seasonal variability in the carrying capacity may result in hantavirus outbreaks in rodent populations [4]. McCormack and Allen applied SI and SIR models to investigate the role of spillover species [21] and the importance of multiple habitats or patches on hantavirus persistence [22]. The models of Abramson and colleagues [1, 2] were applied to one of the most common hantaviruses in the United States, Sin Nombre virus, whose reservoir species is deer mice. Their models were reaction-diffusion systems of partial differential equations for susceptible and infected mice. Traveling wave solutions were studied as a function of a variable carrying capacity. The models of Sauvage and colleagues [28, 29, 36] were applied to a hantavirus common in Europe and Asia, Puumala virus, whose reservoir species is bank voles. Their model was a system of ordinary differential equations, where rodents were infected in two habitats: optimal and suboptimal [28]. In addition, the indirect effect of viral contamination of the ground was considered in both rodents and humans. The effects of a periodic birth and carrying capacity and direct and indirect transmission in a rodent population were investigated [28, 29, 36] as well as the effect of indirect transmission on human infection [29, 36]. The model of Allen et al. [5] was applied to a hantavirus (Black Creek Canal virus) and to an arenavirus (Tamiami virus), present in the United States, both of whose reservoir species is cotton rats. Their model distinguished between the modes of transmission; the hantavirus was transmitted horizontally, whereas the arenavirus primary mode of transmission was vertical. Conditions were determined for the two strains to coexist in a cotton rat population. The hantavirus model developed by Wesley et al. [35] was a system of difference equations, structured by the stages of the infection (susceptible and infected), the stages of development (juvenile, subadult and adult) and the sex of the rodent (male and female). The basic reproduction number was calculated for this model and its sensitivity to model parameters was examined.

Our new model for Machupo virus includes some of the features of these hantavirus models. The rodent population is divided into the following disease stages: susceptible, infectious and recovered. As was the case for most of the hantavirus models, we assume that horizontal transmission is density-dependent (mass action incidence). Increases in rodent population density increase the probability of contact and consequently, increase horizontal transmission. Unlike the hantavirus models, we include vertical and sexual transmission and two immune states in the infectious stage, either immunocompetent or immunotolerant, as suggested by the data on Machupo virus [32, 33, 34]. In a recent model developed by Dimitrov et al. [13] both the immunology and the epizootiology are included in a model for the spread of rabies in a bat population; sexual transmission does not occur.

Sexually transmitted diseases occur throughout the animal kingdom and they affect the host population dynamics very differently than do other directly transmitted infectious diseases [26]. In sexual transmission, it is often assumed that the rate of spread depends on the proportion or frequency rather than the population density (standard incidence) [24, 26]. But it has also been suggested that in sexually transmitted diseases, density-dependent transmission is more appropriate than frequency-dependent transmission [26]. In our model, we assume frequency-dependent sexual transmission (standard incidence).

In the next section, we formulate a general model for Machupo virus infection in a rodent population. The model is formulated in terms of a system of ordinary differential equations for the different stages of infection (susceptible, infectious and recovered), the sex of the rodent (male and female) and the immune response of infectious individuals (immunocompetent and immunotolerant). The general model consists of eight differential equations, four for males and four for females. The basic reproduction number is computed for this general model. Two special cases of the general model are studied in Sections 3 and 4, an SIR model, where all infected individuals are immunocompetent and eventually recover and an SI model where all infected individuals are immunotolerant and remain infected. For these two models, the basic reproduction numbers $\mathcal{R}_0$ are computed and for the SI model, a second reproduction number $\mathcal{R}$, associated with an enzootic equilibrium, is computed. The SI model is simplified further so that males and females are not differentiated; only females are modeled so there is no sexual transmission (Section 5). In this simple model, the dynamics are completely analyzed. The dynamics of the models are illustrated in several numerical examples. The concluding section is a summary of our findings and a discussion of control measures for reduction of BHF in humans and of future research goals.

2. General model.

2.1. Model formulation.

The underlying assumptions in the mathematical models for Machupo virus infection in a population of *C. callosus* are based on published work [14, 15, 17, 19, 32, 33, 34]. Machupo virus is transmitted horizontally, sexually, and vertically, and rodents infected with Machupo virus have a split response. Infectious rodents either shed the virus continuously and are antibody-negative I^t, or they shed virus for a short period of time, become antibody-positive I^c and eventually recover.

The four disease stages of the general model are susceptible (uninfected) S, infectious and antibody-negative I^t, infectious and antibody-positive I^c and recovered R^c. The susceptible rodents infected with Machupo virus follow one of two paths: $S \to I^t$ or $S \to I^c \to R^c$. The stages for males are denoted by a subscript m and females by a subscript f. For example, uninfected male rodents are denoted as S_m and recovered immunocompetent males are denoted as I^c_m.

To simplify the notation in the model, we let $N_m = S_m + R^c_m$ and $I_m = I^t_m + I^c_m$ denote the densities of noninfectious and infectious male rodents, respectively. Similar definitions apply to females (N_f and I_f). In addition, we let $N = N_m + N_f$ and $I = I_m + I_f$ denote the densities of noninfectious and infectious rodents, respectively. Finally, we let $M = N_m + I_m$, $F = N_f + I_f$ and $T = M + F$ denote the total population densities of males, females and both males and females, respectively.

Other model assumptions and model parameters are defined. The recovery rate for immunocompetent males is γ_m, and for immunocompetent females it is γ_f. Disease-related death rates for male and female rodents in stages I^t are δ_m and δ_f, respectively. No disease-related deaths occur in stage I^c. Because of the split response, the transmission and birth rates of infectious rodents are split into two parts. The average number of rodents, born to infectious parents, that survive to reproductive age, is split between immunotolerant and immunocompetent newborns, b^t and b^c, respectively, where $b^t + b^c \leq b$, $0 \leq b^t < b^c$ and b is the number of

rodents, born to noninfectious parents, that survive to reproductive age. Immunocompetent males and females may also develop persistent infections and become immunotolerant at a rate ϵ [16], a switch of immune response.

Studies show that contacts between two males (aggressive behavior to defend the territory) are greater than between two females. Therefore, we assume different transmission coefficients for males and females. The horizontal transmission coefficient for males is β_m while all other horizontal transmission coefficients are β. It follows for a Machupo virus infection that $\beta_m \gg \beta$. However, for comparison purposes, we consider the special case where horizontal transmission is the same for both sexes, $\beta_m = \beta$. Horizontal transmission is density-dependent (mass action incidence) with transmission split between immunocompetent and immunotolerant. The transmission coefficient for males is $\beta_m = \beta_m^t + \beta_m^c$ and for females it is $\beta = \beta^t + \beta^c$. For example, susceptible males can be infected by infectious males or infectious females:

$$S_m[(\beta_m^t + \beta_m^c)I_m + (\beta^t + \beta^c)I_f].$$

The immune response is not a genetic trait but an individual response; thus, contact with infectious rodents that are either immunocompetent or immunotolerant results in infectious rodents of one of the two types.

The sexual transmission coefficient is $\lambda = \lambda^t + \lambda^c$ (mating that results in a susceptible adult becoming infectious), where rate of sexual transmission is frequency-dependent (standard incidence):

$$(\lambda_m^t + \lambda_m^c)\frac{S_m I_f}{T} \quad \text{and} \quad (\lambda_f^t + \lambda_f^c)\frac{S_f I_m}{T}.$$

Sexual transmission is included in one of the birth terms in that newborns from mating between an infectious male parent I_m and a noninfectious female parent N_f result in an infectious newborn, either immunocompetent or immunotolerant (equally divided among males and female newborns),

$$b^c\frac{I_m N_f}{T} \quad \text{or} \quad b^t\frac{I_m N_f}{T}.$$

Vertical transmission from infectious mothers is also part of the birth terms,

$$b^c\frac{MI_f}{T} \quad \text{or} \quad b^t\frac{MI_f}{T}.$$

Therefore, the total birth rate for infectious rodents leads to

$$b^c\frac{N_m I_f + FI_m}{T} \quad \text{or} \quad b^t\frac{N_m I_f + FI_m}{T}$$

and the birth rate for noninfectious rodents is

$$\frac{bN_m N_f}{T}.$$

The expression for the birth function is based on the harmonic mean (one of the most commonly used birth functions) in that the total number of births for a population that is not infected is $2bMF/T$ [9]. In this formulation, complete vertical transmission is assumed; all newborns from infectious parents are infectious.

Finally, in the absence of infection, the rodent population is assumed to follow logistic growth, dependent on the environmental carrying capacity K. The natural

death rate $d(T)$ is a linear increasing function of the total population size T, $d(T) = a + cT$, with the property that $d(K) = b/2$ or

$$K = \frac{b/2 - a}{c} > 0. \tag{1}$$

This latter assumption is due to the fact that the population stabilizes when the birth rate is equal to the death rate. The fraction $b/2$ appears rather than b because only half of the population (females) is responsible for the births. In a male-female population with no infection, the population size will approach the carrying capacity K.

Based on the preceding assumptions, the following four differential equations model the dynamics of the male population:

$$\begin{aligned}
\frac{dS_m}{dt} &= \frac{bN_mN_f}{T} - (\lambda_m^t + \lambda_m^c)\frac{S_mI_f}{T} - S_m[(\beta_m^t + \beta_m^c)I_m + (\beta^t + \beta^c)I_f] - d(T)S_m \\
\frac{dI_m^t}{dt} &= b^t\frac{N_mI_f + FI_m}{T} + \lambda_m^t\frac{S_mI_f}{T} + S_m(\beta_m^tI_m + \beta^tI_f) - \delta_mI_m^t + \epsilon I_m^c - d(T)I_m^t \\
\frac{dI_m^c}{dt} &= b^c\frac{N_mI_f + FI_m}{T} + \lambda_m^c\frac{S_mI_f}{T} + S_m(\beta_m^cI_m + \beta^cI_f) - \gamma_mI_m^c - \epsilon I_m^c - d(T)I_m^c \\
\frac{dR_m^c}{dt} &= \gamma_mI_m^c - d(T)R_m^c.
\end{aligned} \tag{2}$$

Similar equations apply to females, with the exception that horizontal transmission coefficients for females differ from males:

$$\begin{aligned}
\frac{dS_f}{dt} &= \frac{bN_mN_f}{T} - (\lambda_f^t + \lambda_f^c)\frac{S_fI_m}{T} - S_f(\beta^t + \beta^c)I - d(T)S_f \\
\frac{dI_f^t}{dt} &= b^t\frac{N_mI_f + FI_m}{T} + \lambda_f^t\frac{S_fI_m}{T} + \beta^tS_fI - \delta_fI_f^t + \epsilon I_f^c - d(T)I_f^t \\
\frac{dI_f^c}{dt} &= b^c\frac{N_mI_f + FI_m}{T} + \lambda_f^c\frac{S_fI_m}{T} + \beta^cS_fI - \gamma_fI_f^c - \epsilon I_f^c - d(T)I_f^c \\
\frac{dR_f^c}{dt} &= \gamma_fI_f^c - d(T)R_f^c.
\end{aligned} \tag{3}$$

Parameters b, a and c are positive and all other parameters are nonnegative. Initial conditions are nonnegative with $M(0) > 0$ and $F(0) > 0$. It is straightforward to show that solutions are nonnegative for $t \geq 0$.

A compartmental diagram for one sex (either male or female) is graphed in Figure 1. The diagram illustrates the transition rates between stages (disease transmission or recovery), death rates and birth rates.

In the absence of infection, $I_m^k \equiv 0 \equiv I_f^k$, $k = t, c$, the total population size satisfies a logistic growth assumption for males and females:

$$\begin{aligned}
\frac{dN_m}{dt} &= b\frac{N_mN_f}{T} - d(T)N_m \\
\frac{dN_f}{dt} &= b\frac{N_mN_f}{T} - d(T)N_f,
\end{aligned} \tag{4}$$

where $T = N_m + N_f$. The population model (4) has a unique, globally stable equilibrium at $\bar{N}_m = K/2 = \bar{N}_f$ (see [6], pp. 522-523). Therefore, the total population size $T(t) \to K$, the environmental carrying capacity, and $R_m^c(t), R_f^c(t) \to$

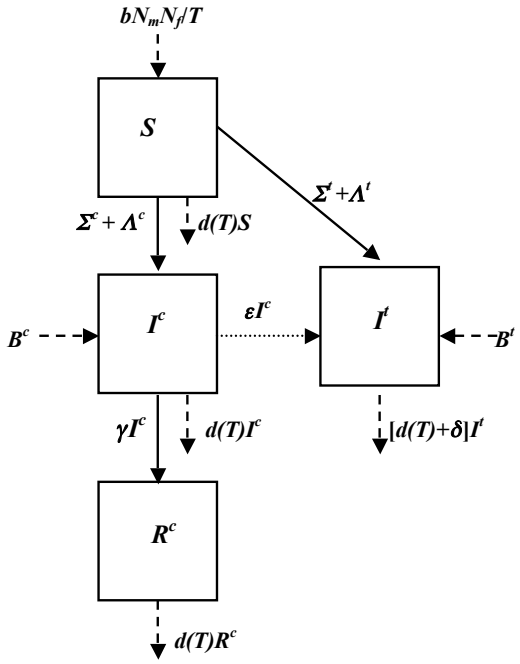

FIGURE 1. Compartmental diagram of the SIR model for one sex; subscripts m and f are omitted on the variables S, I^t, I^c, R and on the parameters for disease-related deaths δ and for per capita recovery rate γ. Vertical incidence rates for males or females for the immunotolerant and immunocompetent stages are $B^t = b^t(N_mI_f + FI_m)/T$ and $B^c = b^c(N_mI_f + FI_m)/T$, respectively. Horizontal incidence rates for males for the immunotolerant and immunocompetent stages are $\Sigma^t+\Lambda^t = S_m(\beta^t_mI_m+\beta^tI_f)+\lambda^t_mS_mI_f/T$ and $\Sigma^c + \Lambda^c = S_m(\beta^c_mI_m + \beta^cI_f) + \lambda^c_mS_mI_f/T$, respectively. Horizontal incidence rates for females for the immunotolerant and immunocompetent stages are $\Sigma^t + \Lambda^t = \beta^tS_fI + \lambda^t_fS_fI_m/T$ and $\Sigma^c + \Lambda^c = \beta^cS_fI + \lambda^c_fS_fI_m/T$, respectively.

0 as $t \to \infty$. Hence, in the absence of disease, the rodent population approaches a unique disease-free equilibrium (DFE), where

$$\bar{S}_m = \frac{K}{2} = \bar{S}_f \tag{5}$$

and the equilibrium value for all of the other disease stages is zero.

With infection, the total population size is reduced below the carrying capacity. This can be seen from the following inequality:

$$\frac{dT}{dt} \le 2b\frac{MF}{T} - d(T)T \le T\left[\frac{b}{2} - d(T)\right] = T\left[\frac{b}{2} - a - cT\right].$$

Comparison of this differential equation with the solution $u(t)$ to the differential equation $du/dt = u[b/2 - a - cu]$, where $u(0) = T(0)$, it follows that $T(t) \le u(t)$ for

$t > 0$. But $u(t) \to K$. Hence, when there is infection, the total population size T will be less than the carrying capacity K.

For the general male-female epizootic model (2)-(3) we will determine conditions for stability of the DFE by applying the next generation matrix approach [12, 30]. There exist other equilibria, the extinction equilibrium and enzootic equilibria, where some rodents are infectious, but explicit forms for the enzootic equilibria are hard to compute for the general model (2)-(3). In the numerical examples (Section 6), we show existence and stability of an enzootic equilibrium for model (2)-(3). The extinction or zero equilibrium exists for the general model as a limiting case. Letting all of the state variables approach zero (through positive values) forces the right side of the differential equations to approach zero. For example, note that

$$\lim_{N_m, N_f \to 0^+} \frac{bN_m N_f}{T} = 0 = \lim_{S_m, S_f \to 0^+} \frac{S_m I_f}{T}.$$

We do not study the stability of the extinction equilibrium for any of the models except in a special case of the simple SI model in Section 5. Linear stability analyses cannot be applied to the extinction equilibrium because of the singularity at the origin. However, we found in all of the numerical examples that solutions did not approach the origin; the extinction equilibrium was not stable.

2.2. **Analysis of the general model.** We calculate the basic reproduction $\mathcal{R}_0$ for the general male-female model (2)-(3) based on the next generation matrix approach [12, 30]. The system is rearranged so that the first four equations represent the infectious states and the last four the noninfectious states:

$$\dot{x} = \mathcal{F}(x) - \mathcal{V}(x),$$

where $x = \left[I_m^t, I_m^c, I_f^t, I_f^c, S_m, S_f, R_m^c, R_f^c\right]^T$, $\mathcal{F}(x)$ equals

$$\begin{bmatrix} b^t \dfrac{N_m I_f + F I_m}{T} + \lambda_m^t \dfrac{S_m I_f}{T} + S_m(\beta_m^t I_m + \beta^t I_f) \\ b^c \dfrac{N_m I_f + F I_m}{T} + \lambda_m^c \dfrac{S_m I_f}{T} + S_m(\beta_m^c I_m + \beta^c I_f) \\ b^t \dfrac{N_m I_f + F I_m}{T} + \lambda_f^t \dfrac{S_f I_m}{T} + \beta^t S_f I \\ b^c \dfrac{N_m I_f + F I_m}{T} + \lambda_f^c \dfrac{S_f I_m}{T} + \beta^c S_f I \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

and $\mathcal{V}(x)$ equals

$$\begin{bmatrix} \delta_m I_m^t + d(T) I_m^t - \epsilon I_m^c \\ \gamma_m I_m^c + d(T) I_m^c + \epsilon I_m^c \\ \delta_f I_f^t + d(T) I_f^t - \epsilon I_f^c \\ \gamma_f I_f^c + d(T) I_f^c + \epsilon I_f^c \\ -\dfrac{bN_m N_f}{T} + (\lambda_m^t + \lambda_m^c)\dfrac{S_m I_f}{T} + S_m[(\beta_m^t + \beta_m^c) I_m + (\beta^t + \beta^c) I_f] + d(T) S_m \\ -\dfrac{bN_m N_f}{T} + (\lambda_f^t + \lambda_f^c)\dfrac{S_f I_m}{T} + S_f(\beta^t + \beta^c) I + d(T) S_f \\ -\gamma_m I_m^c + d(T) R_m^c \\ -\gamma_f I_f^c + d(T) R_f^c \end{bmatrix}.$$

Differentiation of the right side of $\dot{x}$ and evaluation at the DFE (given by (5) but denoted x_o) leads to the following matrix:

$$\mathcal{D}(F-V)(x_o) = \begin{bmatrix} F-V & O \\ A & J \end{bmatrix}, \tag{6}$$

where O is the zero matrix and J equals

$$J = \begin{bmatrix} -\frac{b}{4} - c\frac{K}{2} & \frac{b}{4} & 0 & 0 \\ \frac{b}{4} & -\frac{b}{4} - c\frac{K}{2} & 0 & 0 \\ 0 & 0 & -\frac{b}{2} & 0 \\ 0 & 0 & 0 & -\frac{b}{2} \end{bmatrix}, \tag{7}$$

where $c = d'(K)$. Matrix J is block-diagonal with 2×2 block matrices along the diagonal. Each of the 2×2 matrices have traces that are negative and determinants that are positive. Hence by the Routh-Hurwitz criteria the eigenvalues of J have negative real parts [3]. Matrix A plays no role in stability of the DFE. Thus, the DFE is locally asymptotically if $F - V$ has eigenvalues with negative real parts. Van den Dreissche and Watmough [30] (Theorem 2, p. 33) have shown that linear stability is equivalent to the spectral radius of the next generation matrix FV^{-1} satisfying $\rho(FV^{-1}) < 1$. This latter expression is known as the basic reproduction number,

$$\mathcal{R}_0 = \rho(FV^{-1}).$$

Matrices F and V^{-1} equal

$$\begin{bmatrix} \frac{\beta_m^t K + b^t}{2} & \frac{\beta_m^t K + b^t}{2} & \frac{\beta^t K + b^t + \lambda_m^t}{2} & \frac{\beta^t K + b^t + \lambda_m^t}{2} \\ \frac{\beta_m^c K + b^c}{2} & \frac{\beta_m^c K + b^c}{2} & \frac{\beta^c K + b^c + \lambda_m^c}{2} & \frac{\beta^c K + b^c + \lambda_m^c}{2} \\ \frac{\beta^t K + b^t + \lambda_f^t}{2} & \frac{\beta^t K + b^t + \lambda_f^t}{2} & \frac{\beta^t K + b^t}{2} & \frac{\beta^t K + b^t}{2} \\ \frac{\beta^c K + b^t + \lambda_f^c}{2} & \frac{\beta^c K + b^t + \lambda_f^c}{2} & \frac{\beta^c K + b^c}{2} & \frac{\beta^c K + b^c}{2} \end{bmatrix}$$

and

$$\begin{bmatrix} \frac{1}{\delta_m + b/2} & \frac{\epsilon}{(\delta_m + b/2)(\gamma_m + b/2 + \epsilon)} & 0 & 0 \\ 0 & \frac{1}{\gamma_m + b/2 + \epsilon} & 0 & 0 \\ 0 & 0 & \frac{1}{\delta_f + b/2} & \frac{\epsilon}{(\delta_m + b/2)(\gamma_f + b/2 + \epsilon)} \\ 0 & 0 & 0 & \frac{1}{\gamma_f + b/2 + \epsilon} \end{bmatrix},$$

respectively. Thus, for model (2)-(3), the next generation matrix FV^{-1} is

$$\begin{bmatrix} \frac{(\beta_m^t K + b^t)/2}{\delta_m + b/2} & \frac{\Delta_m(\beta_m^t K + b^t)/2}{\gamma_m + b/2 + \epsilon} & \frac{(\beta^t K + b^t + \lambda_m^t)/2}{\delta_f + b/2} & \frac{\Delta_f(\beta^t K + b^t + \lambda_m^t)/2}{\gamma_f + b/2 + \epsilon} \\ \frac{(\beta_m^c K + b^c)/2}{\delta_m + b/2} & \frac{\Delta_m(\beta_m^c K + b^c)/2}{\gamma_m + b/2 + \epsilon} & \frac{(\beta^c K + b^c + \lambda_m^c)/2}{\delta_f + b/2} & \frac{\Delta_f(\beta^c K + b^c + \lambda_m^c)/2}{\gamma_f + b/2 + \epsilon} \\ \frac{(\beta^t K + b^t + \lambda_f^t)/2}{\delta_m + b/2} & \frac{\Delta_m(\beta^t K + b^t + \lambda_f^t)}{\gamma_m + b/2 + \epsilon} & \frac{(\beta^t K + b^t)/2}{\delta_f + b/2} & \frac{\Delta_f(\beta^t K + b^t)/2}{\gamma_f + b/2 + \epsilon} \\ \frac{(\beta^c K + b^c + \lambda_f^c)}{\delta_m + b/2} & \frac{\Delta_m(\beta^c K + b^c + \lambda_f^c)/2}{\gamma_m + b/2 + \epsilon} & \frac{(\beta^c K + b^c)/2}{\delta_f + b/2} & \frac{\Delta_f(\beta^c K + b^c)/2}{\gamma_f + b/2 + \epsilon} \end{bmatrix},$$

where

$$\Delta_m = \frac{\delta_m + b/2 + \epsilon}{\delta_m + b/2} \quad \text{and} \quad \Delta_f = \frac{\delta_f + b/2 + \epsilon}{\delta_f + b/2}.$$

Matrix FV^{-1} has two zero eigenvalues, and the remaining eigenvalues are the solutions to a quadratic equation. Hence, the spectral radius of matrix FV^{-1} or $\mathcal{R}_0$ can be expressed as

$$\mathcal{R}_0 = \rho(FV^{-1}) = B + \sqrt{B^2 - C}. \tag{8}$$

For the case $\epsilon = 0$, $\Delta_m = 1 = \Delta_f$, the coefficients B and C in (8) are

$$\begin{aligned} B &= \frac{1}{4}\left[\frac{\beta_m^t K + b^t}{\delta_m + b/2} + \frac{\beta_m^c K + b^c}{\gamma_m + b/2} + \frac{\beta^t K + b^t}{\delta_f + b/2} + \frac{\beta^c K + b^c}{\gamma_f + b/2}\right] \\ C &= \frac{1}{4}\frac{(\beta^t K + b^t + \lambda_f^t)(\beta^t K + b^t + \lambda_m^t) - (\beta_m^t K + b^t)(\beta^t K + b^t)}{(\delta_f + b/2)(\delta_m + b/2)} \\ &\quad + \frac{1}{4}\frac{(\beta^t K + b^t + \lambda_m^t)(\beta^c K + b^c + \lambda_f^c) - (\beta_m^t K + b^t)(\beta^c K + b^c)}{(\delta_m + b/2)(\gamma_f + b/2)} \\ &\quad + \frac{1}{4}\frac{(\beta^t K + b^t + \lambda_f^t)(\beta^c K + b^c + \lambda_m^c) - (\beta_m^c K + b^c)(\beta^t K + b^t)}{(\delta_f + b/2)(\gamma_m + b/2)} \\ &\quad + \frac{1}{4}\frac{(\beta^c K + b^c + \lambda_f^c)(\beta^c K + b^c + \lambda_m^c) - (\beta_m^c K + b^c)(\beta^c K + b^c)}{(\gamma_f + b/2)(\gamma_m + b/2)}. \end{aligned}$$

In general, $\mathcal{R}_0$ increases with ϵ (as more rodents become persistently infectious or immunotolerant). Applying Theorem 2 in [30] (p. 33) to model (2)-(3), we have the following result concerning local stability of the DFE.

THEOREM 2.1. *The general male-female epizootic model (2)-(3) has a unique DFE given by (5) and a basic reproduction $\mathcal{R}_0$ defined in (8). If $\mathcal{R}_0 < 1$, then the DFE is locally asymptotically stable and if $\mathcal{R}_0 > 1$, it is unstable.*

The form of $\mathcal{R}_0$ is quite complicated but specific terms can be interpreted. For example, note that each of the four terms in the expression for B (when $\epsilon = 0$) is the sum of two terms, horizontal and vertical transmission. Hence, the four terms in the expression for B represent secondary transmission due to horizontal and vertical transmission from (1) the male immunotolerant class, (2) the male immunocompetent class, (3) the female immunotolerant class and (4) the female immunocompetent class.

If $\mathcal{R}_0 > 1$, there is a potential for disease outbreak and for the disease to persist in the population. If $\epsilon = 0$, we consider several special cases. First, suppose there

is no sexual transmission, $\lambda_j^k = 0$, $j = m, f$, $k = t, c$ and equal male and female transmission, $\beta_m^t = \beta^t$ and $\beta_m^c = \beta^c$; then

$$\mathcal{R}_0 = \frac{1}{2}\left[\frac{\beta^t K + b^t}{\delta_m + b/2} + \frac{\beta^t K + b^t}{\delta_f + b/2} + \frac{\beta^c K + b^c}{\gamma_m + b/2} + \frac{\beta^c K + b^c}{\gamma_f + b/2}\right]. \tag{9}$$

The basic reproduction number $\mathcal{R}_0$ is just the sum of transmission from the four classes described previously. If, in addition, $\delta_m = \delta_f = \delta$ and $\gamma_m = \gamma_f = \gamma$ so that the disease-related death rates and recovery rates are the same for both males and females, then the expression for $\mathcal{R}_0$ simplifies even further,

$$\mathcal{R}_0 = \frac{\beta^t K + b^t}{\delta + b/2} + \frac{\beta^c K + b^c}{\gamma + b/2}. \tag{10}$$

It is clear from the previous expressions that $\mathcal{R}_0$ can be greater than one if the horizontal and/or vertical transmission parameters are sufficiently large. But it is also possible for vertical or sexual transmission alone to result in disease outbreaks (with $\mathcal{R}_0 > 1$). As a second case, suppose there is no horizontal nor sexual transmission, only vertical transmission, $\beta_j^k = 0$ and $\lambda_j^k = 0$, $j = m, f$; $k = t, c$. Then

$$\mathcal{R}_0 = \frac{b^t}{2}\left[\frac{1}{\delta_f + b/2} + \frac{1}{\delta_m + b/2}\right] + \frac{b^c}{2}\left[\frac{1}{\gamma_f + b/2} + \frac{1}{\gamma_m + b/2}\right]. \tag{11}$$

If b^t and b^c are sufficiently large, then there is a possibility of disease outbreak due to vertical transmission. As a third case, suppose there is no horizontal nor vertical transmission, only sexual transmission, $b^t = 0 = b^c$ and $\beta_j^k = 0$, $j = m, f$; $k = t, c$ (infectious individuals do not reproduce). Then $\mathcal{R}_0$ simplifies to

$$\frac{1}{2}\left[\frac{\lambda_m^t \lambda_f^t}{(\delta_m + b/2)(\delta_f + b/2)} + \frac{\lambda_m^t \lambda_f^c}{(\delta_m + b/2)(\gamma_f + b/2)} + \frac{\lambda_m^c \lambda_f^t}{(\gamma_m + b/2)(\delta_f + b/2)} + \frac{\lambda_m^c \lambda_f^c}{(\gamma_m + b/2)(\gamma_f + b/2)}\right]^{1/2}. \tag{12}$$

If the parameters, λ_j^k, $j = m, f$; $k = t, c$, are sufficiently large, then there is a potential for disease outbreak due to sexual transmission.

To better understand the role played by the immunocompetent and immunotolerant disease stages, simplifications of the general male-female model (2)-(3) are studied in the next two sections. Two models are considered, where animals exhibit only one type of immune response, either immunocompetent or immunotolerant. For these two models, their basic reproduction numbers are calculated and their relationship to the basic reproduction number for the general male-female model is shown. In addition, it is shown that if there is no recovery, then vertical transmission in the male-female immunotolerant model (Section 4) may result in bistability.

3. **SIR model.**

3.1. **Model description.**

The general male-female model is simplified to one where there are only immunocompetent animals. In this case there are only three disease stages: susceptible (uninfected) S, infectious I^c and recovered R^c. The difference between this new SIR model and model (2)-(3) is that there is no I^t stage. All the infectious rodents ultimately recover. There are still three modes of transmission: horizontal, sexual and vertical. We use the same notation as in the general male-female model (2)-(3). The horizontal transmission coefficients are β_m^c (male-to-male

transmission) and β^c (all other horizontal transmission). The sexual transmission coefficients are λ_m^c for males and λ_f^c for females. The recovery rates are γ_m for males and γ_f for females. The death rate $d(T) = a + cT$, where the carrying capacity K is given by (1). In addition, let $M = S_m + I_m^c + R_m^c$, $F = S_f + I_f^c + R_f^c$, $I = I_m^c + I_f^c$, $N_m = S_m + R_m^c$, $N_f = S_f + R_f^c$ and $T = M + F$.

The differential equations for the SI^cR^c model have the following form:

$$\begin{aligned}
\frac{dS_m}{dt} &= \frac{bN_mN_f}{T} - \lambda_m^c \frac{S_m I_f^c}{T} - S_m[\beta_m^c I_m^c + \beta^c I_f^c] - d(T)S_m \\
\frac{dI_m^c}{dt} &= b^c \frac{N_m I_f^c + F I_m^c}{T} + \lambda_m^c \frac{S_m I_f^c}{T} + S_m[\beta_m^c I_m^c + \beta^c I_f^c] - \gamma_m I_m^c - d(T)I_m^c \\
\frac{dR_m^c}{dt} &= \gamma_m I_m^c - d(T)R_m^c
\end{aligned} \tag{13}$$

$$\begin{aligned}
\frac{dS_f}{dt} &= \frac{bN_mN_f}{T} - \lambda_f^c \frac{S_f I_m^c}{T} - \beta^c S_f I - d(T)S_f \\
\frac{dI_f^c}{dt} &= b^c \frac{N_m I_f^c + F I_m^c}{T} + \lambda_f^c \frac{S_f I_m^c}{T} + \beta^c S_f I - \gamma_f I_f^c - d(T)I_f^c \\
\frac{dR_f^c}{dt} &= \gamma_f I_f^c - d(T)R_f^c.
\end{aligned} \tag{14}$$

Parameters b, a and c are positive and all other parameters are nonnegative. Initial conditions are nonnegative with $M(0) > 0$ and $F(0) > 0$. In addition, $b \geq b^c$. Solutions to (13)-(14) are nonnegative for $t \geq 0$ and $T(t) > 0$ for $t \geq 0$. If there is no reduction in fertility for the immunocompetent individuals (and no immunotolerant class for this model), then, as noted by Webb et al. [34], $b^c = b$. Hence, the male and female subpopulations satisfy the differential equations given in (4). That is,

$$\begin{aligned}
\frac{dM}{dt} &= b\frac{MF}{T} - d(T)M \\
\frac{dF}{dt} &= b\frac{MF}{T} - d(T)F,
\end{aligned} \tag{15}$$

where $T = M + F$. Hence, $M(t), F(t) \to K/2$ and $T(t) \to K$ as $t \to \infty$. There is no reduction in the population size.

3.2. **Analysis of the SIR model.** For model (13)-(14) the unique DFE is given by (5), the same equilibrium as in the general male-female model. To calculate the basic reproduction number $\mathcal{R}_0$ for the SIR model (13)-(14), the terms are rearranged so that

$$\dot{x} = \left[\dot{I}_m^c, \dot{I}_f^c, \dot{S}_m, \dot{S}_f, \dot{R}_m^c, \dot{R}_f^c\right]^T = \mathcal{F}(x) - \mathcal{V}(x),$$

where

$$\mathcal{F}(x) = \begin{bmatrix}
b^c \dfrac{N_m I_f^c + F I_m^c}{T} + \lambda_m^c \dfrac{S_m I_f^c}{T} + S_m[\beta_m^c I_m^c + \beta^c I_f^c] \\
b^c \dfrac{N_m I_f^c + F I_m^c}{T} + \lambda_f^c \dfrac{S_f I_m^c}{T} + \beta^c S_f I \\
0 \\ 0 \\ 0 \\ 0
\end{bmatrix}$$

and

$$\mathcal{V}(x) = \begin{bmatrix} \gamma_m I_m^c + d(T) I_m^c \\ \gamma_f I_f^c + d(T) I_f^c \\ -\dfrac{bN_m N_f}{T} + \dfrac{\lambda_m^c S_m I_f^c}{T} + S_m[\beta_m^c I_m^c + \beta^c I_f^c] + d(T) S_m \\ -\dfrac{bN_m N_f}{T} + \dfrac{\lambda_f^c S_f I_m^c}{T} + \beta_c S_f I + d(T) S_f \\ -\gamma_m I_m^c + d(T) R_m^c \\ -\gamma_f I_f^c + d(T) R_f^c \end{bmatrix}.$$

Differentiation and evaluation at the DFE x_o leads to a matrix of the form (6), where O is the zero matrix and matrix J is given by (7). Matrices F and V^{-1} are

$$F = \begin{bmatrix} \dfrac{\beta_m^c K + b^c}{2} & \dfrac{\beta^c K + b^c + \lambda_m^c}{2} \\ \dfrac{\beta^c K + b^c + \lambda_f^c}{2} & \dfrac{\beta^c K + b^c}{2} \end{bmatrix}$$

and

$$V^{-1} = \begin{bmatrix} \dfrac{1}{\gamma_m + b/2} & 0 \\ 0 & \dfrac{1}{\gamma_f + b/2} \end{bmatrix}$$

so that

$$FV^{-1} = \begin{bmatrix} \dfrac{(\beta_m^c K + b^c)/2}{\gamma_m + b/2} & \dfrac{(\beta^c K + b^c + \lambda_m^c)/2}{\gamma_f + b/2} \\ \dfrac{(\beta^c K + b^c + \lambda_f^c)/2}{\gamma_m + b/2} & \dfrac{(\beta^c K + b^c)/2}{\gamma_f + b/2} \end{bmatrix}.$$

The basic reproduction number is given by

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{1}{2}\left(B + \sqrt{B^2 - 4C}\right), \tag{16}$$

where

$$B = \frac{(\beta_m^c K + b^c)(2\gamma_f + b) + (\beta^c K + b^c)(2\gamma_m + b)}{(2\gamma_m + b)(2\gamma_f + b)},$$

$$C = \frac{[(\beta_m^c K + b^c)(\beta^c K + b^c) - (\beta^c K + b^c + \lambda_m^c)(\beta^c K + b^t + \lambda_f^c)]}{[(2\gamma_m + b)(2\gamma_f + b)]^2}.$$

Now we apply Theorem 2 in [30] (p. 33) to obtain the stability result for model (13)-(14).

THEOREM 3.1. *The SIR male-female epizootic model (13)-(14) has a unique DFE given by (5) and a basic reproduction number $\mathcal{R}_0$ defined in (16). If $\mathcal{R}_0 < 1$, then the DFE is locally asymptotically stable and if $\mathcal{R}_0 > 1$, it is unstable.*

Suppose $\beta_m^c = \beta^c$ and $\lambda_m^c = 0 = \lambda_f^c$ (no distinction between male and female transmission and no sexual transmission). In this case,

$$\mathcal{R}_0 = \frac{(\beta^c K + b^c)/2}{\gamma_m + b/2} + \frac{(\beta^c K + b^c)/2}{\gamma_f + b/2}. \tag{17}$$

The two terms in formula (17) correspond to male and female reproduction numbers. They also correspond to the third and fourth terms in the expression for the basic

reproduction number for the general male-female model, given in (9). If, in addition, $\gamma_m = \gamma_f = \gamma$ in (17), then

$$\mathcal{R}_0 = \frac{\beta^c K + b^c}{\gamma + b/2}. \tag{18}$$

Formula (18) corresponds to the second term in the expression for the basic reproduction number for the general male-female model, given in (10). If there is only vertical transmission or only sexual transmission, then the expressions for $\mathcal{R}_0$ reduce to

$$\mathcal{R}_0 = \frac{b^c}{2}\left[\frac{1}{\gamma_f + b/2} + \frac{1}{\gamma_m + b/2}\right]$$

or

$$\mathcal{R}_0 = \frac{1}{2}\left[\frac{\lambda_m^c \lambda_f^c}{(\gamma_m + b/2)(\gamma_f + b/2)}\right]^{1/2},$$

respectively. These expressions agree with those given in (11) and in (12) when there is no immunotolerant stage.

4. **SI model.**

4.1. **Model description.** Another simplification of the general male-female model (2)-(3) is considered, where only immunotolerant rodents are included. Two disease stages are included, susceptible S and infectious and antibody negative I^t. The parameters have the same meaning as in the general male-female model. We assume $b^t < b$; infectious rodents have a lower birth rate than susceptible rodents. There is complete vertical transmission as in the other models; all rodents born to infectious mothers are infectious. The death rate $d(T) = a + cT$, where the carrying capacity K is given by (1). Let $M = S_m + I_m^t$, $F = S_f + I_f^t$, $I = I_m^t + I_f^t$ and $T = M + F$. The SI^t model has the following form:

$$\begin{aligned}
\frac{dS_m}{dt} &= \frac{bS_mS_f}{T} - \lambda_m^t \frac{S_mI_f^t}{T} - S_m[\beta_m^t I_m^t + \beta^t I_f^t] - d(T)S_m \\
\frac{dI_m^t}{dt} &= b^t \frac{S_mI_f^t + FI_m^t}{T} + \lambda_m^t \frac{S_mI_f^t}{T} + S_m[\beta_m^t I_m^t + \beta^t I_f^t] - \delta_m I_m^t - d(T)I_m^t
\end{aligned} \tag{19}$$

$$\begin{aligned}
\frac{dS_f}{dt} &= \frac{bS_mS_f}{T} - \lambda_f^t \frac{S_fI_m^t}{T} - \beta^t S_f I - d(T)S_f \\
\frac{dI_f^t}{dt} &= b^t \frac{S_mI_f^t + FI_m^t}{T} + \lambda_f^t \frac{S_fI_m^t}{T} + \beta^t S_f I - \delta_f I_f^t - d(T)I_f^t.
\end{aligned} \tag{20}$$

Parameters b, a and c are positive and all other parameters are nonnegative. Initial conditions are nonnegative with $M(0) > 0$ and $F(0) > 0$. Therefore, solutions are nonnegative for $t \geq 0$ and $T(t) > 0$ for $t \geq 0$.

4.2. **Analysis of the SI model.** For model (19)-(20), there is a unique DFE given by (5) and a unique enzootic equilibrium (EE), where all animals are infectious. In addition, for certain parameter values there may exist other enzootic equilibria, where there are both susceptible and infectious animals. We do not study these other enzootic equilibria here (the equilibria are solutions to four nonlinear equations). However, in the numerical examples, another EE is shown to exist where both susceptible and infectious animals have positive values. For some parameter values this EE is shown to be stable and for others it is shown to be unstable.

Model (19)-(20) is analyzed near the DFE and near the EE, where all animals are infectious.

4.2.1. *Disease-free equilibrium.* The basic reproduction number $\mathcal{R}_0$ for the male-female SI model (19)-(20) is calculated based on the next generation matrix approach [12, 30]. Let

$$\dot{x} = \left[\dot{I}_m^t, \dot{I}_f^t, \dot{S}_m, \dot{S}_f\right]^T = \mathcal{F}(x) - \mathcal{V}(x),$$

where

$$\mathcal{F}(x) = \begin{bmatrix} b^t \dfrac{S_m I_f^t + F I_m^t}{T} + \lambda_m^t \dfrac{S_m I_f^t}{T} + S_m[\beta_m^t I_m^t + \beta^t I_f^t] \\ b^t \dfrac{S_m I_f^t + F I_m^t}{T} + \lambda_f^t \dfrac{S_f I_m^t}{T} + \beta^t S_f I \\ 0 \\ 0 \end{bmatrix}$$

and

$$\mathcal{V}(x) = \begin{bmatrix} \delta_m I_m^t + d(T) I_m^t \\ \delta_f I_f^t + d(T) I_f^t \\ -\dfrac{b S_m S_f}{T} + \dfrac{\lambda_m^t S_m I_f^t}{T} + S_m[\beta_m^t I_m^t + \beta^t I_f^t] + d(T) S_m \\ -\dfrac{b S_m S_f}{T} + \dfrac{\lambda_f^t S_f I_m^t}{T} + \beta^t S_f I + d(T) S_f \end{bmatrix}.$$

Differentiation and evaluation at the DFE x_o lead to a matrix of the form (6), where O is the zero matrix and matrix J equals

$$J = \begin{bmatrix} -\dfrac{b}{4} - c\dfrac{K}{2} & -\dfrac{b}{4} \\ -\dfrac{b}{4} & -\dfrac{b}{4} - c\dfrac{K}{2} \end{bmatrix},$$

where $c = d'(K) > 0$. It is straightforward to see that the trace of J is negative and the determinant of J is positive. Hence, by the Routh-Hurwitz criteria, the eigenvalues of J have negative real parts. Matrices F and V^{-1} are

$$F = \begin{bmatrix} \dfrac{\beta_m^t K + b^t}{2} & \dfrac{\beta^t K + b^t + \lambda_m^t}{2} \\ \dfrac{\beta^t K + b^t + \lambda_f^t}{2} & \dfrac{\beta^t K + b^t}{2} \end{bmatrix}$$

and

$$V^{-1} = \begin{bmatrix} \dfrac{1}{\delta_m + b/2} & 0 \\ 0 & \dfrac{1}{\delta_f + b/2} \end{bmatrix}$$

so that

$$FV^{-1} = \begin{bmatrix} \dfrac{\beta_m^t K + b^t}{2\delta_m + b} & \dfrac{\beta^t K + b^t + \lambda_m^t}{2\delta_f + b} \\ \dfrac{\beta^t K + b^t + \lambda_f^t}{2\delta_m + b} & \dfrac{\beta^t K + b^t}{2\delta_f + b} \end{bmatrix}.$$

The basic reproduction number is given by

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{1}{2}\left(B + \sqrt{B^2 - 4C}\right) \tag{21}$$

where

$$B = \frac{(\beta_m^t K + b^t)(2\delta_f + b) + (\beta^t K + b^t)(2\delta_m + b)}{(2\delta_m + b)(2\delta_f + b)},$$

$$C = \frac{[(\beta_m^t K + b^t)(\beta^t K + b^t) - (\beta^t K + b^t + \lambda_m^t)(\beta^t K + b^t + \lambda_f^t)]}{[(2\delta_m + b)(2\delta_f + b)]^2}.$$

Thus, a stability result for model (19)-(20) holds, a result similar to the previous models (Theorems 2.1 and 3.1).

THEOREM 4.1. *The SI male-female epizootic model (19)-(20) has a unique DFE given by (5) and a basic reproduction number $\mathcal{R}_0$ defined in (21). If $\mathcal{R}_0 < 1$, then the DFE is locally asymptotically stable and if $\mathcal{R}_0 > 1$, it is unstable.*

In the case that $\beta_m^t = \beta^t$ and $\lambda_m^t = 0 = \lambda_f^t$. That is, there is no distinction between male and female transmission and there is no sexual transmission, then

$$\mathcal{R}_0 = \frac{(\beta^t K + b^t)/2}{\delta_m + b/2} + \frac{(\beta^t K + b^t)/2}{\delta_f + b/2}. \tag{22}$$

Formula (22) corresponds to the first two terms in the expression for $\mathcal{R}_0$ in the general male-female model, given in (9). In addition, if $\delta_m = \delta_f = \delta$ in (22), then

$$\mathcal{R}_0 = \frac{\beta^t K + b^t}{\delta + b/2}. \tag{23}$$

Formula (23) corresponds to the first term in the expression for the basic reproduction number for the general model, given in (10). If there is only vertical transmission or only sexual transmission, then the expressions for $\mathcal{R}_0$ reduce to the ones computed for the general male-female model with no immunocompetent stage; i.e.,

$$\mathcal{R}_0 = \frac{b^t}{2}\left[\frac{1}{\delta_f + b/2} + \frac{1}{\delta_m + b/2}\right]$$

or

$$\mathcal{R}_0 = \frac{1}{2}\left[\frac{\lambda_m^t \lambda_f^t}{(\delta_m + b/2)(\delta_f + b/2)}\right]^{1/2},$$

respectively.

4.2.2. *Enzootic equilibrium.* To find an enzootic equilibrium where the infectious states are positive, $\bar{I}_m^t > 0$, $\bar{I}_f^t > 0$ and $S_m = 0 = S_f$, the following equations must be satisfied:

$$\frac{b^t \bar{I}_f^t}{T} - (a + cT) - \delta_m = 0 \tag{24}$$

and

$$\frac{b^t \bar{I}_m^t}{T} - (a + cT) - \delta_f = 0. \tag{25}$$

Adding equations (24) and (25) and substituting $T = \bar{I}_m^t + \bar{I}_f^t$ yields

$$T = \frac{b^t - \delta_m - \delta_f - 2a}{2c}. \tag{26}$$

Hence, the equilibrium values for an enzootic equilibrium (EE) are

$$\bar{I}_f^t = \frac{(a + cT + \delta_m)T}{b^t} \quad \text{and} \quad \bar{I}_m^t = \frac{(a + cT + \delta_f)T}{b^t}, \tag{27}$$

where T is defined in (26). For $\bar{I}_m^t > 0$ and $\bar{I}_f^t > 0$, then

$$b^t - \delta_m - \delta_f - 2a > 0. \tag{28}$$

To determine the stability of the equilibrium, defined in (27), for model (19)-(20), the Jacobian matrix J is evaluated at this equilibrium. Matrix J has the following form:

$$J = \begin{bmatrix} J_1 & 0 \\ 0 & J_2 \end{bmatrix}.$$

After simplification, J_1 and J_2 satisfy

$$J_1 = \begin{bmatrix} -\dfrac{\lambda_m^t B}{A+B} - \beta_m^t A - \beta^t B - c(A+B) & 0 \\ 0 & -\dfrac{\lambda_f^t A}{A+B} - \beta^t(A+B) - a - c(A+B) \end{bmatrix}$$

and

$$J_2 = \begin{bmatrix} -\dfrac{b^t AB}{(A+B)^2} - cA & \dfrac{b^t A^2}{(A+B)^2} - cA \\ \dfrac{b^t B^2}{(A+B)^2} - cB & -\dfrac{b^t AB}{(A+B)^2} - cB \end{bmatrix},$$

where $A = \bar{I}_m^t$, $B = \bar{I}_f^t$ and $A + B = T$. It is straightforward to see that the eigenvalues of J_1 are negative and the trace of J_2 is also negative if A and B are positive. Also the determinant of J_2 simplifies to

$$\det(J_2) = \frac{2cb^t AB}{A+B}.$$

Thus if $A, B > 0$, the trace of J_2 is negative and the determinant of J_2 is positive. Applying the Routh-Hurwitz criteria implies the eigenvalues of J_2 have negative real parts provided the equilibrium values are positive [3]. Whether the equilibrium values are positive and the equilibrium is locally asymptotically stable depends on inequality (28). Hence, the following ratio is defined as a reproduction number for the EE (27),

$$\mathcal{R} = \frac{b^t}{\delta_m + \delta_f + 2a}. \tag{29}$$

The expression for $\mathcal{R}$ is the ratio of the birth rate to death rates for the infectious stage. The results are summarized for the EE of the SI model in the next theorem.

THEOREM 4.2. *The SI male-female model (19)-(20) has a unique EE, where* $\bar{S}_m = 0 = \bar{S}_f$ *and* $\bar{I}_m^t$ *and* $\bar{I}_f^t$ *are defined in (27). This EE is locally asymptotically stable if* $\mathcal{R} > 1$ *and unstable if* $\mathcal{R} < 1$, *where* $\mathcal{R}$ *is defined in (29).*

It is interesting to note that there exist parameter values such that $\mathcal{R}_0 < 1$ and $\mathcal{R} > 1$, so that the DFE (5) and the EE (27) are both locally asymptotically stable, a case of bistability. A numerical example of bistability is given in Section 6.

5. **Simple SI model.**

5.1. **Model description.** A simplification of model (19)-(20) is considered that does not differentiate between the sexes. Therefore, the differences in sexual behavior and sexual transmission are not included. In this model, there are approximately the same number of males and females, so that only females are modeled (alternately, only males could be modeled). Let S = number of susceptible females, I = number of infectious, immunotolerant females and $T = S + I$ = total number of females (the superscript t on I is omitted for simplicity). The birth rates are simplified. The expression bS_mS_f/T is replaced by $bS/2$ and $b^t(S_mI_f + FI_m)/T$ is replaced by $b^tI/2$. The fraction $1/2$ is included because the litter size in the new model only includes females. The simplified SI model has the following form:

$$\begin{aligned} \frac{dS}{dt} &= S\left(\frac{b}{2} - d(T) - \beta^t I\right) \\ \frac{dI}{dt} &= I\left(\frac{b^t}{2} - \delta - d(T) + \beta^t S\right), \end{aligned} \tag{30}$$

where $d(T) = a + 2cT$, $0 < a < b/2$, $c > 0$, $b > b^t$ and $d\,(K/2) = b/2$. Note that $d(T)$ differs from previous models because only half of the population is modeled, $2T$=males + females. These are reasonable assumptions if males and females are approximately equal in number. Initial conditions and parameters are assumed to be positive. Therefore, solutions are positive for $t \geq 0$.

Model (30) is similar to a model developed by Busenberg and Cooke [8]. But Busenberg and Cooke do not assume density-dependent deaths. They assume $d(T) = r \equiv$ constant. In addition, Busenberg and Cooke assume incomplete vertical transmission. That is, $b^tI/2$ is split into two rates; $pb^tI/2$ is the rate at which new susceptibles are born (from infectious mothers) and $qb^tI/2$ is the rate at which new infectives are born, $p + q = 1$.

Although the simple model (30) does not distinguish between males and females and therefore, may be somewhat unrealistic for Machupo virus, the effect of vertical transmission can be more clearly seen in this simple model. In addition, model (30) can be completely analyzed and the results interpreted in terms of $\mathcal{R}_0$.

5.2. **Analysis of the simple model.** Model (30) has four equilibria. These four equilibria are differentiated by subscripts on the variables, the zero equilibrium, $(\bar{S}_0, \bar{I}_0) = (0, 0)$, the DFE,

$$(\bar{S}_1, \bar{I}_1) = \left(\frac{b/2 - a}{2c}, 0\right) = \left(\frac{K}{2}, 0\right),$$

and possibly two enzootic equilibria,

$$(\bar{S}_2, \bar{I}_2) = \left(0, \frac{b^t/2 - (a + \delta)}{2c}\right),$$

and

$$(\bar{S}_3, \bar{I}_3) = \left(\frac{2c(\bar{S}_1 - \bar{I}_2) - \beta^t\bar{I}_2}{(\beta^t)^2/2c}, \frac{\beta^t\bar{S}_1 - 2c(\bar{S}_1 - \bar{I}_2)}{(\beta^t)^2/2c}\right).$$

The DFE is always positive since $(b/2 - a)/(2c) = K/2 > 0$.

At the enzootic equilibrium $(\bar{S}_2, \bar{I}_2)$, $\bar{S}_2 = 0$ and $\bar{I}_2 > 0$, if

$$\frac{b^t}{2} > a + \delta. \tag{31}$$

This inequality can be rewritten as $b^t/(2a + 2\delta) > 1$, which is equivalent to the inequality $\mathcal{R} > 1$ in (29) when $\delta_m = \delta_f = \delta$.

At the enzootic equilibrium $(\bar{S}_3, \bar{I}_3)$, $\bar{S}_3 > 0$ and $\bar{I}_3 > 0$, if $2c(\bar{S}_1 - \bar{I}_2) > \beta^t \bar{I}_2$ and $\beta^t \bar{S}_1 > 2c(\bar{S}_1 - \bar{I}_2)$. Simplifying the latter two inequalities leads to

$$\bar{S}_1 > \left(\frac{\beta^t}{2c} + 1\right) \bar{I}_2 > \left(1 - \left(\frac{\beta^t}{2c}\right)^2\right) \bar{S}_1. \tag{32}$$

Note that $\bar{I}_2$ may not be feasible ($\bar{I}_2 \leq 0$), and the enzootic equilibrium $(\bar{S}_3, \bar{I}_3)$ could still be positive. In particular, $\bar{I}_2 \leq 0$, $\bar{S}_3 > 0$ and $\bar{I}_3 > 0$, provided $\beta^t > 2c$ and $-\bar{I}_2 < (\beta^t/2c - 1)\, \bar{S}_1$. In addition, if $\bar{I}_2 \leq 0$ and if $\bar{S}_3 > 0$, it follows from the definition of $\bar{S}_3$ that $\bar{S}_3 < \bar{S}_1$. On the other hand, if $\bar{I}_3 > 0$ its value may be less than or greater than $\bar{I}_2$ depending on the magnitude of horizontal transmission. If $\bar{I}_3 > 0$ and $\beta^t > 2c$, then the definition of $\bar{I}_3$ implies $\bar{I}_3 > \bar{I}_2$. But if $\bar{I}_3 > 0$ and $\beta^t < 2c$, then $\bar{I}_3 < \bar{I}_2$.

Next, the local stability of each equilibrium is studied. The Jacobian matrix of model (30) evaluated at the zero equilibrium is

$$J_0 = \begin{bmatrix} \dfrac{b}{2} - a & 0 \\ 0 & \dfrac{b^t}{2} - \delta - a \end{bmatrix}.$$

The eigenvalues of J_0 are $b/2 - a > 0$ and $b^t/2 - \delta - a$. If $b^t/2 > \delta + a$, then the zero equilibrium is an unstable node. If $b^t/2 < \delta + a$, then the zero equilibrium is a saddle point.

The Jacobian matrix evaluated at the DFE $(\bar{S}_1, \bar{I}_1)$ simplifies to

$$J_1 = \begin{bmatrix} -\dfrac{cK}{2} & -(\beta^t + 2c)\dfrac{K}{2} \\ 0 & \dfrac{b^t - b + \beta^t K}{2} - \delta \end{bmatrix}.$$

The DFE is locally asymptotically stable if $(b^t - b + \beta^t K)/2 < \delta$. This latter inequality is equivalent to

$$\frac{(\beta^t K + b^t)/2}{\delta + b/2} < 1. \tag{33}$$

The left side of (33) is the basic reproduction number for model (30),

$$\mathcal{R}_0 = \frac{(\beta^t K + b^t)/2}{\delta + b/2}. \tag{34}$$

Note that the value of $\mathcal{R}_0$ is equal to the female reproduction number for the male-female SI model, given in (22). Calculation of $\mathcal{R}_0$ can also be found from the criteria of van den Driessche and Watmough [30].

At the enzootic equilibrium $(\bar{S}_2, \bar{I}_2) = (0, \bar{I}_2)$, the Jacobian matrix has the form

$$J_2 = \begin{bmatrix} \dfrac{b}{2} - a - 2cT - \beta^t \bar{I}_2 & 0 \\ \bar{I}_2 \beta^t - 2c\bar{I}_2 & \dfrac{b^t}{2} - \delta - a - 2cT - 2c\bar{I}_2 \end{bmatrix}.$$

Eigenvalues of J_2 are given by $b/2 - a - (2c + \beta^t)\bar{I}_2$ and $-2c\bar{I}_2$ where $T = \bar{I}_2$. For the first eigenvalue to be negative requires that $(2c + \beta^t)\bar{I}_2 > 2c\bar{S}_1$ or equivalently

$$\bar{S}_1 < \left(\frac{\beta^t}{2c} + 1\right) \bar{I}_2, \tag{35}$$

where $\bar{S}_1 = K/2$. Inequality (35) contradicts (32). Thus, if the enzootic equilibrium $(\bar{S}_2, \bar{I}_2)$ is stable, then the enzootic equilibrium $(\bar{S}_3, \bar{I}_3)$ is not feasible (not positive). Conversely, if the enzootic equilibrium $(\bar{S}_3, \bar{I}_3)$ is positive, the inequalities in (32) hold and equilibrium $(\bar{S}_2, \bar{I}_2)$ is unstable.

Next, evaluating the Jacobian matrix at $(\bar{S}_3, \bar{I}_3)$, leads to

$$J_3 = \begin{bmatrix} \frac{b}{2} - a - 2cT - \beta^t \bar{I}_3 - 2c\bar{S}_3 & -\beta^t \bar{S}_3 - 2c\bar{S}_3 \\ \beta^t \bar{I}_3 - 2c\bar{I}_3 & \frac{b^t}{2} - \delta - a - 2cT + \beta^t \bar{S}_3 - 2c\bar{I}_3 \end{bmatrix},$$

where $T = \bar{S}_3 + \bar{I}_3$. The trace of J_3 simplifies to $-(b - b^t + 2\delta)c/\beta^t$. It is negative since $b + 2\delta > b^t$. The determinant of J_3 simplifies to $(\beta^t)^2 \bar{S}_3 \bar{I}_3$. It is positive if $\bar{I}_3 > 0$ and $\bar{S}_3 > 0$. It follows from the Routh-Hurwitz criteria that the enzootic equilibrium is locally asymptotically stable if $\bar{I}_3 > 0$ and $\bar{S}_3 > 0$.

The expression $\mathcal{R}_0 < 1$, where $\mathcal{R}_0$ is defined in (34), is equivalent to

$$\bar{S}_1 \left(1 - \frac{\beta^t}{2c}\right) > \bar{I}_2. \tag{36}$$

This latter inequality is the reverse of the second inequality in (32). Therefore, for $(\bar{S}_3, \bar{I}_3)$ to be positive, it must be the case that $\mathcal{R}_0 > 1$. Also note that $\mathcal{R}_0 \leq 1$ and $\bar{I}_2 > 0$ imply that $\bar{I}_2$ cannot be locally asymptotically stable. This result comes from the following observations. If $\bar{I}_2 > 0$ is locally asymptotically stable, then inequalities (35) and (36) imply

$$\bar{I}_2 < \bar{S}_1 \left(1 - \frac{\beta^t}{2c}\right) < \left(1 - \left(\frac{\beta^t}{2c}\right)^2\right) \bar{I}_2,$$

a contradiction. Consequently, this rules out bistability for the simple SI model when $\mathcal{R}_0 < 1$. The preceding local asymptotic stability results together with Poincaré-Bendixson theory [11] for autonomous two-dimensional systems will be used to verify that the local results are global results for model (30).

THEOREM 5.1. *Let $\mathcal{R}_0$ be defined in (34).*

(a) *If $\mathcal{R}_0 \leq 1$, then the DFE $(\bar{S}_1, \bar{I}_1)$ of model (30) is globally asymptotically stable.*

(b) *If $\mathcal{R}_0 > 1$, then there are two mutually exclusive cases.*

(i) *If the inequalities (31) and (35) are satisfied, then the enzootic equilibrium $(\bar{S}_2, \bar{I}_2)$ of model (30) is globally asymptotically stable.*

(ii) *If one of the inequalities in (31) or (35) is not satisfied, then inequality (32) is satisfied and the enzootic equilibrium $(\bar{S}_3, \bar{I}_3)$ of model (30) is globally asymptotically stable.*

Proof. First, it is shown that solutions to model (30) are bounded. Solutions are bounded below by zero. To show solutions are bounded above, consider

$$\frac{dS}{dt} \leq S\left(\frac{b}{2} - a - 2cS\right).$$

The solution S can be compared to the solution u_1 that satisfies the following differential equation:

$$\frac{du_1}{dt} = u_1\left(\frac{b}{2} - a - 2cu_1\right).$$

For $u_1(0) = S(0) > 0$, the solution $u_1(t)$ satisfies $\lim_{t\to\infty} u_1(t) = K/2$. In addition $u_1(t)$ approaches $K/2$ monotonically. Thus, $S(t) \le u_1(t)$ for $t \ge 0$ which implies $S(t) \le \max_{t\ge 0}\{u_1(t)\} \le \max\{S(0), K/2\} = \hat{S}$. Applying this inequality to $I(t)$ in model (30) yields

$$\frac{dI}{dt} \le I\left(\frac{b^t}{2} - \delta - a - 2cI + \beta^t \hat{S}\right).$$

Again the solution I can be compared to the solution u_2, where

$$\frac{du_2}{dt} = u_2\left(\frac{b^t}{2} - \delta - a - 2cu_2 + \beta^t \hat{S}\right)$$

with $u_2(0) = I(0) > 0$. Since the solution of $u_2(t)$ is bounded, $I(t)$ is bounded, $I(t) \le u_2(t), \quad t \ge 0$.

Note that three of the equilibria lie on the boundary of the S-I phase plane and (S_3, I_3) is the only one that may lie in the interior. The origin is always unstable and no solutions beginning in the interior of the S-I phase plane can approach (S_0, I_0).

(a) The assumptions in part (a) imply there is no interior equilibrium $(\bar{S}_3, \bar{I}_3)$. There are only three boundary equilibria. The origin $(\bar{S}_0, \bar{I}_0)$ is an unstable node (if $\bar{I}_2 \le 0$) or a saddle point (if $\bar{I}_2 > 0$). Also, as noted previously, if $\mathcal{R}_0 < 1$, $(\bar{S}_2, \bar{I}_2)$ is not locally asymptotically stable. Hence, applying Poincaré-Bendixson theory, solutions must approach $(\bar{S}_1, \bar{I}_1)$.

(b) Assume $\mathcal{R}_0 > 1$.

(i) The assumptions in part (i) imply $\bar{I}_2 > 0$, $(\bar{S}_2, \bar{I}_2)$ is locally asymptotically stable and $(\bar{S}_3, \bar{I}_3)$ is not in the interior of the S-I phase plane. In addition, the two boundary equilibria $(\bar{S}_0, \bar{I}_0)$ and $(\bar{S}_1, \bar{I}_1)$ are unstable nodes. Hence, applying Poincaré-Bendixson theory, solutions must approach the stable equilibrium $(\bar{S}_2, \bar{I}_2)$.

(ii) Suppose inequality (31) does not hold. That is $b^t/2 \le a + \delta$. This latter inequality with the assumption $\mathcal{R}_0 > 1$ imply $\beta^t > 2c$. But this means that the inequalities in (32) are satisfied; (S_3, I_3) lies in the interior of the S-I phase plane. Now suppose inequality (35) does not hold. Then $\bar{S}_1 \ge (\beta^2/(2c) + 1)\bar{I}_2$ and $\mathcal{R}_0 > 1$ imply that the inequalities (32) are satisfied and again (S_3, I_3) lies in the interior of the S-I phase plane.

It has already been shown that if the inequalities in (32) hold (also $\mathcal{R}_0 > 1$) and if $\bar{I}_2 > 0$, then the boundary equilibrium $(\bar{S}_2, \bar{I}_2) = (0, \bar{I}_2)$ is unstable (with unstable trajectory pointing into the interior of the S-I phase plane). In addition, the other two boundary equilibria $(\bar{S}_0, \bar{I}_0)$ and $(\bar{S}_1, \bar{I}_1)$ are unstable with trajectories pointing into the interior of the S-I phase plane.

Periodic solutions need to be ruled out. We apply Dulac's criterion. Let D be an open region in the positive quadrant of the S-I phase plane and let $f(S, I)$ and $g(S, I)$ be the right sides of the differential equations for S and I in model (30), respectively. In addition, for the Dulac function $B(S, I) = 1/(SI)$,

$$\frac{\partial(Bf)}{\partial S} + \frac{\partial(Bg)}{\partial I} = -\left(\frac{2c}{I} + \frac{2c}{S}\right) < 0.$$

Dulac's criterion implies there are no periodic solutions in D [3]. Thus, Poincaré-Bendixson theory implies solutions must approach an equilibrium, a homoclinic trajectory or a heteroclinic trajectory. Since $(\bar{S}_3, \bar{I}_3)$ is locally asymptotically stable and the boundary equilibria are all unstable, solutions must approach $(\bar{S}_3, \bar{I}_3)$. □

In Figure 2 the stable equilibria are graphed as a function of $\mathcal{R}_0(\beta^t)$. All parameters are fixed except β^t ($b = 3$, $b^t = b/3$, $K = 10,000$, $a = 0.25$ and $\delta = 0.5$). The basic reproduction number $\mathcal{R}_0$ is an increasing function of β^t. Two bifurcations occur, one at $\mathcal{R}_0 = 1$, where I switches from 0 to I_3 and a second one at $\mathcal{R}_0 = 7.88$, where I switches from I_3 to $I_2 \approx 455$.

The SI model with vertical transmission can result in the entire population becoming infectious (at the equilibrium value $\bar{I}_2$). This result also occurs in the SI male-female model (Theorem 4.2) and is a consequence of vertical transmission. The results of Theorem 5.1 show that bistability, observed in the SI male-female model, does not occur in the simple SI model.

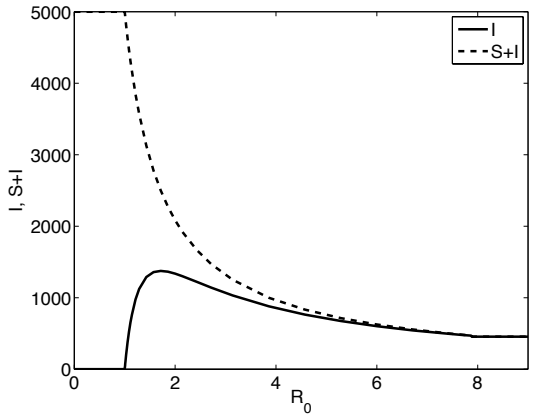

FIGURE 2. Bifurcation diagram of the stable equilibria as a function of $\mathcal{R}_0$ for the SI model (30), where $\mathcal{R}_0$ is an increasing function of β^t, $\mathcal{R}_0 \equiv \mathcal{R}_0(\beta^t)$. Other parameter values are $b = 3$, $b^t = b/3$, $K = 10,000$, $a = 0.25$ and $\delta = 0.5$. The dashed curve is the stable total population size $S + I$ and the solid curve is the stable infectious population size I.

6. **Numerical examples.**

6.1. **Basic parameter values.**

Several numerical examples are presented and discussed that illustrate the dynamics of the models. Basic parameter values for the numerical examples are listed in Table 1. Time units are measured in increments of three months, since the gestation period until sexual maturity is approximately three months [17]. Hence, 10 time units equal 2.5 years and 20 time units equal 5 years.

The per capita natural birth rate (and survival for three months, until reproductive) is assumed to be $b = 6$ [17]. For the general model, $b^t + b^c \leq b$ and $b^t < b^c$. Therefore, we assume $b^t = b/3$ and $b^c = b/2$. Horizontal transmission between males is greater than between males and females or between females. Therefore, $\beta^t = \beta^t_m/10$ and $\beta^c = \beta^c_m/10$. A range of values is selected for β^t_m, $\beta^t_m \in [0.0002, 0.004]$. The carrying capacity K is equal to 10,000 rodents. The per capita density-independent natural death rate is $a = 0.25$ and the per capita

TABLE 1. Basic Parameter Values

Parameter	Value	Parameter	Value
b	6	λ_m^t	0.01
b^t	$b/3$	$\lambda_m^c,\ \lambda_f^t,\ \lambda_f^c$	λ_m^t
b^c	$b/2$	γ_m	5
β_m^t	0.0002 to 0.004	γ_f	$2\gamma_m$
β_m^c	β_m^t	δ_m	0.5 to 3
$\beta^t,\ \beta^c$	$\beta_m^t/10$	δ_f	$\delta_m/2$
a	0.25	K	10,000
ϵ	0.1	c	$(b/2-a)/K$

density-dependent natural death rate $c = (b/2 - a)/K$. Thus, the average life-expectancy in the absence of density-dependent effects is $1/a \approx 1$ year. The sexual transmission coefficients are assumed to be the same for males and females and both infectious stages; although unknown, relatively small values are assumed $\lambda_m^t = \lambda_f^t = \lambda_m^c = \lambda_f^c = 0.01$. The transition rate from the immunocompetent stage to the immunotolerant stage is assumed to be $\epsilon = 0.1$. The per capita male recovery rate is $\gamma_m = 5$ with female recovery rate, $\gamma_f = 2\gamma_m$ (male infectious period is greater than female, e.g., $1/\gamma_m = 1/5 = 2.4$ weeks versus $1/\gamma_f = 1/10 = 1.2$ weeks) and the per capita male disease-related death rate is in the range $\delta_m \in [0.5, 3]$ with lower death rate for females $\delta_f = \delta_m/2$ (e.g., $1/\delta_m = 1 = 3$ months, death occurs 3 months after infection). The values for many of these parameters are unknown but the values chosen for the simulations are biologically reasonable. The dynamics of two of the models, general male-female model and male-female SI model, are illustrated using the baseline parameter values given in Table 1.

6.2. **General model.** Two numerical examples illustrate the stability of the DFE ($\mathcal{R}_0 < 1$) and of an enzootic equilibrium ($\mathcal{R}_0 > 1$) for the general male-female model (2)-(3).

Example 1: In the first numerical example, let $\beta_m^t = 0.0002$ and $\delta_m = 3$. The remaining parameters are given in Table 1. The basic reproduction number is $\mathcal{R}_0 = 0.911$. According to Theorem 2.1, the DFE is locally asymptotically stable. Solutions approach the DFE very rapidly (see Figure 3), $\bar{S}_m = 5000 = \bar{S}_f$. As sexual or horizontal transmission rates increase or as the recovery rates or disease-related death rates decrease or as transition to the immunotolerant stage increases, then the basic reproduction number increases. For example, if ϵ is increased from 0.1 to 1 or to 10, then $\mathcal{R}_0 = 0.933$ for $\epsilon = 1$ and $\mathcal{R}_0 = 1.047$ for $\epsilon = 10$.

Example 2: In the second numerical example, the disease-related death rates are decreased to $\delta_m = 0.5$ and $\delta_f = \delta_m/2 = 0.25$. The remaining parameter values are the same as in Example 1. The basic reproduction number is $\mathcal{R}_0 = 1.213$. According to Theorem 2.1, the DFE is unstable. An enzootic equilibrium is reached,

$$\begin{aligned} &\bar{S}_m \approx 2303,\ \bar{I}_m^t \approx 826,\ \bar{I}_m^c \approx 460,\ \bar{R}_m^c \approx 847 \\ &\bar{S}_f \approx 2683,\ \ \bar{I}_f^t \approx 715,\ \bar{I}_f^c \approx 240,\ \bar{R}_f^c \approx 885. \end{aligned} \tag{37}$$

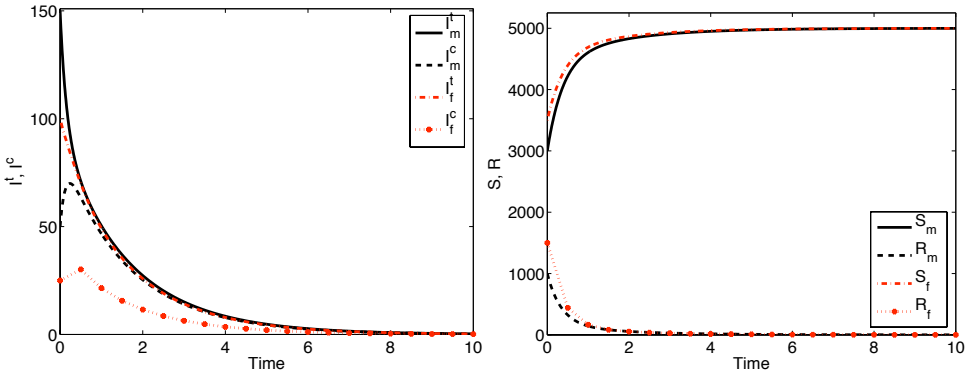

FIGURE 3. Solutions corresponding to Example 1, the general male-female model (2)-(3), where $\mathcal{R}_0 = 0.911$ with the initial conditions $S_m(0) = 3000$ $S_f(0) = 3500$, $I^t_m(0) = 150$, $I^t_f(0) = 100$, $I^c_m(0) = 50$, $I^c_f(0) = 25$, $R^c_m(0) = 1000$ and $R^c_f(0) = 1500$. Solutions approach the DFE, $\bar{S}_m = 5000 = \bar{S}_f$.

The total population size is less than the carrying capacity due to reduced fertility and disease-related deaths, $\bar{T} = 8,959 < 10,000 = K$. A linear stability analysis shows that this enzootic equilibrium is locally asymptotically stable. Figure 4 shows rapid convergence to this enzootic equilibrium. For the parameter values in Table 1 and for a range of other values, numerical solutions for the general male-female model exhibited only the two types of behavior illustrated in Examples 1 and 2.

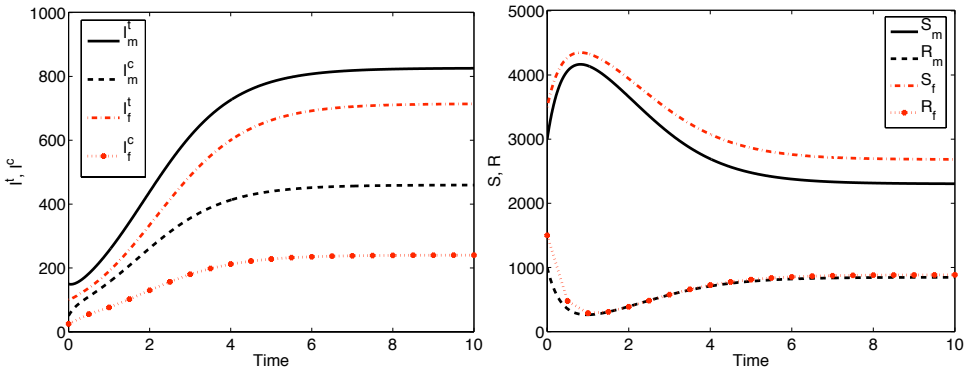

FIGURE 4. Solutions corresponding to Example 2, the general male-female model (2)-(3), where $\mathcal{R}_0 = 1.213$ with the same initial conditions as in Example 1. Solutions approach the enzootic equilibrium (37).

6.3. **The SI model.** Three numerical examples illustrate some of the dynamics for the SI^t male-female model (19)- (20).

Example 3: Let $\beta^t_m = 0.0002$ and $\delta_m = 0.5$. The remaining parameter values are given in Table 1. The basic reproduction number for the DFE is $\mathcal{R}_0 = 0.803 < 1$

and the reproduction number for the EE is $\mathcal{R} = 1.6 > 1$. According to Theorems 4.1 and 4.2, the DFE, $\bar{S}_m = 5000 = \bar{S}_f$ and the EE, $\bar{I}_m \approx 597$, $\bar{I}_f \approx 767$, are locally asymptotically stable. Depending on the initial conditions, solutions may tend to one of these equilibria. For initial conditions close to the DFE, solutions tend to DFE, but for initial conditions close to the EE, solutions tend to the EE. This is a case of bistability.

Example 4: In this numerical example, we use the same parameter values as in Example 3 with the exception that β_m^t is increased to $\beta_m^t = 0.0006$. Then both reproduction numbers are greater than one, $\mathcal{R}_0 = 1.308$ and $\mathcal{R} = 1.6$. According to Theorems 4.1 and 4.2, the DFE is unstable and the EE, $\bar{I}_m \approx 597$, $\bar{I}_f \approx 767$, is locally asymptotically stable. For all of the numerical simulations, with $I_m(0) > 0$ and $I_f(0) > 0$, we found that solutions approached the EE (see Figure 5).

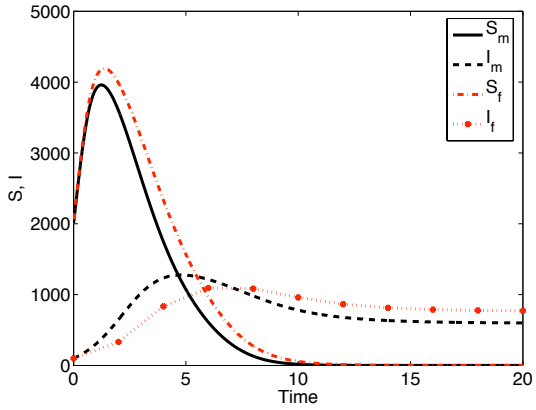

FIGURE 5. Solution to the SI^t male-female model (19)- (20), corresponding to the parameter values given in Example 4. A stable enzootic equilibrium is reached, where $\bar{I}_m \approx 597$, $\bar{I}_f \approx 767$, $\mathcal{R}_0 = 1.308$ and $\mathcal{R} = 1.6$.

Example 5: As a final example, we show the existence of an EE different from the one predicted in Theorem 4.2. This EE is stable for some parameter values if $\mathcal{R}_0 > 1$ and $\mathcal{R} < 1$ but becomes unstable as horizontal transmission β_m^t increases. Let $\beta_m^t = 0.0008$ and $\delta_m = 1.5$ with the remaining parameter values as in Table 1. In this case, $\mathcal{R}_0 = 1.245$ and $\bar{R} = 0.727$. There exists a stable EE,

$$\bar{S}_m \approx 2304,\ \bar{I}_m^t \approx 753,\ \bar{S}_f = 2889,\ \bar{I}_f^t \approx 529.$$

The total population size $\bar{T} \approx 6475$ is much reduced from a carrying capacity of $K = 10,000$. As β_m^t increases, the enzootic equilibrium loses its stability and solutions exhibit cyclic behavior. For example, if β_m^t is increased to $\beta_m^t = 0.004$ but $\delta_m = 1.5$ remains the same with all other parameters as in Table 1, then $\mathcal{R}_0 = 4.8$ and $\mathcal{R} = 0.727$; solutions appear to converge to a periodic solution. There may exist a Hopf bifurcation as the value of $\mathcal{R}_0(\beta_m^t)$ increases, but the existence of a Hopf bifurcation has not been verified. Solutions graphed over time and in the S_m-I_m phase plane in Figure 6 show the convergence to a periodic solution. Because the infectious cycles are very close to zero for part of the cycle, the disease may not

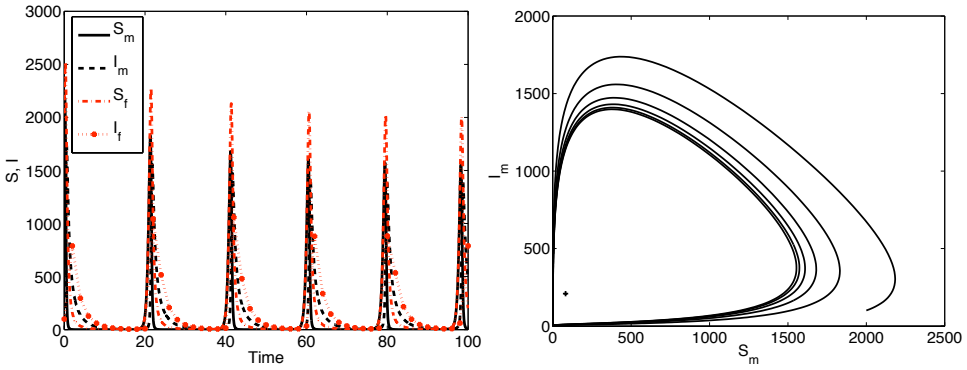

FIGURE 6. Cyclic behavior for the SI^t male-female model (19)-(20) when $\mathcal{R}_0 = 4.8$ and $\mathcal{R} = 0.727$ ($\beta_m^t = 0.004$, $\delta_m = 1.5$ and other parameter values are given in Table 1). The figure on the left is a graph of the solutions over time and the figure on the right is the graph of the solution in the S_m-I_m phase plane. The + in the figure on the right identifies the unstable enzootic equilibrium $\bar{S}_m \approx 81.3$, $\bar{I}_m \approx 208.5$.

persist in the long run, and only an outbreak (not cyclic behavior) may be observed. For example, stochastic simulations show that the disease does not persist [7].

Acknowledgment: This paper is dedicated to Professor Thomas G. Hallam, in honor of his 70th birthday.

7. **Conclusion.** Deterministic mathematical models were formulated that describe the epizootiology of Machupo virus in its reservoir host, *C. callosus*. The models follow the changes in the disease stages of the rodent population over time. Rodents are classified as susceptible, infectious or recovered. The models incorporate the differences in male and female behavior, vertical, horizontal and sexual modes of transmission and differences in immune response, immunocompetent and immunotolerant. A general male-female model was formulated and analyzed, model (2)-(3). The possible roles played by the immunocompetent and immunotolerant infectious stages were investigated in two special cases of this general model, where only one type of immune response was considered, SI^cR^c model and SI^t model, respectively. For each of these models, formulas were derived for the basic reproduction number $\mathcal{R}_0$, one of the most important parameters in mathematical epidemiology. When $\mathcal{R}_0 < 1$, if a small number of infectious rodents are introduced into the population, the disease does not persist, but if $\mathcal{R}_0 > 1$, then an outbreak may occur and the disease may approach an enzootic level. It was shown that the basic reproduction number depends on a combination of parameters, including parameters for horizontal, vertical and sexual transmission, birth rates for susceptible and infected rodents, disease-related death rates, natural death rates and the carrying capacity of the rodent population.

The dynamics of the models were studied analytically and numerically. In the general male-female model (2)-(3) and the SI^cR^c male-female model (13)-(14), for the chosen parameter values, the numerical results indicated global stability of

the DFE when $\mathcal{R}_0 < 1$. However, in the SI^t model, more complex behavior was observed–periodicity and bistability. In Example 5, the SI^t model exhibited cyclic behavior for large values of $\mathcal{R}_0 > 1$ and $\mathcal{R} < 1$ (Figure 6). In the cyclic behavior of Example 5, an outbreak occurs then disappears rapidly but then occurs again. But when $\mathcal{R}_0 < 1$ and $\mathcal{R} > 1$ in the SI^t model, bistability occurs: either the disease dies out or the disease persists at an enzootic level (Example 3). If the disease persists, the entire population becomes infected. This type of behavior makes it very difficult to control a disease; it is not sufficient to reduce $\mathcal{R}_0$ below unity; $\mathcal{R}$ must also be reduced below unity. In the simple SI model, where only females are modeled, bistability does not occur. Therefore, the male-female dynamics are important for bistability. Although these simpler models provide insight into the roles played by the immunocompetent and immunotolerant stages of infection, their individual dynamics may not be observed in the more general male-female model.

The general male-female model (2)-(3) is the one that best describes the epizootiology and immunology of *C. callosus* infected with Machupo virus. For the range of parameter values used in the numerical experiments, the general model did not exhibit the behavior shown in the SI^t model–bistability or periodicity. The SI^cR^c model with only the immunocompetent stage did not exhibit these properties either. The immunocompetent stage may provide greater population stability to the general male-female model. The basic reproduction number for the general model male-female (2)-(3), given in (9), shows that disease outbreaks or disease persistence ($\mathcal{R}_0$ greater than unity) are a result of both of these infectious stages. In addition, the population size in the general model will be reduced below carrying capacity when there is infection due to reduced fertility and disease-related deaths caused by the immunotolerant stage. Horizontal, vertical and sexual transmission all contribute to the persistence of the disease in the general male-female model. Individually or collectively, these three modes of transmission can lead to disease outbreaks or disease persistence in a rodent population (equations (9), (11) and (12)).

To control the disease in a rodent population and prevent human infection, rodent control is the obvious method and the one applied in Bolivia during the 1960s [18]. Rodent control programs have the effect of reducing the value of K, thereby reducing $\mathcal{R}_0$. No cases of BHF were reported from 1973 to 1992 [18]. More recently, cases of BHF have been reported in Bolivia but may be due to lack of continued aggressive rodent control measures [18].

Our future goals are to obtain better estimates for the model parameters and a better understanding of the functional forms for transmission (frequency versus density-dependent transmission). Estimates of the model parameters are needed to determine the threshold parameter $\mathcal{R}_0$ and to provide realistic model simulations. Analysis of these models has given us a greater understanding of the dynamics that are possible in the Machupo-rodent model. Whether all of these dynamics occur in nature require further study. The effects of spatial and environmental variations on the population and the disease dynamics need to be considered in a more complex model.

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E-mail address: linda.j.allen@ttu.edu