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Bayesian Compartmental Models and Associated Reproductive Numbers for an Infection with Multiple Transmission Modes

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Summary:

Zoonotic visceral leishmaniasis (ZVL) is a serious neglected tropical disease that is endemic in 98 countries. ZVL is primarily transmitted via a sand fly vector. In the United States, it is enzootic in some canine populations; it is transmitted from infectious mother to pup transplacentally, and vector-borne transmission is absent. This absence affords a unique opportunity to study (1) vertical transmission dynamics in dogs and (2) the importance of vertical transmission in maintaining an infectious reservoir in the presence of a vector. In this paper, we present Bayesian compartmental models and reproductive number formulations to examine (1) and (2), providing a mechanism to plan and evaluate interventions in regions where both transmission modes are present. First, we propose an individual-level SIR model to study the effect of maternal infection status during pregnancy on pup infection progression. We provide evidence that pups born to diagnostically positive mothers during pregnancy are more likely to become diagnostically positive both earlier in life, and at some point during their lifetime, than those born to diagnostically negative mothers. Second, we propose a population-level SIR model to study the impact of a vertically-maintained reservoir on propagating infection in a naive canine population through emergent vector transmission using simulation studies. We also present reproductive numbers to quantify contributions of vertically-infected and vector-infected dogs to maintaining infection in the population. We show that a vertically-maintained canine reservoir can propagate infection in a

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Supporting Information

The Web Appendix, referenced in Sections 2, 3, and 5, and a zip file with software and example data are available with this paper at the Biometrics website on Wiley Online Library.

theoretical naive population in the presence of a vector. Key words: Empirically-adjusted reproductive number; SIR; vertical transmission; visceral leishmaniasis.

1. Introduction

Zoonotic visceral leishmaniasis (ZVL) is a neglected tropical disease that places approximately 350 million people and millions of dogs at risk globally (Alvar et al. 2012, Desjeux 2004, Toepp et al. 2017). ZVL is characterized in part by an asymptomatic period, where individuals are not clinically ill, but can still transmit infection (Fakhar et al. 2008, Laurenti et al. 2013). It also has multiple transmission modes. In the Americas, ZVL is caused by the protozoan parasite *Leishmania infantum* (*L. infantum*). In endemic areas it is transmitted primarily by an infected female *Lutzomyia longipalpis* sand fly bite (Desjeux 2004). A second mode of transmission is vertical; this is the primary transmission route in dogs in non-endemic areas - infectious dams can pass infection to their pups transplacentally (da Silva et al. 2009).

In the United States, ZVL is enzootic in some hound populations. Infection is maintained through vertical transmission; vector transmission is absent (Duprey et al. 2006, Petersen and Barr 2009, Schantz et al. 2005). In 1999, canine leishmaniasis broke out in a New York dog kennel. The Centers for Disease Control and Prevention, Division of Parasitic Diseases, began widespread surveillance of dog kennels in 2000 (Petersen and Barr 2009). Surveillance efforts are ongoing among participating kennels. The lack of vector transmission in the United States allows us to study vertical transmission dynamics only, versus the combination of vertical and vector transmission. This can help kennel owners decide on breeding practices and treatments. Through population level simulations, we can gain insight into the potential impact of a vertically-maintained canine reservoir in endemic countries like Brazil, where control measures do not fully address the secondary transmission mode (Claborn 2010).

In this paper, previous models for vertical and vector transmission are discussed in Section 1.1. In Section 2, a novel individual-level Bayesian compartmental model to study vertical transmission in isolation is proposed in the form of a Susceptible, Infectious, Removed (SIR) model (diamonds, Figure 1). In Section 3, a population level SIR model to study the potential impact of vector transmission in a vertically-maintained reservoir on a naive population is presented (Figure 1). In Section 4, reproductive numbers for both models are proposed. We introduce the **I**nfection **S**ource-specific **E**mpirically **A**djusted **R**eproductive **N**umber (ISEARN) to quantify vertical and vector infected group contributions to maintaining population infection. Results and discussion are presented in Sections 5 and 6, respectively.

1.1 Epidemic Compartmental Models

Considerable work has been done in both deterministic and stochastic epidemic compartmental modeling, primarily for horizontal transmission (e.g., Kermack and McKendrick 1927; Lekone and Finkenstädt 2006). Some of this work has focused specifically on vector-transmitted infections, where a compartmental model for the vector

species is included (Samat and Percy 2012; Mukhtar et al. 2018). This approach depends on estimating the total number of infective individuals in the vector species. Many diseases also can be transmitted vertically, including rubella, Chagas' disease, and AIDS (Busenberg and Cooke 1993). Relatively few models address vertical transmission, since it is often considered less important. When it is included, the vertical mode is incorporated into population-level models (with horizontal transmission) through a birth process (Anderson and May 1979; Li et al. 2001; Zou et al. 2017). Models for vertical transmission alone have not been introduced, since this mode usually accompanies horizontal transmission. However, vertical is the only known transmission mode for ZVL in the United States, so this demands a new modeling approach.

To this end, we propose an individual-level compartmental model to study purely vertical transmission dynamics. This allows us to leverage a known contact process and incorporate individual covariates into the model while using a framework that is compatible with population-level epidemic compartmental models. We also incorporate the vertical and vector-infected host contributions and vector species into the familiar population-level SIR framework through a transition probability.

1.2 Reproductive Numbers

A reproductive number (RN) is an important quantity in epidemiology. In its simplest form, the basic reproductive number (BRN) is the total number of secondary cases produced by a primary case in a completely susceptible population (Dietz 1993). While this quantity is most naturally explored in the context of horizontally-transmitted infections, it is also meaningful for vertical transmission. We view each litter as completely susceptible and contacting one infectious individual, the mother. Then, the BRN is the expected number of pups that ever progress to infection per infectious mother. We calculate BRNs for both diagnostically negative and positive mothers to assess the impact of mother's status on pup health.

This definition is limiting in two important ways, so it is problematic for application to ZVL vector transmission. First, it requires a completely susceptible population, which is seldomly realistic and is inappropriate for established infections in a population. Second, it remains constant across time, which is too restrictive. For example, if there is infection seasonality, or if an intervention is introduced, a constant RN cannot capture these changes; it would have to be recalculated under a number of specific conditions. Researchers have introduced more general RNs to address these drawbacks, including temporally varying and scaled versions, called effective reproductive numbers (Chowell et al. 2004, Lekone and Finkenstädt 2006).

Brown, Oleson, and Porter (2016) introduced a more flexible quantity, the "empirically adjusted reproductive number", which requires only the expected number of secondary infections produced by a single infected individual in the population of interest to define a RN. While this has a natural representation for the stochastic SIR model employed here, in its current formulation, it accommodates a model with a single infectious class. In our application, there are two different infectious sources: vertically (I^*), and vector infected individuals (I). Under the assumption that these transmission modes are disjoint (dogs can be

infected through one mode, but not both) we extend the empirically adjusted reproductive number to derive the ISEARN. This is an additive quantity applicable to diseases with multiple hosts that quantifies each infection source contribution to maintaining disease.

2. Individual SIR Model: Vertical Transmission

2.1 Data and Classification

Data were collected from 2005–2018 by the Centers for Disease Control and the Petersen Lab at the University of Iowa through an ongoing surveillance study of hunting hound populations predominantly located in the Midwestern United States. Although vertical transmission of *L. infantum* has been observed in multiple breeds (Rosypal et al. 2005, Gaskin et al. 2002), we restrict our analyses to Foxhounds because the infection process can vary by breed (Moreno and Alvar 2002). The data set has 70 individual pups, each with individual level data including birth year, and results of at least one of three diagnostic tests for at least two time points: immunofluorescence anti-*Leishmania* antibody test (IFAT), quantitative polymerase-chain reaction (qPCR), and Dual-Path Platform (DPP®) canine visceral leishmaniasis (CVL). We also have at least one of these test results for the mother of each pup for the pup's birth year. All dogs included in this data set were born to mothers that became positive on at least one test at some point in their lives, so all pups were exposed to *L. infantum in utero*. An exploratory analysis is available in the Web Appendix.

For each pup, mother's status during pregnancy and pup's status at each time are classified as $\mathcal{S}$ (susceptible) or $\mathcal{I}$ (infectious) based on the results of up to three tests: IFAT, qPCR, and DPP® CVL. For IFAT, dilutions at or above 1⁄64 are positive. The qPCR test gives a positive/negative result based on a standard curve and a cutoff of 41. For DPP® CVL, if the test was positive within 15 minutes, it was positive. A dog is classified into $\mathcal{S}$ if it has all negative test results. While we use "susceptible" to be consistent with infectious disease modeling terminology, dogs in $\mathcal{S}$ are exposed, but have parasite levels below the limits of detection for the tests. If at least one test is positive, we classify a dog into $\mathcal{I}$, as these tests correlate well with infection, based on parasite culture and physical exams (Larson et al. 2017). We refer to this as "diagnostically positive". Dogs are classified as removed ($\mathcal{R}$) upon death or other removal from the population. Of the 70 dogs, 22 were born to $\mathcal{S}$ and 48 were born to $\mathcal{I}$ mothers. Dogs are assumed to progress as in Figure 1, left column.

2.2 Likelihood and Priors

We employ a multinomial model (Ozanne et al. 2019). Let Z_{ij}^{c} denote the infection state of the i^{th} dog at time j for $i = 1,\ldots, N$, $j = 1,\ldots, T$, and $c \in \{\mathcal{S}, \mathcal{I}, \mathcal{R}\}$. The time index, j, is j^{th} year since surveillance began. The transition probabilities are inverse logit functions of age and maternal status during pregnancy (see Web Appendix). The likelihood is

$$\left(Z_{i,j+1}^{\mathcal{I}}, Z_{i,j+1}^{\mathcal{R}}, Z_{i,j+1}^{\mathcal{S}}\right) \mid Z_{ij}^{\mathcal{S}} \sim \text{Multinomial}\left(1, \phi_{ij}^{(\mathcal{S}\cdot)}\right); \quad (1)$$

$$Z_{i,j+1}^{\mathcal{R}} \mid Z_{ij}^{\mathcal{I}} \sim \text{Bernoulli}\left(\phi_{ij}^{(\mathcal{I}\mathcal{R})}\right). \quad (2)$$

Dogs are usually members of a litter, so transition probabilities for this application could incorporate a random litter term. However, we are modeling infection progression in purebred Foxhounds from a few hunts that interbreed - a fairly homogeneous group. Conditional on mother's status during pregnancy and pup age, pups can be considered independent. We placed $N(0,1)$ priors on $\boldsymbol{\beta}$, $\boldsymbol{\theta}$, and $\boldsymbol{\xi}$; more diffuse priors gave comparable estimates.

2.3 Model Fitting and Validation

The individual-level SIR model for vertical transmission was fit using Markov chain Monte Carlo (MCMC). Updates were performed using the Metropolis-within-Gibbs algorithm. Relevant distributions, the algorithm, and R code are available in the web appendices. Model fit was assessed by comparing the observed counts in each compartment ($\mathcal{S}, \mathcal{I}, \mathcal{R}$) at each age (0–10) to the posterior predictive counts using a posterior predictive p-value (Gelman et al. 1996). For the observed data, $\mathbf{Y}^{obs}$, and for each posterior predictive data set, $\mathbf{Y}^{(\ell)} (\ell = 1, \ldots, n)$, the test statistic $X^2(\mathbf{Y}) = \sum_{c \in \{\mathcal{S}, \mathcal{I}, \mathcal{R}\}} \sum_{j=0}^{T_{max}} \frac{\left[Y_{jc} - \mathrm{E}\left(\mathbf{Y}^*_j\right)\right]^2}{\mathrm{Var}\left(\mathbf{Y}^*_{jc}\right)}$ was calculated. $\mathrm{E}\left(\mathbf{Y}^*_{jc}\right)$ and $\mathrm{Var}\left(\mathbf{Y}^*_{jc}\right)$ denote the posterior predictive mean and variance, respectively, and T_{max} is the maximum observed age. Then, the posterior predictive p-value is $P\left[X^2\left(\mathbf{Y}^{(\ell)}\right) > X^2\left(\mathbf{Y}^{obs}\right) \mid \mathbf{Y}^{obs}\right] \approx \sum_{\ell=1}^{n} \mathbb{1}\left\{X^2\left(\mathbf{Y}^{(\ell)}\right) > X^2\left(\mathbf{Y}^{obs}\right)\right\}/n$. For T_{max} between two and five, the posterior predictive p-value was greater than 0.3. It was 0.416 for a T_{max} of 4, which corresponds to the average observed death age. Where data were more sparse, lower predictive p-values were observed. For example, after age 5, more than half of the observations were missing (see Web Appendix) and the available data mainly were a result of the removed category being an absorbing state, i.e. dogs removed at or before age 5 remain in that category and do not inform any compartment transitions. Nevertheless, where the model is constrained by observation of non-absorbing states, the fit was adequate.

3. Population SIR Model: Vector Transmission

While vertical transmission of *L. infantum* exists in endemic areas like Brazil (da Silva et al. 2009), we cannot study this transmission mode directly because vertically-infected and vector-infected dogs are indistinguishable. Since vertical is the only known transmission mode in canines in the United States (Duprey et al. 2006, Schantz et al. 2005, Schaut et al. 2015, Weng et al. 2012), we have a unique opportunity to study not only the individual-level dynamics of the infection, but also the potential implications for infection spread in the larger (naive) canine population, should vector transmission emerge in the United States. The vertically-maintained reservoir is the initial infection source for the vector (Figure 1). Naive dogs can acquire infection from the vector and become a second infectious source.

To study the impact of an existing, vertically-infected canine population, $\mathscr{C}^*$, on infection spread in a naive canine population, $\mathscr{C}$ (Note: $\mathscr{C}^* + \mathscr{C} = \mathscr{C}^{all}$, all dogs in a particular area), we propose a population-level SIR model. In simulation studies, we examine the ISEARNs for various choices of infection rate, λ and population size ($|\mathscr{C}|$). Although we examine *L. infantum* transmission dynamics on an individual level for vertical transmission, it is

important to study the vector transmission on a population level because this best reflects the data available in endemic countries like Brazil, where extensive information is rarely available for individual dogs. We can track vertical and vector derived infections in these simulations, so vertically-exposed dogs ($\mathscr{C}^*$) progress according to the individual-level model.

3.1 Sand fly Data

As part of an effort to understand sand fly feeding behaviors, sand flies were fed on sedated dogs with varying ZVL clinical status. Standard procedures were used to identify infected flies; 192 of 292 fed flies were infected. See Web Appendix for procedure details.

3.2 Data Model

As described in Section 3.1, we have data on the proportions of female *Lutzomyia longipalpis* sand flies that became infected when fed on vertically-infected dogs in the United States. We assume any vector would become infected at similar rates to *Lutzomyia longipalpis* used in experiments, and all flies are equally likely to become infected after biting infectious dogs.

Let $Z_I^{(\mathrm{SF})}$ denote the number of sand flies that were found to be infected when they were fed on diagnostically positive dogs. While vertically exposed diagnostically negative mothers can transmit infection to their offspring, parasite load is too low to transmit through a vector (Vida et al. 2016). The model is $Z_I^{(\mathrm{SF})} \sim \mathrm{Binomial}\left(N^{(\mathrm{SF})}, \rho_I\right)$; $N^{(\mathrm{SF})} = 292$ and $\rho_I = 0.65$.

3.3 Process Model

We are interested in how new vector transmission in a vertically-exposed population may impact naive dogs. In the presence of vector transmission, we propose the following process model, with a chain binomial structure. This could be expressed using a multinomial likelihood, but the chain binomial structure is more commonly used for population level epidemic compartmental models (Brown et al. 2016, Lefevre 1990, Lekone and Finkenstädt 2006). For the k^{th} month since vector emergence, $k \in 1,\ldots,24$ with $\pi^{(\mathcal{SI})}(t_k) + \pi^{(\mathcal{SR})}(t_k) < 1$,

$$I^{(\mathcal{SI})}(t_k) \sim \mathrm{Binomial}\left(S(t_{k-1}), \pi^{(\mathcal{SI})}(t_k)\right), \tag{3}$$

$$R^{(\mathcal{SR})}(t_k) \sim \mathrm{Binomial}\left(S(t_{k-1}) - I^{(\mathcal{SI})}(t_k), \pi^{(\mathcal{SR})}(t_k)\right), \tag{4}$$

$$R^{(I\mathcal{R})}(t_k) \sim \mathrm{Binomial}\left(I(t_{k-1}), \pi^{(\mathcal{IR})}(t_k)\right). \tag{5}$$

At time k+1, the compartment totals for dogs in $\mathscr{C}$ are deterministic functions of those totals at time k and the transition compartments at time $k + 1$. For dogs in $\mathscr{C}$, the probability of transitioning from $\mathcal{S} \rightarrow \mathcal{I}$ at time k depends on the proportions of infectious dogs and the

probability that sand flies become infectious from feeding on infectious individuals. The counts at time k are $S^*(t_k) = \sum_{i=1}^{N_k^*} Z_{ij(k)}^{\mathcal{S}}$, $I^*(t_k) = \sum_{i=1}^{N_k^*} Z_{ij(k)}^{\mathcal{I}}$, and $N^*(t_k) = S^*(t_k) + I^*(t_k)$.

3.4 Parameter Model

We assume a homogeneous Poisson contact process. Dogs are bitten at rate λ_k for month k. If a dog in $\mathscr{C}$ is bitten by an infected sand fly, it will become infected with probability p. The proportion of infectious sand flies in the population should depend on the proportions of vertically and vector infected dogs at time k and the probability that an uninfected sand fly becomes infectious after contact with an infected dog. Assuming no biting preference, $\delta_k = \rho_I\left(\frac{I(t_k-1)}{N(t_k-1)+N^*(t_k-1)}\right) + \rho_I\left(\frac{I^*(t_k-1)}{N(t_k-1)+N^*(t_k-1)}\right) = \delta_k^I + \delta_k^{I^*}$. This term captures both the vector and vertical transmission contributions, where the latter ($I^*(t_{k-1})$), is calculated using the individual-level vertical transmission model from Section 3.

Lutzomyia longipalpis sand flies typically live 10 days or less (Dia-Albiter et al. 2011). We assume a vector in the United States would have a similar lifespan and account for flies that are infectious at the beginning of a month and those that are not, but can become infectious during that month and then bite a susceptible dog. The $\mathcal{S} \to \mathcal{I}$ transition probability is a first order Markov Process: $\pi^{(\mathcal{SI})}(t_k) = 1 - e^{-\left\{\delta_{k-1} I(k>0) + (1-\delta_{k-1})^{I(k>0)}\delta_k\right\}\{\lambda_k p\}}$. For $k > 0$, δ_k is the proportion of infectious sand flies; $(1-\delta_k)\delta_k$ denotes the probability that noninfectious sand flies become infectious. At $k = 0$, no flies are infectious. We decompose $\pi^{(\mathcal{SI})}(t_k)$ to obtain transition probabilities from $\mathcal{S} \to \mathcal{I}$ due to vector transmission, where the vector derives infection from two distinct sources: $\mathcal{I}$, and $\mathcal{I}^*$, and associated RNs. The probability of an $\mathcal{S} \to \mathcal{I}$ transition due to exposure from a vector source ($\mathcal{I}$), for example, is $\pi^{(\mathcal{SI})}(t, s_I) = \pi_{I \mid !I^*}(t)[1 - P(A(t, s_{I^*}))]$. $P(A(t, s_{I^*})$ is the probability of getting infected at time t due to a vertically-infected sand fly bite; $\pi^{(\mathcal{SI})}(t_k, s_I) = 1 - e^{-\left\{\delta_{k-1}^I I(k>0) + \left(1-\delta_{k-1}^I\right)^{I(k>0)}\delta_k^I\right\}\{\lambda_k p\}}$. See Web Appendix for derivations. Other probabilities are $\pi^{(\mathcal{SR})}(t_k) \sim \text{Beta}\left(\alpha^{(\mathcal{SR})}, \beta^{(\mathcal{SR})}\right)$ and $\pi^{(\mathcal{IR})}(t_k) \sim \text{Beta}\left(\alpha^{(\mathcal{IR})}, \beta^{(\mathcal{IR})}\right)$, assumed constant over time.

3.5 Simulation Studies

These simulations serve two purposes. First, we demonstrate a potential modeling approach for areas with both vertical and horizontal transmission. Developing methodology which can be applied in regions with both transmission modes is neccessary to comprehensively plan and evaluate public health interventions. Programs which target vector transmission, and those which target vertical transmission operate differently, and may need to be coordinated or combined (Miró et. al. 2018). Moreover, common reservoir control methods (e.g., culling) which disregard the details of vertical transmission may prove ineffective in controlling the maintenance of the infectious organism in the population. Second, we can assess how a vertically-maintained canine reservoir could infect a naive canine population in the presence of emergent vector transmission. Specifically, we look at what could happen if a vector emerged at the last time point we consider in the vertical transmission model (2018 in this

case) and assume we can observe this process from emergence. We examine the infection behavior with different combinations of $(p \cdot \lambda, N)$; we consider all combinations of $p = 0.01$, λ from 10 to 200 (average bites per month), $N = \{50,100,500\}$. Note that λ and p are unidentifiable, so we fix p for the simulations and vary λ. We assume that $\mathbb{E}\left(\pi^{(\mathcal{SR})}\right) = 0.0005$, $\beta^{(\mathcal{SR})} = 1$, $\mathbb{E}\left(\pi^{(\mathcal{IR})}\right) = 0.2$, and $\beta^{(\mathcal{IR})} = 1$. We sample with replacement 1000 times the posterior parameter estimates from fitting the vertical transmission compartmental model to the ZVL surveillance data. Then, we use posterior estimates to propagate the vertically-exposed canine population forward for twenty-four months, and count the number of vertically-infected dogs at each month k. Simultaneously, we simulate vector infection data according to the population model described in Section 3 for all combinations of $(p \cdot \lambda, N)$.

4. Reproductive Numbers - Two Transmission Modes

A RN is the most common method for quantifying infection transmissibility in a population (Anderson and May 1991). In this section, we provide RN formulations for vertical and vector transmission as a result of vertically and vector-maintained reservoirs.

4.1 Basic Reproductive Numbers for Vertical Transmission

When infection is transmitted transplacentally, an infectious female dog only passes infection to her pups, so the number of potentially infectious contacts is the number of pups in a litter. To calculate a BRN for vertical transmission from $\mathcal{I}$ mothers, for instance, we determine the expected number of pups (born to $\mathcal{I}$ mothers) that become infected somtime in their lives.

We simulate realizations of vertically-exposed pups to estimate reproductive numbers as follows. We sample with replacement 1000 times the posterior parameter estimates from fitting the vertical transmission SIR model to the ZVL data. For each $\ell \in \{1, 2, \ldots, 1000\}$, we consider $N^* = 70$ pups, starting at age 0, and distribute these pups between $\mathcal{S}$ mothers and $\mathcal{I}$ mothers according to a Binomial(N^*, 1/2) distribution. We assume there are an equal number of $\mathcal{S}$ and $\mathcal{I}$ mothers (7 each). Using the posterior parameter estimates $(\beta, \theta, \xi)^{\ell}$, we propagate the pups forward and count the number that ever enter the $\mathcal{I}$ category. Formally, let $Z_{ij}^{\mathcal{I} \mid \mathcal{S}}$ be 1 if individual i becomes newly seropositive $(\mathcal{I})$ at time j and 0 otherwise. Let $Z_i^M(m)$ be 1 if individual i's mother was in infection category m at the time of i's birth and 0 otherwise. Then, an empirical estimate of the BRN for mothers in $m \in \mathcal{M} = \{S^*, I^*\}$ is $\mathcal{R}_0^m = \frac{\sum_{j=1}^{J} \sum_{i \in N_m^*} Z_{ij}^{\mathcal{I} \mid S}}{M(m)}$. If $\mathcal{R}_0^m > 1$, infection will persist in the population due to source m.

4.2 ISEARNs for Vector Transmission

Let $I_i(t_k, s_b)$ be the event that individual i becomes infected after being bitten by a sand fly that derived its infection from an individual in $b \in \mathcal{B} = \{I, I^*\}$. Then, the expected number of secondary infections attributable to an individual in b is

$\mathbb{E}\left[\sum_{i=0}^{N_k}(I_i(t_k, s_b))\right] = S(t_k) \cdot P(I_i(t_k, s_b) \mid i \in \mathcal{S}) = S(t_k) \cdot \pi^{(\mathcal{S}\mathcal{J})}(t_k, s_b)$. Furthermore, the average number of infections per infectious individual in b is the next generation term (Allen and van den Driessche 2008) $G(t_k, s_b) = \frac{S(t_k) \cdot P(I_i(t_k, s_b) \mid i \in \mathcal{S})}{b(t_k)}$. The next generation matrix is

$$\mathbf{G}(t_k) = \begin{array}{c} \\ \mathcal{J} \\ \mathcal{J}^* \end{array} \begin{array}{c} \begin{array}{cc} \mathcal{J} & \mathcal{J}^* \end{array} \\ \begin{vmatrix} \frac{\pi^{(\mathcal{S}\mathcal{J})}(t_k, s_I)S(t_k)}{I(t_k)} & \frac{\pi^{(\mathcal{S}\mathcal{J})}(t_k, s_{I^*})S(t_k)}{I^*(t_k)} \\ 0 & 0 \end{vmatrix} \end{array}.$$

If $b(t_k)$ is 0, $G(t_k, s_b)$ is defined to be 0. We account for the probability that an individual remains in an infectious state at each time, t, and calculate the total number of expected infections over time to generalize the result to the pathogen's lifetime. This gives the ISEARN,

$$\mathcal{R}^{(\mathcal{E}\mathcal{A})}(t_k, s_b) = \sum_{t=t_k}^{t_\infty} G(t, s_b)\left(\frac{b(t)}{\sum_{b \in \mathcal{B}} b(t)}\right)\left(1 - \pi^{(\mathcal{J}\mathcal{R})}\right)^{t_k}. \quad (6)$$

Equation 6 allows us to calculate the expected number of (vector-transmitted) infections attributable to a single type of infectious individual, lending insight into an infectious group's relevance to maintaining infection in a population. For example, $\mathcal{R}^{(\mathcal{E}\mathcal{A})}(t_k, s_{I^*})$ is the expected number of new vector-borne infections per vertically infected dog at time k. We can interpret ISEARNs like other RNs. If $\mathcal{R}^{(\mathcal{E}\mathcal{A})}(t_k, s_b)$ is greater than one, then the parasite is expected to further colonize the population due to vector transmission from infectious source $b \in \mathcal{B}$.

If $\mathcal{R}^{(\mathcal{E}\mathcal{A})}(t_k, s_b) < 1 \; \forall b$, no one source results in further parasite colonization, but together multiple sources may. We can calculate an overall RN to capture the total expected number of new infections due to vector exposure from all sources. To derive the $\mathcal{S} \rightarrow \mathcal{J}$ transition probability, we assume that the set of events $\{I(t, s_b)\}$ are mutually disjoint. Consequently, $\sum_{b \in \mathcal{B}} \pi^{(\mathcal{S}\mathcal{J})}(t, s_b) = \pi^{(\mathcal{S}\mathcal{J})}(t)$ (Web Appendix). Then, $\mathcal{R}^{(\mathcal{E}\mathcal{A})}_{add}(t_k) = \sum_{b \in \mathcal{B}} \sum_{t=t_k}^{t_\infty} G(t, s_b)\left(\frac{b(t)}{\sum_{b \in \mathcal{B}} b(t)}\right)\left(1 - \pi^{(\mathcal{J}\mathcal{R})}\right)^{t_k}$. This is consistent with Brown, Oleson and Porter (2016) - empirically-adjusted reproductive numbers are additive across spatial locations. If $\mathcal{R}^{(\mathcal{E}\mathcal{A})}_{add}$ is greater than one, infection will grow in the population due to vector transmission.

5. Inference

5.1 Vertical Transmission

We implemented the individual-level SIR model (Section 2) using the data described in Section 2.1. The posterior medians and 95% credible intervals for the parameters in this

model are shown in Table 1. The estimated intercepts are negative and relatively large. This corresponds to a small probability of transitioning out of the $\mathcal{S}$ category at very young ages, which agrees with observed transition behavior. The 95% credible interval for the coefficient for mother's status (1 if diagnostically negative, 0 otherwise) is right-skewed; 85.5% of sampled parameter estimates are less than zero. This suggests some protective effect of being born to an $\mathcal{S}$ mother. This corresponds to a greater risk for an $\mathcal{S} \rightarrow \mathcal{I}$ transition before age 3 for pups born to $\mathcal{I}$ mothers (Figure 2, center). This is also apparent in the results for β_3, the interaction between pup age and mother's status (Table 1).

In Figure 2, we examine the log relative risk (RR) of transitions from $\mathcal{S}$ (to $\mathcal{S}$, $\mathcal{I}$, and $\mathcal{R}$) as a function of pup age. There is considerable variability in this process; for all transitions, the 95% credible bands for the log RR cover zero. While pups born to $\mathcal{I}$ mothers are more likely to transition from $\mathcal{S}$ to $\mathcal{I}$ before age 3, they are less likely to transition after age 3. This suggests pups born to $\mathcal{I}$ mothers are likely to transition to $\mathcal{I}$ early in life. If we examine the data, these same dogs also die early. In contrast, those pups born to $\mathcal{I}$ mothers that do not transition before age 3 are likely healthier because they live longer and transition later (see Web Appendix). Some of the later results appear to be driven by a survivor bias.

Separate BRNs for vertical transmission are calculated for pups born to $\mathcal{S}$ mothers and to $\mathcal{I}$ mothers as described in Section 4.1. The median BRN is 2.83, with a 95% credible interval of (2.20, 3.47) for the former and 3.37 with a 95% credible interval of (2.54, 4.04) for the latter. Results are summarized in Figure 3. For 86.3% of the posterior predictive data sets, $\mathcal{R}_0^{\mathcal{I}} > \mathcal{R}_0^{\mathcal{S}}$. This is compelling given the data. It suggests that dogs born to $\mathcal{I}$ mothers are more likely to progress to infection at some point in their lives than those born to $\mathcal{S}$ mothers. For young dogs (<3 years), the median risk for the $\mathcal{S} \rightarrow \mathcal{I}$ transition is smaller for dogs born to $\mathcal{S}$ moms; the RR difference is not significant, likely due to sample size.

5.2 Simulated Vector Transmission

As described in Section 3.5, we conducted simulation studies to assess vertically-maintained reservoir contributions to infection in unexposed dogs in the presence of emergent vector transmission. We considered dogs present in the data set in 2018 and studied the potential impact of these vertically-exposed dogs on non-vertically exposed canine populations of various sizes in the presence of a vector. In this data set, there were four dogs that were seropositive in 2018. To investigate the contributions of the infectious classes (vertically and vector infected dogs) to infection in the simulated populations, we examine the ISEARNs.

The potential for vector transmission in a vertically-maintained reservoir to propogate infection in an unexposed population depends on average monthly bite rate (λ) and the probability that an infectious bite results in infection (p). When $N = 100$, the median total RN exceeds one for $\lambda \geq 20$, and drops below one when the susceptible individuals in $\mathcal{C}$ are exhausted (Figure 4). The RN also depends on the size of the naive population (N). For $\lambda = 25$, the median reproductive numbers and and associated variability increase as N increases. These results suggest that under reasonable conditions, a vertically-maintained canine reservoir could lead to infection of naive dogs in the area in the presence of a vector. Importantly, while the shapes of the vertical and vector ISEARN curves are similar in this

simulated example, providing separate estimates allows these results and methods to inform the separate public health interventions which would address each transmission mechanism. While, from a simple fit perspective, a more basic model might provide reasonable estimates of an overall reproductive numbers, such an approach would nevertheless sacrifice biological and practical relevance for diseases such as VL.

Recall, these simulations are performed assuming no immigration or births. If new susceptibles entered the population, infection could be sustained in the population (reproductive numbers greater than or equal to one) even when the initial population size was small. Also, we assume that $\mathbb{E}\left(\pi^{(\mathcal{IR})}\right) = 0.2$ and $\beta^{(\mathcal{IR})} = 1$.

6. Discussion

In this paper, we present two Bayesian compartmental models and associated RNs: an individual-level SIR model designed to study infection progression as a result of vertical pathogen exposure used to study *L. infantum* vertical transmission dynamics in canines in the Americas and a population level SIR model that incorporates contributions of two infectious hosts and a vector to study the potential impact of emergent vector transmission in a vertically-maintained canine reservoir on a naive population (Figure 1). We present RNs for each model to quantify the different infectious groups' average contributions to maintaining infection in the population, either through vertical or vector transmission.

6.1 Vertical Transmission

The finding that mother status impacts vertical transmission attributable infection has direct implications for ongoing studies of VL transmission in northern Brazil. When designing surveillance and culling programs, knowledge of the role of dam health on pup pathogen load (and thus infectiousness) supports efforts to evaluate related groups of dogs. In addition, study of the vertical transmission process in isolation allows the current study to directly provide prior information concerning the relevant transmission parameters in ecological models with mixed transmission.

6.2 Potential Vector Transmission

Similarly, vector control measures in an area with vector transmission could be effective only temporarily and vulnerable to regression in the presence of a vertically-maintained reservoir. To appropriately evaluate multiple overlapping interventions, therefore, future models should relate each intervention to the transmission process (vertical or horizontal) that is targeted. While the overall goal of such an intervention will be to reduce the overall RN below the replacement threshold of 1, with multiple transmission mechanisms and corresponding interventions, such an outcome could be pursued via multiple intervention strategies. By separately evaluating the impact of vertical and vector targeted interventions, future studies will also allow assessment of the cost effectiveness of different intervention regimes.

6.3 Limitations and Future Work

While both the vertical model and vector simulation results provide important insights into transmission dynamics, this work has limitations. First, the sample size was small because only dogs with an established lineage could be used to study the effect of mother's health on *L. infantum* infection progression. Thus, an objective of this paper is to establish methodology to study these progression dynamics. Surveillance efforts are ongoing, so these models can be applied to larger samples in the future. Also, a birth process was not incorporated into the vector transmission simulations. This is valid if the non-vertically exposed canine population ($\mathscr{C}$) consists of spayed/neutered individuals. In the presence of a birth or immigration process, we expect the infection to persist in the population because the number of susceptible individuals will be sustained. Finally, a vertically-maintained canine reservoir likely also would impact humans, so additional simulations could address human health.

Finally, this paper groups all infected individuals into a single category due to the small available sample. However, *L. infantum*-infected individuals can be classified as asymptomatic or symptomatic (Fakhar et al. 2008, Laurenti et al. 2013, Sanchez et al. 2004). Time spent asymptomatic is often much longer than that spent symptomatic, and rates at which individuals in each category transmit infection to sand flies vary (Laurenti et al. 2013).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Allen LJ and van den Driessche P (2008). The basic reproduction number in some discrete-time epidemic models. Journal of Difference Equations and Applications 14, 1127–1147.

Alvar J, Veléz ID, Bern C, Herrero M, Desjeux P, Cano J, et al. (2012). Leishmaniasis worldwide and global estimates of its incidence. PLoS One 7, e35671. [PubMed: 22693548]

Anderson RM and May RM (1979). Population biology of infectious diseases: Part I. Nature 280, 361–367. [PubMed: 460412]

Anderson RM and May RM (1991). Infectious Diseases of Humans: Dynamics and Control. Oxford: Oxford University Press.

Brown GD, Oleson JJ and Porter AT (2016). An empirically adjusted approach to reproductive number estimation for stochastic compartmental models: a case study of two Ebola outbreaks. Biometrics 72, 335–343. [PubMed: 26574727]

Busenberg S and Cooke K (1993). Vertically Transmitted Diseases. Models and Dynamics, Biomathematics 23 Berlin: Springer-Verlag.

Chowell G, Hengartner NW, Castillo-Chavez C, Fenimore PW and Hyman JM (2004). The basic reproductive number of Ebola and the effects of public health measures: the cases of Congo and Uganda. Journal of Theoretical Biology 229, 119–126. [PubMed: 15178190]

Claborn DM (2010). The biology and control of visceral leishmaniasis. Journal of Global Infectious Diseases 2, 127–134. [PubMed: 20606968]

da Silva SM, Ribeiro VM, Ribeiro RR, Tafuri WL, Melo MN and Michalick MSM (2009). First report of vertical transmission of leishmania (leishmania) infantum in a naturally infected bitch from Brazil. Veterinary Parasitology 166, 159–162. [PubMed: 19733439]

Desjeux P (2004). Leishmaniasis: current situation and perspectives. Comparative Immunology, Microbiology, and Infectious Diseases 27, 305–318.

Diaz-Albiter H, Mitford R, Genta FA, Sant'Anna MRV and Dillon RJ (2009). Reactive oxygen species scavenging by catalase is important for female *Lutzomyia longipalpis* fecundity and mortality. PLoS One 6, e17486.

Dietz K (1993). The estimation of the basic reproduction number for infectious diseases. Statistical Methods in Medical Research 2, 23–41. [PubMed: 8261248]

Duprey ZH, Steurer FJ, Rooney JA, Kirchhoff LV, Jackson JE, Rowton ED, et al. (2006). Canine visceral leishmaniasis, United States and Canada: 2000–2003. *Veterinary Parasitology*: Regional Studies and Reports 12, 440–446.

Fakhar M, Motazedian MH, Hatam GR, Asgari Q, Kalantari M and Mohebali M (2008). Asymptomatic human carriers of Leishmania infantum: possible reservoirs for Mediterranean visceral leishmaniasis in southern Iran. Annals of Tropical Medicine & Parasitology 102, 577–583. [PubMed: 18817598]

Gaskin AA, Schantz P, Jackson J, Birkenheuer A, Tomlinson L, Gramiccia M, et al. (2002). Visceral leishmaniasis in a New York foxhound kennel. Journal of Veterinary Internal Medicine 16, 34–44. [PubMed: 11822802]

Gelman A, Meng X, and Stern H (1996). Posterior predictive assessment of model fitness via realized discrepancies. Statistica Sinica 6, 766–807.

Kermack WO and McKendrick AG (1927). A contribution to the mathematical theory of epidemics. Proceedings of the Royal Society of London A: Mathematical, Physical, and Engineering Sciences 115, 700–721.

Larson M, Toepp A, Scott B, Kurtz M, Fowler H, Esfandiari J, et al. (2017). Semi-quantitative measurement of asymptomatic L. infantum infection and symptomatic visceral leishmaniasis in dogs using Dual-Path Platform CVL. Applied Microbiology and Biotechnology 101, 381–390. [PubMed: 27796441]

Laurenti MD, Rossi CN, Ribeiro da Matta VL, Tomokane TY, Corbett CEP, Secundino NFC, et al. (2013). Asymptomatic dogs are highly competent to transmit *Leishmania* (*Leishmania*) *infantum chagasi* to the natural vector. Veterinary Parasitology 196, 296–300. [PubMed: 23562649]

Lefévre C (1990). Stochastic epidemic models for S-I-R infectious diseases: a brief survey of the recent general theory Stochastic Processes in Epidemic Theory (Lecture Notes in Biomathematics Vol 86) Berlin: Springer-Verlag.

Lekone PE and Finkenstädt BF (2006). Statistical inference in a stochastic epidemic SEIR model with control intervention: Ebola as a case study. Biometrics 62, 1170–1177. [PubMed: 17156292]

Li MY, Smith HL, and Wang L (2001). Global dynamics of an SEIR model with vertical transmission. SIAM Journal of Applied Mathematics 62, 58–69.

Miró G, Petersen C, Cardoso L, Bourdeau P, Baneth G, Solano-Gallego L, et al. (2018). Novel Areas for Prevention and Control of Canine Leishmaniosis. Trends in Parasitology 33, 718–730

Moreno J and Alvar J (2002). Canine leishmaniasis: epidemiological risk and the experimental model. Trends in Parasitology 18, 399–405. [PubMed: 12377257]

Mukhtar AYA, Munyakazi JB, Ouifki R, and Clark AE (2018). Modelling the effect of bednet coverage on malaria transmission in South Sudan. PLOS One 13, e0198280. [PubMed: 29879166]

Ozanne M, Brown G, Oleson J, Lima I, Queiroz J, Jeronimo SMB, et al. (2019). Bayesian compartmental model for an infectious disease with dynamic states of infection. Journal of Applied Statistics 46, 1043–1065. [PubMed: 31537954]

Petersen CA and Barr SC (2009). Canine leishmaniasis in North America: emerging or newly recognized? Veterinary Clinics of North America: Small Animal Practice 39, 1065–1074(vi). [PubMed: 19932363]

Rosypal AC, Troy GC, Zajac AM, Frank G and Lindsay DS (2005). Transplacental transmission of a North American isolate of Leishmania infantum in an experimentally infected beagle. Journal of Parasitology 91, 970–972. [PubMed: 17089780]

Samat NA and Percy DF (2012). Vector-borne infectious disease mapping with stochastic difference equations: an analysis of dengue disease in Malaysia. Journal of Applied Statistics 39, 2029–2046.

Sanchez MA, Diaz NL, Zerpa O, Negron E, Convit J and Tapia FJ (2004). Organ-specific immunity in canine visceral leishmaniasis: analysis of symptomatic and asymptomatic dogs naturally infected with leishmania chagasi. American Journal of Tropical Medicine and Hygiene 70, 618–624. [PubMed: 15211002]

Schantz PM, Steurer FJ, Duprey Z, Kurpel K, Barr SC, Jackson J, et al. (2005). Autochthonous visceral leishmaniasis in dogs in North America. Journal of the American Veterinary Medical Association 226, 1316–1322. [PubMed: 15844420]

Schaut RG, Robles-Murguia M, Juelsgaard R, Esch KJ, Bartholomay LC, Ramalho-Ortigao M and Petersen CA (2015). Vectorborne transmission of *Leishmania infantum* in hounds, United States. Emerging Infectious Diseases 21, 4100–4109.

Toepp A, Schaut R, Scott B, Mathur D and Berens A (2017). Leishmania incidence and prevalence in U.S. hunting hounds maintained via vertical transmission. Veterinary Parasitology: Regional Studies and Reports 10, 75–81.

Vida B, Toepp A, Shaut RG, Esch K, Juelsgaard R, Shimak RM, et al. (2016). Immunologic progression of canine leishmaniosis following vertical transmission in United States dogs. Veterinary Immunology and Immunopathology 169, 34–38. [PubMed: 26827836]

Weng JL, Young SL, Gordon DM, Claborn D, Petersen C and Ramalho-Ortigao M (2012). First report of phlebotomine sand flies (Diptera: Psychodidae) in Kansas and Missouri, and a PCR method to distinguish Lutzomyia shannoni from Lutzomyia vexator. Journal of Medical Entomology 49, 1460–1465. [PubMed: 23270176]

Zou L, Chen J, and Ruan S (2017). Modeling and analyzing the transmission dynamics of visceral leishmaniasis. Mathematical Biosciences and Engineering 14, 1585–1604. [PubMed: 29161877]

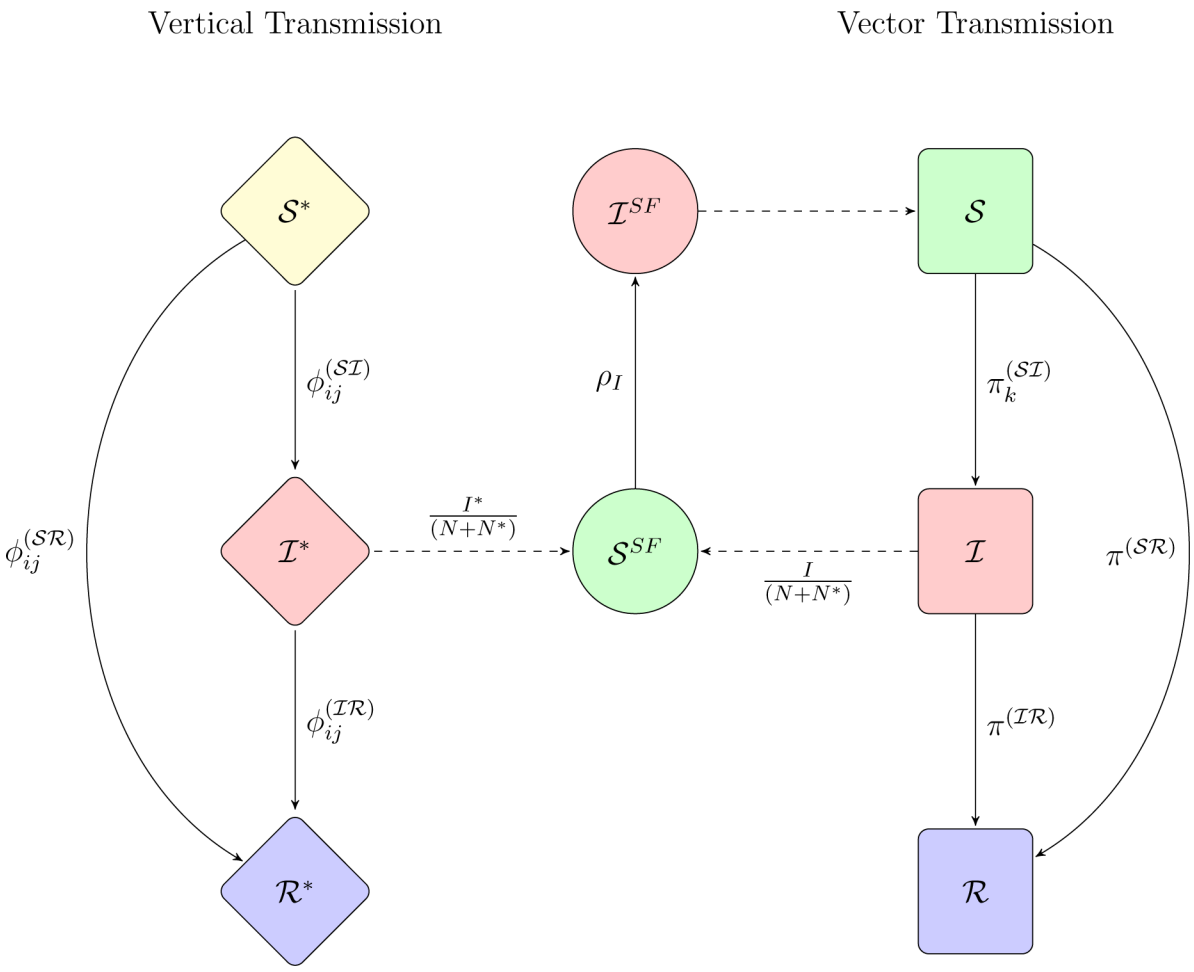

Figure 1.

Schematic for the two proposed SIR models. The vertically-derived infection progression process is at the individual level and is represented by diamonds ($\mathcal{S}^*$=susceptible, $\mathcal{I}^*$=infected, $\mathcal{R}^*$=removed). In the presence of an emergent vector (circles, $\mathcal{S}^{SF}$=susceptible, $\mathcal{I}^{SF}$=infected), the vector initially will become infected by biting a vertically-infected individual ($i \in \mathcal{I}^*$) and can then pass on infection to naive dogs (in $\mathcal{S}$), represented by squares. Once $|\mathcal{I}| > 0$, uninfected vectors can derive infection from either vertically-infected or vector-infected individuals (dashed lines) and to different infection states ($\mathcal{I}$ = infected, $\mathcal{R}$ = removed) according to a population-level model (solid lines). This figure appears in color in the electronic version of this article, and any mention of color refers to that version.

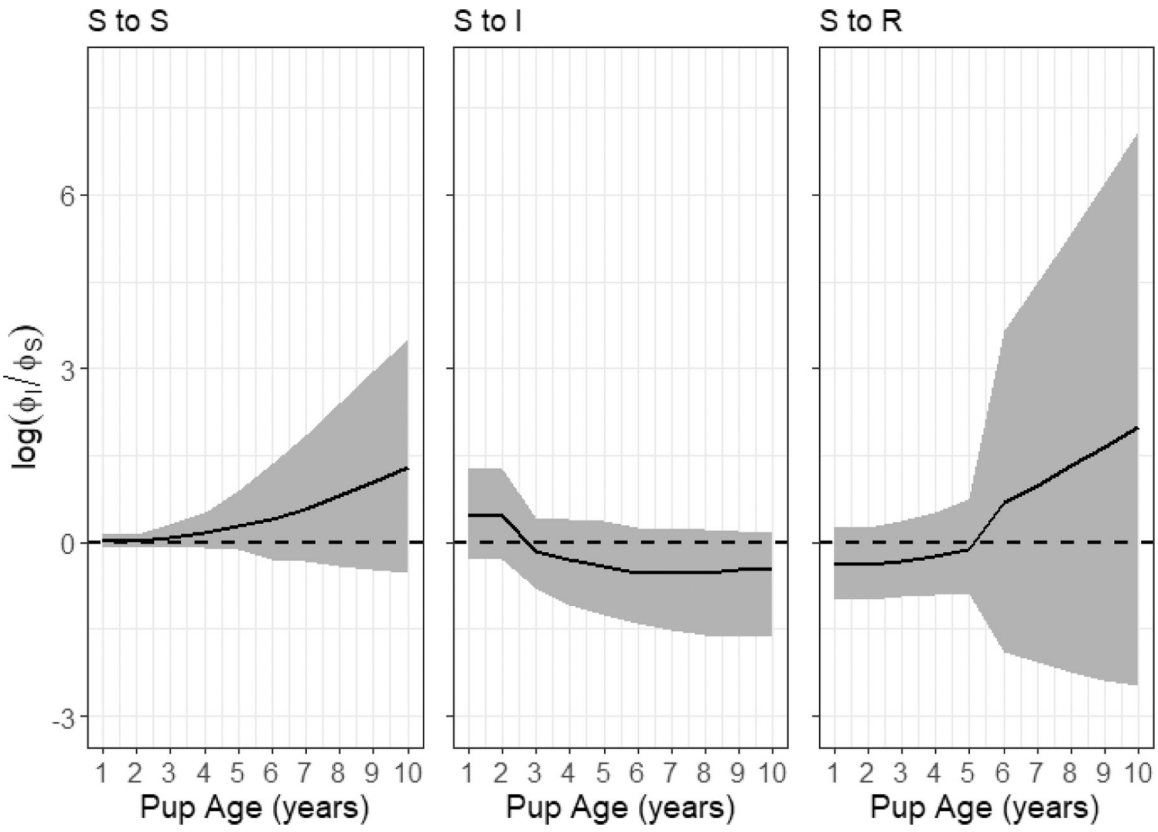

Figure 2.

The median log relative risk (and 95% credible intervals) of staying in $\mathcal{S}$ (left), transitioning from $\mathcal{S} \rightarrow \mathcal{I}$ (center), and from $\mathcal{S} \rightarrow \mathcal{R}$ (right) for dogs born to mothers in $\mathcal{I}$ versus dogs born to mothers in $\mathcal{S}$. Before age 3, pups born to $\mathcal{I}$ mothers are more likely to transition from $\mathcal{S} \rightarrow \mathcal{I}$.

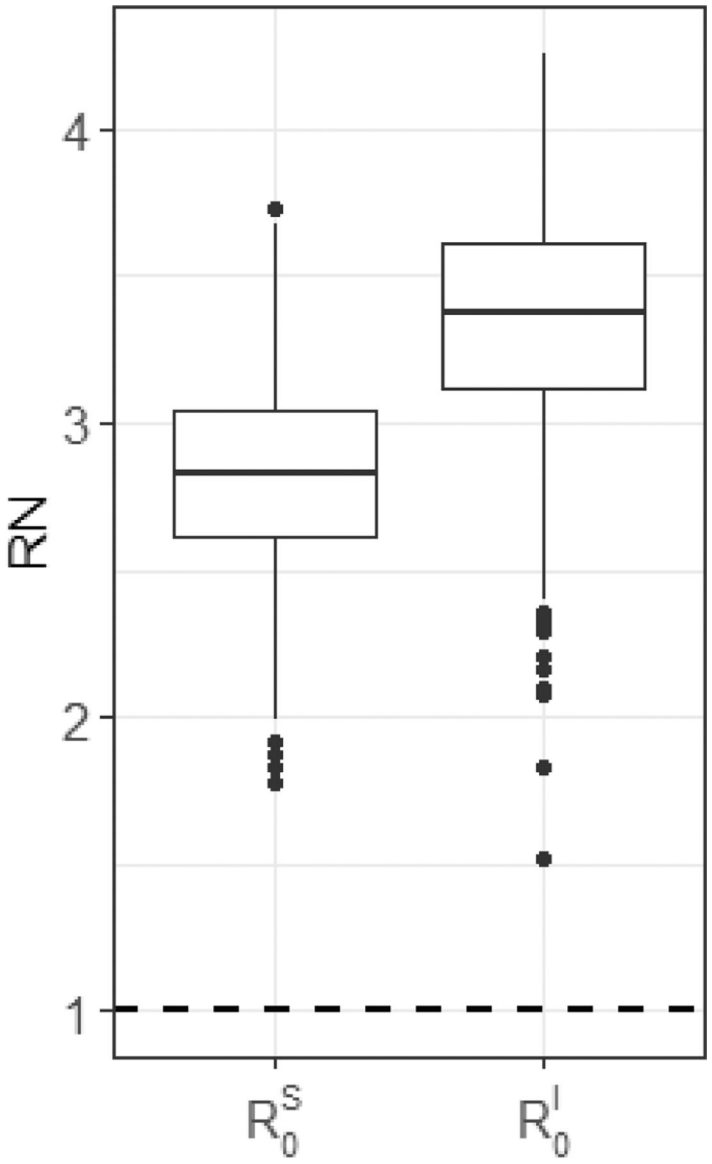

Figure 3.

Box plots for reproductive numbers for vertical transmission. The estimates exceed 1 for both groups, so either degree of maternal infection in pregnancy can increase the number of infected dogs from generation to generation. The 95% credible interval for $\mathscr{R}_0^{\mathcal{I}}/\mathscr{R}_0^{\mathcal{S}}$ is (0.870, 1.603). $\mathscr{R}_0^{\mathcal{I}} > \mathscr{R}_0^{\mathcal{S}}$ for 86.3% of the posterior predictive data sets.

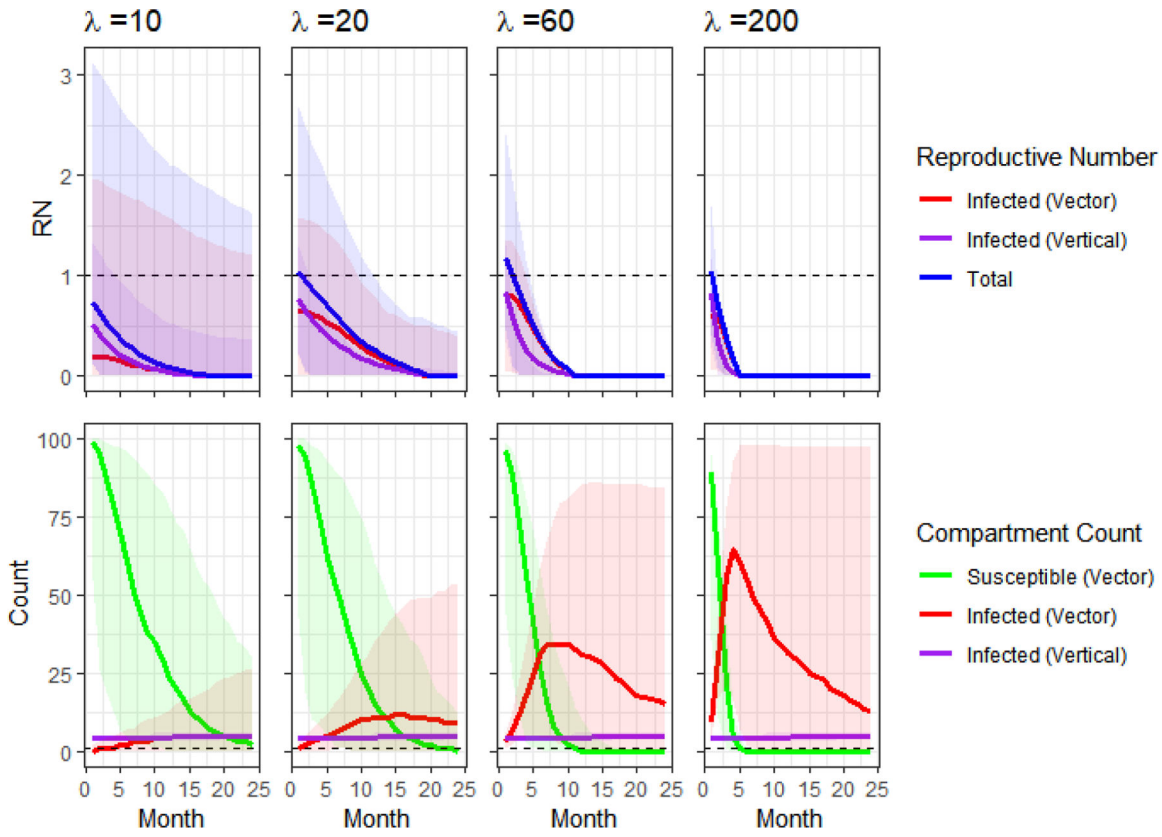

Figure 4.

ISEARN and 90% credible intervals for $N = 100$, $p = 0.01$, and $\lambda = 10$ (left), $\lambda = 20$ (left center), $\lambda = 60$ (right center), $\lambda = 200$ (right), and corresponding compartment counts. This figure appears in color in the electronic version of this article, and color refers to that version.

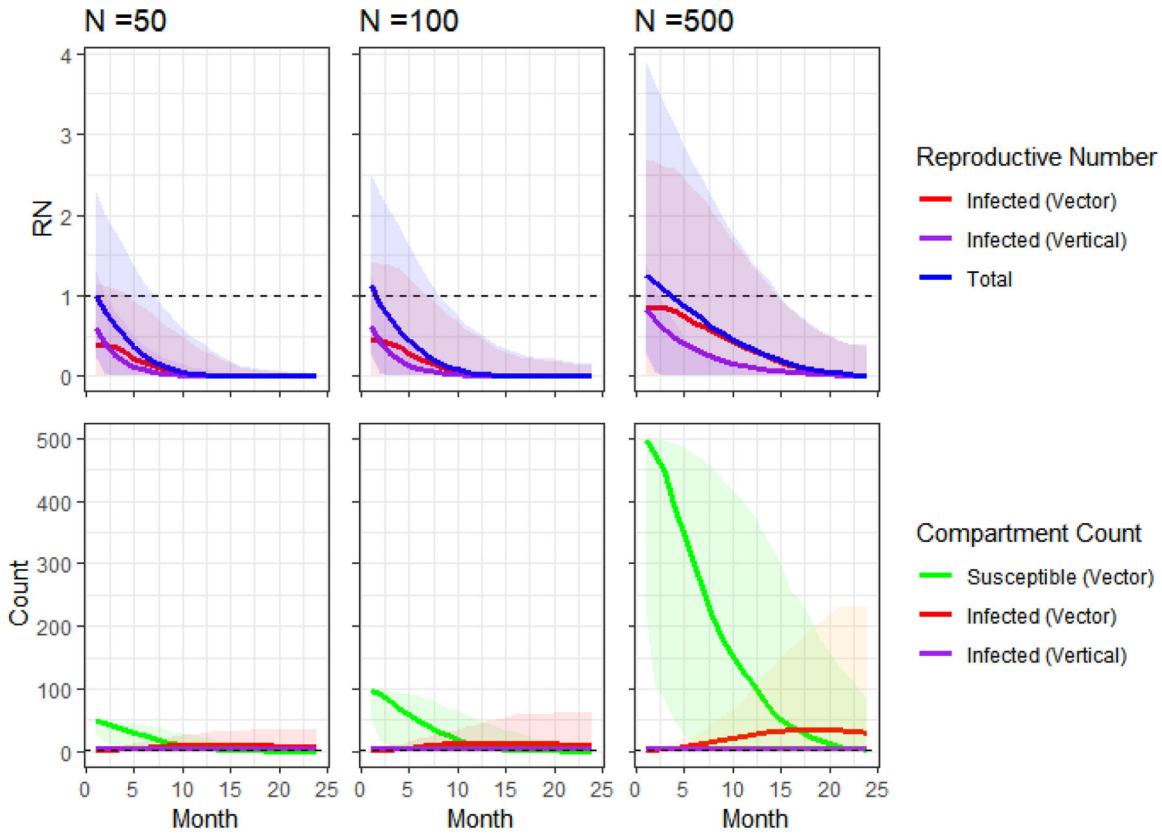

Figure 5.

ISEARNs and 90% credible intervals for $\lambda = 25$, $p = 0.01$, and $N = 50$ (left), $N = 100$ (center), $N = 500$ (right), and corresponding compartment counts. This figure appears in color in the electronic version of this article, and color refers to that version.

Table 1

Posterior estimates and symmetric 95% credible intervals for the individual-level vertical transmission model parameters.

	Variable	Median	95% Credible Interval
β_0	Intercept	−2.020	(−2.473, −1.609)
β_1	Mother in $\mathcal{S}$	−0.438	(−1.311, 0.365)
β_2	(Pup Age)$\left(\mathbb{1}\{Age > 2\}\right)$	0.244	(0.052, 0.426)
β_3	(Mother in $\mathcal{S}$*Pup Age)$\left(\mathbb{1}\{Age > 2\}\right)$	0.230	(−0.067, 0.546)
θ_0	Intercept	−2.219	(−2.714, −1.780)
θ_1	Mother in $\mathcal{S}$	0.406	(−0.342, 1.122)
θ_2	(Pup Age)$\left(\mathbb{1}\{Age > 5\}\right)$	0.032	(−0.322, 0.290)
θ_3	(Mother in $\mathcal{S}$*Pup Age)$\left(\mathbb{1}\{Age > 5\}\right)$	−0.110	(−0.636, 0.374)
ξ_0	Intercept	−1.396	(−2.929, 0.079)
ξ_1	Pup Age	−0.449	(−1.031, −0.007)