Journal of Applied Statistics

ISSN: 0266-4763 (Print) 1360-0532 (Online) Journal homepage: http://www.tandfonline.com/loi/cjas20

Bayesian compartmental model for an infectious disease with dynamic states of infection

Marie V. Ozanne, Grant D. Brown, Jacob J. Oleson, Iraci D. Lima, Jose W. Queiroz, Selma M. B. Jeronimo, Christine A. Petersen & Mary E. Wilson

To cite this article: Marie V. Ozanne, Grant D. Brown, Jacob J. Oleson, Iraci D. Lima, Jose W. Queiroz, Selma M. B. Jeronimo, Christine A. Petersen & Mary E. Wilson (2018): Bayesian compartmental model for an infectious disease with dynamic states of infection, Journal of Applied Statistics, DOI: 10.1080/02664763.2018.1531979

To link to this article: https://doi.org/10.1080/02664763.2018.1531979

JOURNAL OF APPLIED STATISTICS
https://doi.org/10.1080/02664763.2018.1531979

Taylor & Francis
Taylor & Francis Group

Bayesian compartmental model for an infectious disease with dynamic states of infection

Marie V. Ozanne [a], Grant D. Brown[a], Jacob J. Oleson[a], Iraci D. Lima[b], Jose W. Queiroz[b], Selma M. B. Jeronimo[c,d,e], Christine A. Petersen[f,g] and Mary E. Wilson[f,h,i,j]

[a]Department of Biostatistics, University of Iowa College of Public Health, Iowa City, USA; [b]Department of Infectious Diseases, Universidade Federal do Rio Grande do Norte, Natal, Brazil; [c]Institute of Tropical Medicine, Universidade Federal do Rio Grande do Norte, Natal, Brazil; [d]Department of Biochemistry, Universidade Federal do Rio Grande do Norte, Natal, Brazil; [e]National Institute of Science and Technology in Tropical Diseases, Salvador, Bahia, Brazil; [f]Department of Epidemiology, University of Iowa College of Public Health, Iowa City, USA; [g]Center for Emerging Infectious Diseases, University of Iowa College of Public Health, Iowa City, USA; [h]Department of Internal Medicine, University of Iowa Roy J and Lucille A Carver College of Medicine, Iowa City, USA; [i]Department of Microbiology, University of Iowa Roy J and Lucille A Carver College of Medicine, Iowa City, USA; [j]Iowa City VA Medical Center, Iowa City, IA, USA

ABSTRACT

Population-level proportions of individuals that fall at different points in the spectrum [of disease severity], from asymptomatic infection to severe disease, are often difficult to observe, but estimating these quantities can provide information about the nature and severity of the disease in a particular population. Logistic and multinomial regression techniques are often applied to infectious disease modeling of large populations and are suited to identifying variables associated with a particular disease or disease state. However, they are less appropriate for estimating infection state prevalence over time because they do not naturally accommodate known disease dynamics like duration of time an individual is infectious, heterogeneity in the risk of acquiring infection, and patterns of seasonality. We propose a Bayesian compartmental model to estimate latent infection state prevalence over time that easily incorporates known disease dynamics. We demonstrate how and why a stochastic compartmental model is a better approach for determining infection state proportions than multinomial regression is by using a novel method for estimating Bayes factors for models with high-dimensional parameter spaces. We provide an example using visceral leishmaniasis in Brazil and present an empirically-adjusted reproductive number for the infection.

ARTICLE HISTORY
Received 16 April 2018
Accepted 30 September 2018

KEYWORDS
Multinomial; seasonality; SIR; visceral leishmaniasis; Bayes factor; empirically-adjusted reproductive number

1. Introduction

Statistical modeling is an important tool for understanding the dynamics of the spread of infectious disease. A critical question that can be addressed through statistical modeling relates to the proportions of individuals in the population that develop different clinical

CONTACT M. V. Ozanne marie-ozanne@uiowa.edu

Supplemental data for this article can be accessed here. https://doi.org/10.1080/02664763.2018.1531979

outcomes after infection. In a population exposed to a pathogenic microorganism, there are usually many more individuals harboring the infectious agent than there are persons with recognizable symptoms defining them as having an infectious disease. These population-level infection state proportions are often difficult to observe, but are likely very important determinants of maintaining the disease in an endemic area. Estimation of the proportions of individuals with distinct manifestations of infection can provide insights into the likelihood of expansion versus control of the disease in a particular population.

One commonly applied family of statistical techniques for modeling infection outcomes in large populations is binomial and multinomial logistic regression. Binomial logistic regression has been used to model infectious diseases in a variety of contexts. For example, it has been used to differentiate infectious diseases based on clinical and laboratory characteristics to facilitate diagnosis; Chadwick *et al.* apply it to distinguish dengue fever from other infections in Singapore [10] and Bonsu and Harper use it to differentiate between bacterial and viral meningitis [6]. This method has also been used to identify the relative importance of prognostic factors in particular disease outcomes, such as death [43].

Multinomial logistic regression, an extension of binomial logistic regression, has been used in dengue hemorrhagic fever (DHF) research to determine if DHF and signs of clinical disease are associated with each of five serotypes [14]. It also has been used to assess the association between demographic variables and *Leishmania infantum* infection status in neighborhoods near to Natal, Brazil [24].

In addition to examining covariates that may be associated with a particular infection outcome, logistic regression techniques allow us to estimate the proportion of individuals that fall into each clinical state of an infection over time. While these approaches are simple and powerful, they have a number of practical limitations. For instance, regression-type models can incorporate some temporal variability, but they do not naturally accommodate known infectious disease dynamics, such as infectious period duration, heterogeneity in infectivity, and well understood patterns of seasonality [13,29]. One can include temporal covariates, however, large quantities of data may be required to accurately estimate these effects. Considering these limitations, and given the popularity of these methods for modeling infection outcomes, we want to determine whether logistic regression provides an adequate framework for estimating infection state proportions throughout the year.

In this paper, we demonstrate how and why a stochastic compartmental model is a better approach for determining infection state proportions than multinomial regression is. To assess the suitability of multinomial logistic regression for estimating infection state proportions over time, we compare results to those obtained from a Bayesian model where the latent infection states are estimated using a stochastic compartmental model. The stochastic compartmental model allows for greater flexibility in approximating infection prevalence over time because it permits the inclusion of known infectious disease dynamics, and it improves the scientific interpretability of model results. We explore both approaches to prevalence estimation via simulation and in the context of visceral leishmaniasis (VL) in Brazil. Another advantage of this compartmental modeling approach is that it allows the straightforward calculation of a reproductive number, which is not true of the multinomial logistic regression approach. We present an empirically-adjusted reproductive number for VL at each time point, as proposed by Brown *et al.*, along with corresponding credible intervals [8].

It is important to note that while stochastic compartmental models have not been applied to the study of VL, deterministic compartmental models have been used to study the dynamics of VL for the last thirty years [12,37,40]. There are also formulations for many reproductive numbers in this setting [1,17]. The deterministic framework's most notable advantage is that, relative to stochastic compartmental models, analysis is more computationally tractable. Contrary to equivalent deterministic compartmental models, the stochastic compartmental models need to be relatively simple mathematically in order to be manageable [3].

When feasible, however, the stochastic framework has some notable advantages, as described by Andersson and Britton. First, it allows one to define a probability of disease transmission between two individuals; this is a natural way to describe infectious disease spread because transmission does not occur deterministically. Second, the stochastic approach provides both estimates of our parameters and measures of uncertainty for those parameters [3].

Stochastic techniques also have formal methods for model comparison. Two methods that are used for Bayesian model evaluation are Bayes factors and the Deviance Information Criterion (DIC) [21,39]. DIC is one of the most popular methods for comparing competing Bayesian models. It has a form similar to other information criteria: $DIC = D(\bar{\theta}) - 2p_D$, where $D(\bar{\theta})$ is the deviance of the average posterior draws and p_D is a penalty term [39]. While it tends to work well in many settings, it has been criticized for lack of a clear theoretical foundation [33]. In the compartmental modeling framework, there are a number of practical challenges associated with using DIC. First, the number of effective parameters in a compartmental model is large compared to the effective number of independent observations, which can be problematic for DIC [33]. Also, compartmental likelihoods are not members of an exponential family; there has been criticism that DIC does not have a natural extension outside of this framework [9]. In addition, the form of the DIC requires a calculation of $\bar{\theta}$ to obtain a plug-in measure of fit, $\mathrm{D}(\bar{\theta})$. In a compartmental model with a large discrete parameter space, $\bar{\theta}$ is not guaranteed to lie within the parameter space (e.g. non-integer valued for binomial distribution), so we require some continuous approximation of this space to calculate DIC. While this is feasible, it is not obvious what continuous approximations will be most suitable. Bayes factors, on the other hand, rest on sound theoretical footing and allow us to compare the probability that the observed data arose from one model relative to another. Nevertheless, with complex or functionally different models, the Bayes factor can be impossible to calculate directly, so numerical methods are required to approximate it. To this end, we will present a novel method that borrows from the approximate Bayesian computation (ABC) framework to compare models that are fit using traditional Markov chain Monte Carlo.

1.1. Visceral Leishmaniasis

VL is one disease for which estimating population-level infection state proportions is pivotal to understanding the chance of expansion versus control. VL is a vector-borne infectious disease caused either by the parasite *Leishmania infantum*, which is transmitted in the New World by the sand fly *Lutzomyia longipalpis*, or *Leishmania donovani*, an Old World parasite causing similar disease [20]. It is endemic in 98 countries, and Brazil accounts for more than 90% of cases in the Americas [2]. Historically, infection has

occurred in rural regions in Brazil, but this has changed as cities have expanded into previously rural areas and rural populations have moved into cities, bringing their infections with them [30]. This has led to peri-urban outbreaks of VL. In the state of Rio Grande do Norte, such outbreaks in peri-urban neighborhoods around the capital city of Natal were used to model key parameters of transmission [11,15,24,25,27].

The status of *Leishmania* spp. infection within a population depends on many variables, including seasonal trends; for instance, the sand fly vector requires adequate rainfall to breed [13]. This seasonality influences the proportion of individuals that fall into various infection categories at different times during the year. For the visceralizing *Leishmania* species in particular, an individual's infection state can be determined according to a measure of adaptive immunity such as a delayed-type hypersensitivity (DTH) skin test or quantiferon, and by serologic status. The DTH used for *L. infantum* testing in Brazil, known as the Montenegro, or leishmanin skin test (LST) is a measure of a Type 1 adaptive immune response against the parasite that develops after cure of active or asymptomatic infection [19]. Serology often rises to high titer during acute infection or active disease, and diminishes later. Serology status was examined with an enzyme-linked immunosorbant assay (ELISA) against soluble leishmania antigen (SLA) to determine the titers of antileishmanial antibodies, compared to negative control sera from individuals who were not exposed to the parasite. In cases where there was serologic evidence of exposure to the parasite, historical symptoms suggestive of VL and documented medical diagnosis of disease were used to discern whether there was a history of symptomatic VL [7,24]. Individuals who had negative tests for LST (LST^-) and serology (SLA^-), and who had no current symptoms of or history suggesting VL (VL^-), were classified as susceptible to disease. Individuals with a positive skin test but no history of disease (LST^+, VL^-) were considered to have asymptomatic infection. Those individuals who were LST^- and VL^-, but were SLA^+ were classified as acute seropositive; these individuals could resolve into an asymptomatic infection (LST^+, VL^-) or symptomatic disease (LST^-, VL^+). With appropriate treatment, 90-95% of infected symptomatic individuals can recover from disease symptoms and develop a positive skin test (LST^+) indicating adequate Type 1 protective immunity has occurred. Development of a positive skin test usually occurs 6 months or more after successful treatment of disease [19].

2. Methods

2.1. Data

This analysis is based on historical data; the original study was published by Lima *et al.* in 2012. During the months of January-February and June-July 2006, a study was conducted in Parnamirim, a city of 180,000 located next to Natal, to determine the covariates that were significantly associated with disease state. Households were chosen according to a random point process; 345 individuals were included in the study. Skin and serology tests were administered once to each study participant, and these test results were used to group people into infection status categories. These tests included an ELISA SLA serology test ($SLA^{+/-}$) and the leishmanial skin test ($LST^{+/-}$), which was administered intradermally and results were read 48–72 hours later. Of the 345 people, 314 had complete test result data. Missing data were usually due to inability to find the individual and read

the LST results within 48–72 hours after test placement, or less often, due to insufficient amounts of serum to run serologic tests; this missingness was assumed to be completely at random. No study participants were positive for acute or past VL, so this analysis focused on asymptomatic infection. In addition to the LST and serology test results, demographic information was also collected including age (dichotomized to ≤ 35 years and > 35 years), sex, and household location (urban, peri-urban, or rural) [24].

2.2. Statistical analyses

Individuals with LST^-, SLA^-, and VL^- test results are classified as susceptible ($\mathcal{S}$), as described in the introduction. Those with LST^-, SLA^+, VL^- results are assumed to have recently acquired infection and is classified as infectious ($\mathcal{I}$); this is the acute seropositive class described in the introduction. These individuals show no signs of infection, but are presumed to be able to transmit infection to the sand fly vector. Individuals with LST^+, $\text{SLA}^{+/-}$, VL^- are classified as removed ($\mathcal{R}$); this is the infected asymptomatic class previously described. Most individuals in this class develop a protective immune response that protects them from reinfection or from symptomatic disease; they develop a protective immune response and remain LST^+ for life [38]. Let $\mathcal{T} = \{1, \ldots, 28\}$ be the set of time points (weeks in a year) over which the endemic infection process is studied, and let $\mathcal{T}^* = \{4, 5, 6, 7, 8, 25, 26, 27, 28\}$ be the weeks at which an individual's blood was drawn, which we will assume accurately describes the time at which the individual occupies a particular infection state.

2.2.1. Previous analysis – multinomial regression results

Lima *et al.* collected these data and analyzed the result [24]. Their multinomial logistic regression model had four categories, but individuals who are LST^+ and VL^- can be classified in the removed (infected asymptomatic) category regardless of SLA status, so the previous analyses were rerun with three categories in the outcome variable [19]. Let π_{ijt} be the probability that the ith individual belongs to the jth category at time t, where $i \in \{1, 2, \ldots, 314\}$, $j \in \{\mathcal{S}, \mathcal{I}\}$ and $t \in \mathcal{T}^*$. The link function is

$$\eta_{ijt} = \log\left(\frac{\pi_{ijt}}{\pi_{i\mathcal{R}t}}\right) = \alpha_j + \mathbf{x}_{it}'\boldsymbol{\beta}_j, \tag{1}$$

where $\boldsymbol{\beta}_j$ includes coefficients for age, sex, household location, and week for the jth disease category.

The multinomial logistic regression coefficient estimates in Table 1 were obtained using the *multinom* function from the `nnet` package in `R` [42]. The baseline category was the removed category.

The coefficient estimates and corresponding standard errors obtained are shown in Table 1. In their 2012 paper, Lima *et al.* did not include the month at which the tests were administered as a covariate [24]. We include an expanded multinomial logistic regression model to accommodate the known seasonality of the infection and to facilitate comparison with estimates obtained using a Bayesian approach, which are shown in Table 2.

Table 1. Frequentist multinomial logistic regression coefficient estimates for outcome with three categories. Time at which the serology tests were administered was not included as a covariate in the original analysis, but it is included here for comparison to the Bayesian multinomial regression results that follow. The baseline disease category was removed, and the baseline area category was rural.

	$\mathcal{S}/\mathcal{R}$		$\mathcal{I}/\mathcal{R}$	
	Estimate	SE	Estimate	SE
Intercept	−0.100	0.317	−0.113	0.388
Area: Urban	0.092	0.335	0.295	0.373
Area: Periurban	0.404	0.344	−0.372	0.478
Sex: Male	−0.515	0.276	−0.840	0.370
Age $>$ 35	−0.811	0.266	−0.223	0.333
Week	0.045	0.015	−0.027	0.023

Table 2. Parameter estimates and symmetric 95% credible intervals for multinomial logistic regression and compartmental models fit to data simulated from multinomial distribution with no variability over time. Note that the effect of week is not significantly different from 0 in either model.

	Multinomial Logistic Regression			
	$\mathcal{S}/\mathcal{R}$		$\mathcal{I}/\mathcal{R}$	
	Estimate	95% Credible Interval	Estimate	95% Credible Interval
Intercept	0.447	(0.178, 0.710)	−3.051	(−4.114, −2.148)
Week	0.000	(−0.016, 0.017)	−0.004	(−0.065, 0.055)

	Compartmental Model	
	Estimate	95% Credible Interval
Intercept	−1.599	(−2.105, −1.104)
Week	−1.076	(−3.390, 1.340)
$\pi^{(\mathcal{IR})}$	0.122	(0.096, 0.152)

2.2.2. Bayesian multinomial regression

The Bayesian multinomial logistic regression model has the same form as detailed in the previous subsection, where π_{ij} be the probability that the ith individual belongs to the jth category, where $i \in \{1, 2, \ldots, 314\}$ and $j \in \{\mathcal{S}, \mathcal{I}\}$, and the link function is the same as in Equation (1). Four covariates were included: age, sex, household location, and week (in the year) at which individuals' LST and serologic testing was done. Normal vague priors were put on the $\alpha_{\mathcal{R}}$ and $\boldsymbol{\beta}_j$ parameters; the mean was 0 in each case, and the variance was 100. The model was fit using the *MCMCmnl* function from the `MCMCpack` package in `R` [26].

2.2.3. Stochastic compartmental model

The multinomial logistic regression models described in the previous two subsections are both regression-type models; some temporal variability can be incorporated easily. However, these models do not naturally accommodate known disease dynamics like patterns of seasonality or infectious period duration, for example. A Bayesian approach where the latent infection states are estimated using a compartmental model is an alternative to multinomial logistic regression. Such an approach allows for the inclusion of prior information about seasonal trends and the pattern of progression through different states of *L. infantum* infection.

2.2.3.1. Data model. Let $\mathbf{Y}_t = (S_t^*, I_t^*, R_t^*)^{\mathrm{T}}$ be a vector of the counts of individuals in the population that are in $\mathcal{S}$, $\mathcal{I}$, and $\mathcal{R}$ at time t, where $N = 180{,}000$, the population of Parnamirim.

For $t \in \mathcal{T}^* \subset \mathcal{T}$,

$$\mathbf{Y}_t \sim \text{Multinomial}\left(m_t, \boldsymbol{\pi}_t = \left(\frac{S_t}{N}, \frac{I_t}{N}, \frac{R_t}{N}\right)\right), \tag{2}$$

where m_t is the number of individuals observed at time t, and S_t, I_t, and R_t are the estimated counts of individuals in $\mathcal{S}$, $\mathcal{I}$, and $\mathcal{R}$, at time t, respectively. These values are unobserved – they are estimated as part of the process model.

Individual-level characteristics play a role in whether an individual becomes infected. Age, sex, and household location can all impact the chance that an individual becomes infected [24]. The composition of the population in an area of interest can influence the proportion of the population that are in $\mathcal{I}$ at a particular time. The distribution in Equation (2) must be amended to reflect the effect of the individual-level covariates.

We assume that the process model, described in the following section, reflects the epidemic for some homogeneous, baseline population. Let $\mathbf{Z}_t$ be the design matrix for individual-level effects at time t and let $\boldsymbol{\gamma}$ be the vector of corresponding coefficients. Then, consider the data model in Equation (3),

$$\mathbf{Y}_t \sim \text{Multinomial}\left(m_t, \boldsymbol{\pi}_t = \left(\frac{S_t}{N}, \frac{I_t^{\text{aug}}}{N}, \frac{R_t}{N}\right)\right), \tag{3}$$

where

$$I_t^{\text{aug}} = I_t + \frac{1}{m_t}\mathbf{Z}_t'\boldsymbol{\gamma}.$$

Assume that $\boldsymbol{\gamma} \sim MVN(\boldsymbol{\mu}_\gamma, \boldsymbol{\Sigma}_\gamma)$, so $\mathbf{Z}_t'\boldsymbol{\gamma}/m_t$, the average contribution of the individual covariates at time t, can either increase or decrease I_t, depending on the composition of the sample. Notice that S_t is not assumed to depend on individual covariates, but both I_t^{aug} and $R_t = N - (S_t + I_t^{\text{aug}})$ are assumed to depend on them. We want to allow some flexibility in the I_t^{aug} and R_t counts due to average individual level contributions, because possible differences in positive LST results and VL disease due to gender, age, and area of residence have been observed [28,44]. While one might contend that S_t should also depend on some average contribution of individual covariates, we need to be careful not to overparameterize the model, and I_t^{aug} and R_t should account for most of the possible heterogeneity effects.

2.2.3.2. Process model. The compartment sizes at each time $t \in \mathcal{T}$ are deterministic functions of the compartment sizes at the previous time point and the transition compartments at the current time point. They have the following form:

$$\begin{aligned} S_t &= S_{t-1} - I_t^{(\mathcal{SI})}, \\ I_t &= I_{t-1} + I_t^{(\mathcal{SI})} - R_t^{(\mathcal{IR})}, \\ R_t &= R_{t-1} + R_t^{(\mathcal{IR})}. \end{aligned}$$

There are two transition compartments, $I_t^{(\mathcal{SI})}$ and $R_t^{(\mathcal{IR})}$. The former denotes the number of individuals that are transitioning from $\mathcal{S}$ to $\mathcal{I}$ at time t. The latter denotes the number of

individuals that are transitioning from $\mathcal{I}$ to $\mathcal{R}$ at time t. These compartments are modeled using a chain binomial structure, as shown in Equations (4) and (5).

$$I_t^{(\mathcal{SI})} \sim \text{Binomial}\left(S_{t-1}, \pi_t^{(\mathcal{SI})}\right) \tag{4}$$

$$R_t^{(\mathcal{IR})} \sim \text{Binomial}\left(I_{t-1}, \pi^{(\mathcal{IR})}\right) \tag{5}$$

Note that for all dynamic endemic sites, we have some initial compartment sizes, S_0, I_0, and R_0. At each iteration, these initial values are allowed to vary. Survey data indicates that the expected proportion of susceptibles is 51%, the expected proportion of infected is 1.9%, and the expected proportion of removed is 35%, as defined above, in the region of interest. Another 12% are estimated to fall into categories defined by positive VL test results, which are not present in this data set [19]. Therefore, to obtain $\pi^{(S_0)}$, $\pi^{(I_0)}$, and $\pi^{(R_0)}$, the three probabilities are normalized to sum to 1. The initial compartments have the following distributions:

$$S_0 \sim \text{Binomial}\left(N, \pi^{(S_0)}\right), \tag{6}$$

$$I_0 \sim \text{Binomial}\left(N, \pi^{(I_0)}\right), \tag{7}$$

$$R_0 = N - (S_0 + I_0). \tag{8}$$

2.2.3.3. Parameter model. We expect $\pi_t^{(\mathcal{SI})}$, the probability of transitioning from $\mathcal{S}$ to $\mathcal{I}$, to be influenced by seasonality, interventions, and other environmental factors. The probability is assumed to have the form

$$\pi_t^{(\mathcal{SI})} = 1 - \exp\left\{-\frac{I_{t-1}}{N} e^{X_t'\boldsymbol{\beta}}\right\}, \tag{9}$$

where X_t contains the information about seasonality or any relevant interventions at time t [8,22].

The prior on $\pi^{(\mathcal{IR})}$, the probability of transitioning from $\mathcal{I}$ to $\mathcal{R}$ is assumed to be

$$\pi^{(\mathcal{IR})} \sim \text{Beta}\left(\alpha^{(\mathcal{IR})}, \beta^{(\mathcal{IR})}\right). \tag{10}$$

There is some information available on exposure time for VL that can be used to determine an informative prior for $\pi^{(\mathcal{IR})}$. Levy *et al.* claim that individuals with VL progress to symptomatic disease within 10 days to 18 months after exposure [23]. Because it is difficult to know the time of exposure in populations living in endemic regions, this estimate is not substantiated by objective observational studies, but rather is derived from other descriptions of disease characteristics. Accidental laboratory infections with species causing human cutaneous leishmaniasis give information on the period between a single known exposure and disease manifestations. Even though this exposure route is not natural and the species of *Leishmania* differs from *L. infantum*, this may be the best source to discern known exposure and infection status. These individuals have a median exposure time of 8–12 weeks [18]. We assume that an immune response decision, i.e. whether

an exposed individual will progress to asymptomatic or symptomatic infection, is made 2–4 weeks prior to immune response detection. Therefore, we expect that an individual may transition from $\mathcal{I}$ to $\mathcal{R}$ within 4–6 weeks after infection. We consider two geometric distributions, one with a median of 4 and one with a median of 6, which correspond to a Geometric(0.15) and a Geometric(0.10) distribution, respectively. Then, we determine $\alpha^{(\mathcal{IR})}, \beta^{(\mathcal{IR})}$ by letting $P(X < 0.05) = 0.10$ and $P(X > 0.95) = 0.15$ and solving these two equations for $\alpha^{(\mathcal{IR})}$ and $\beta^{(\mathcal{IR})}$. The prior distribution can be made more diffuse by looking at a larger interval to establish $\alpha^{(\mathcal{IR})}$ and $\beta^{(\mathcal{IR})}$. In order to get meaningful results for the compartmental model, however, it is important to establish biologically plausible priors, so the prior still needs to be centered in the same place.

2.2.4. Reproductive number

The basic reproductive number, $\mathcal{R}_0$, quantifies the expected number of secondary infections that result from a single infectious individual under the assumption of a totally susceptible population. As in many applications, the assumption of a totally susceptible population is not appropriate for our application. Many authors have provided adaptations to this basic reproduction number; in this paper, we employ the empirically adjusted reproductive number approach proposed by Brown *et al.* [8].

Brown *et al.* propose a general empirically adjusted reproductive number for spatio-temporal data. In our application, we have several simplifications. Let $I_k(t)$ be the event that individual k becomes infected at time t. Then, the expected number of infections is given in Equation (11),

$$\mathbb{E}\left[\sum_{k=0}^{N} I_k(t)\right] = S_t \cdot P\left(I_k(t) \mid k \in \mathcal{S}\right), \tag{11}$$

and the average number of infections per infectious individual is obtained by dividing the expectation from Equation 11 by the number of infectious individuals at time t: $(S_t/I_t) \cdot P(I_k(t) \mid k \in \mathcal{S})$. At each time, this average is a single time, single location analog of the 'next generation matrix', which is given in Equation (12):

$$G(t) = \frac{S_t \cdot P\left(I_k(t) \mid k \in \mathcal{S}\right)}{I_t} = \left(\frac{S_t}{I_t}\right) \pi_t^{(\mathcal{SI})}. \tag{12}$$

Then, Equation (13) gives the empirically adjusted reproductive number at time t:

$$\mathcal{R}^{(EA)}(t) = \sum_{w=t}^{t_\infty} G(w) \cdot \left(1 - \pi^{(\mathcal{IR})}\right)^w. \tag{13}$$

At each time t, we need to compute an infinite sum. As Brown *et al.* note, the pathogen lifespan weighting term, $(1 - \pi^{(\mathcal{IR})})^t$, quickly and monotonically approaches 0, so we compute the summation over a finite number of weeks, after which subsequent terms make a negligible contribution to the sum [8].

2.2.5. Computation

Markov chain Monte Carlo (MCMC) was used to fit the model, where updates were performed using Metropolis-within-Gibbs. The full conditional functions required are detailed in the Appendix. An outline of the algorithm also is included in the Appendix.

2.3. Model comparisons

Bayes factors are a well-known method for Bayesian model comparison that rest on sound theoretical footing. To use Bayes factors for model comparison, we require the use of proper priors for parameters that differ between two models of interest. Providing this requirement is satisfied, as it is in this application, the remaining challenge to using Bayes factors for model comparison is calculation-based. The Bayes factor, B_{12}, is defined as [21]

$$BF_{12} = \frac{P(\mathbf{Y} \mid \mathcal{M}_1)}{P(\mathbf{Y} \mid \mathcal{M}_2)} = \frac{P(\mathcal{M}_1 \mid \mathbf{Y})}{P(\mathcal{M}_2 \mid \mathbf{Y})} \cdot \frac{P(\mathcal{M}_2)}{P(\mathcal{M}_1)},$$

where $P(\mathbf{Y} \mid \mathcal{M}_i)$ is the probability of the observed data given Model i, $i \in \{1, 2\}$. These densities are obtained by integrating the joint posterior density, $P(\mathbf{Y}, \boldsymbol{\theta}_i \mid \mathcal{M}_i)$ over the parameter space, Θ_i. In all but the simplest cases where conjugate distributions are employed, this integration is intractable [21], so one must turn to numerical methods to estimate these quantities. Considerable work has already been done to address this challenge. For example, Kass and Raftery compare a variety of approximation methods [21]. Laplace's method works well in situations where the likelihoods in question do not deviate strongly from normality. The Schwarz criterion relies on determining $\hat{\boldsymbol{\theta}}_i$, the maximum likelihood estimate (MLE) under Model i. The authors also discuss using Monte Carlo integration to estimate these densities; this includes simple Monte Carlo, importance sampling, and adaptive Gaussian quadrature (the latter two methods improve efficiency). The most efficient procedure, adaptive Gaussian quadrature, is effective when the parameter space of the model in question is modest (roughly < 9) [21].

We are interested in comparing a discrete compartmental model to a multinomial regression model. There is no reason that the likelihood associated with the compartmental model should be close to normal. While there may be cases where normal approximations are adequate, part of the appeal of a compartmental model lies in its flexibility, so Laplace's method is not generally applicable. The high-dimensionality of the parameter space for a compartmental model presents problems both for the Schwarz criterion, because calculating the MLE is problematic, and for Monte Carlo integration techniques, because the parameter space is too large. The dimensionality problem becomes even more extreme for spatio-temporal compartmental models.

Approximate Bayesian computation (ABC) methods have been developed to fit large models that have likelihoods that are difficult to specify [41]. While we are able to specify likelihoods for fitting our models of interest in this paper, the framework for estimating Bayes factors for models fit using ABC gives us insight into constructing a method for estimating Bayes factors for models fit using MCMC where at least one candidate models has a non-normal likelihood and a high-dimensional parameter space. In the simplest ABC method for calculating Bayes factors, we simulate data sets from the prior $\pi(\theta_i)$ for each Model i [5]. However, simulating from the prior is likely to be highly inefficient. Simulating data from the posterior MCMC estimates is likely to be more efficient but also biased. We borrow from the logic behind sequential Monte Carlo ABC (SMC-ABC) and use importance sampling to overcome this bias [4]. The procedure is as follows, where we assume that the model priors, $P(\mathcal{M}_1)$ and $P(\mathcal{M}_2)$ are equal:

For $j = 1, \ldots, K$,

(1) Sample $\boldsymbol{\theta}^{(j)}$ from the set of MCMC samples and generate posterior predictive data sets $\mathbf{Y}^{(j)}$.
(2) For MCMC samples $\boldsymbol{\theta}^{(j)}$, find an approximating density, $G(\boldsymbol{\theta}^{(j)})$ (with appropriate support).
(3) Compute importance weights $w_j \propto \pi(\boldsymbol{\theta}^{(j)})/G(\boldsymbol{\theta}^{(j)})$ and normalize them.
(4) Calculate the sum $\sum_{j=1}^{K} \mathbf{1}_{\{\rho(\mathbf{Y}^{(j)}-\mathbf{Y})<\epsilon\}} w_j$, where $\rho(\mathbf{Y}^{(j)} - \mathbf{Y})$ is a measure of the distance between $\mathbf{Y}^{(j)}$ and $\mathbf{Y}$, the observed data.

There is no mutually agreed-upon, best distance metric to use in this scenario. Therefore, we consider several different metrics to assess the sensitivity of results to this choice. We present results using the distance function, $\rho(\cdot)$, to be the Euclidean distance function $\sum_{c\in\{\mathcal{S},\mathcal{I},\mathcal{R}\}} \sum_{t=1}^{\mathrm{T}} (y_{ct}^{(j)} - y_{ct})^2$, which is a natural choice. We also estimate Bayes factors using Manhattan and Chebyshev distance metrics; we find that these results are consistent with those obtained using Euclidean distance, so the details are omitted from the manuscript.

We now have to discuss how to choose the tolerance, ϵ. As detailed by Toni *et al.*, to fit a model using SMC-ABC, particles $\{\boldsymbol{\theta}^{(1)}, \ldots, \boldsymbol{\theta}^{(N^*)}\}$ are sampled from the prior distribution and then propogated through a series of intermediate distributions $\pi(\theta \mid \rho(y, y^*) \leq \epsilon_k)$ for $k = 1, \ldots, K^* - 1$. The algorithm ceases when the particle sample represents a sample from the target distribution $\pi(\theta \mid \rho(y, y^*) \leq \epsilon_{K^*})$ [41]. When implementing SMC-ABC to estimate Bayes factors, traditionally this same set of tolerances, $\{\epsilon_1, \ldots, \epsilon_{K^*}\}$ is used set the tolerances in Step 4 of the previously outlined algorithm.

Since the model fitting process is inherently different for models fit using MCMC, we need to use a different quantity to inform our choice of tolerance. When we use the Metropolis-Hastings algorithm for Markov chain simulation, we accept proposals for each parameter with probabilities that can be tuned such that we will adequately explore the parameter space; this is the well-known acceptance ratio (AR). We propose using these acceptance ratios to inform our choice of ϵ when the candidate models of interest have been fit using MCMC rather than ABC. Let $\{AR_{i1}, \ldots, AR_{im}\}$ be the set of acceptance ratios from Model i ($i = 1,2$), and let $\widehat{AR}_i$ be the median acceptance ratio for Model i. Choosing the median allows us to minimize the effects on tolerance choice from models fit using Metropolis-within-Gibbs (the acceptance ratio for a Gibbs sampler is 1). We wish to choose the strictest tolerance possible, so we use the following algorithm to determine ϵ.

(1) Choose ϵ_i such that $\sum_{j=1}^{K} \mathbf{1}_{\{\rho(\mathbf{Y}_i^{(j)}-\mathbf{Y})<\epsilon_i\}}/K = \min\{\widehat{AR}_1, \widehat{AR}_2\}$. Note that ϵ_i very likely will be different depending on the model.
(2) From $\{\epsilon_1, \epsilon_2\}$ obtained in Step 1, choose $\epsilon = \min\{\epsilon_1, \epsilon_2\}$.
(3) If for this choice of ϵ, $\sum_{j=1}^{K} \mathbf{1}_{\{\rho(\mathbf{Y}_i^{(j)}-\mathbf{Y})<\epsilon\}}/K < 0.001$ for one of the models, choose a tolerance for that model such that $\sum_{j=1}^{K} \mathbf{1}_{\{\rho(\mathbf{Y}_i^{(j)}-\mathbf{Y})<\epsilon\}}/K$ is as close to 0.001 as possible.

For the multinomial logistic regression model ($\mathcal{M}_1$), 5000 MCMC estimates of $\boldsymbol{\beta}$, the regression coefficients, were resampled with replacement to calculate the probabilities of

being in each of the three compartments, $\hat{\boldsymbol{\pi}}_t^{(j)} = (\hat{\pi}_t^{(\mathcal{S})}, \hat{\pi}_t^{(\mathcal{I})}, \hat{\pi}_t^{(\mathcal{R})})^{(j)}$ for each generation $j \in \{1, 2, \ldots, 5000\}$ at each time point, $t \in \mathcal{T}^*$. For each j, samples were drawn from a Multinomial$(m_t, \boldsymbol{\pi}_t^{(j)})$ distribution at each time point. Similarly, for the compartmental model ($\mathcal{M}_2$), 5000 MCMC estimates of $\boldsymbol{\beta}$, $\boldsymbol{\gamma}$, $\pi^{(\mathcal{IR})}$, S_0, and I_0 were resampled with replacement to generate 5000 epidemic processes, with compartment counts at each time point in $\mathcal{T}$. Then, for each of the 5000 processes generated, a sample was drawn at each time point in $\mathcal{T}^*$ according to a multinomial distribution with probabilities as described in Equation (3), where m_t is assumed to be the same as the total sample size in the observed data at each $t \in \mathcal{T}^*$. Visual comparisons based on the posterior predictive distributions were made, and Bayes factors were computed to compare the models for each of the two data generation scenarios.

3. Simulation studies

3.1. Simulation objective

The compartmental modeling approach proposed here naturally accommodates disease dynamics, while the multinomial logistic regression approach does not naturally accommodate such information. In this section, we will compare the estimation performance of these models for two scenarios, a dynamic epidemic and a non-dynamic epidemic. We will show that the compartmental modeling approach is conducive to either scenario. In contrast, the multinomial logistic regression approach cannot attain the same level of accuracy as the compartmental model in the case of a dynamic epidemic for the same number of observations.

3.2. Simulation setup

Counts for each of the three disease states, $\mathcal{S}$, $\mathcal{I}$, and $\mathcal{R}$ were simulated assuming two models. The first model was a multinomial model where the proportions of individuals in each disease state were assumed to be constant over time. The second model was a multinomial model where the proportions of individuals in each disease state at each time point were determined by the proportions in the population, as described in Equation (2). The design matrix, X, had an intercept and a seasonality component, which was a Gaussian kernel centered at Week 15, with a standard deviation of 3. This design matrix is appropriate for our application, which we want our simulation to mirror, but other design matrices should be considered when infections with different dynamics are being modeled. The two simulated data sets were fit using the multinomial logistic regression model and the compartmental model, as previously described, respectively. The estimated proportions of individuals in each disease state for each of the four data-model combinations were compared to the known proportions.

3.3. Simulation results

Two simulated data sets were generated, as described in the previous section. The simulation was performed for two sample sizes. In the first case, 35 observations were made each week for 28 weeks; in the second, 100 observations were made each week. The former

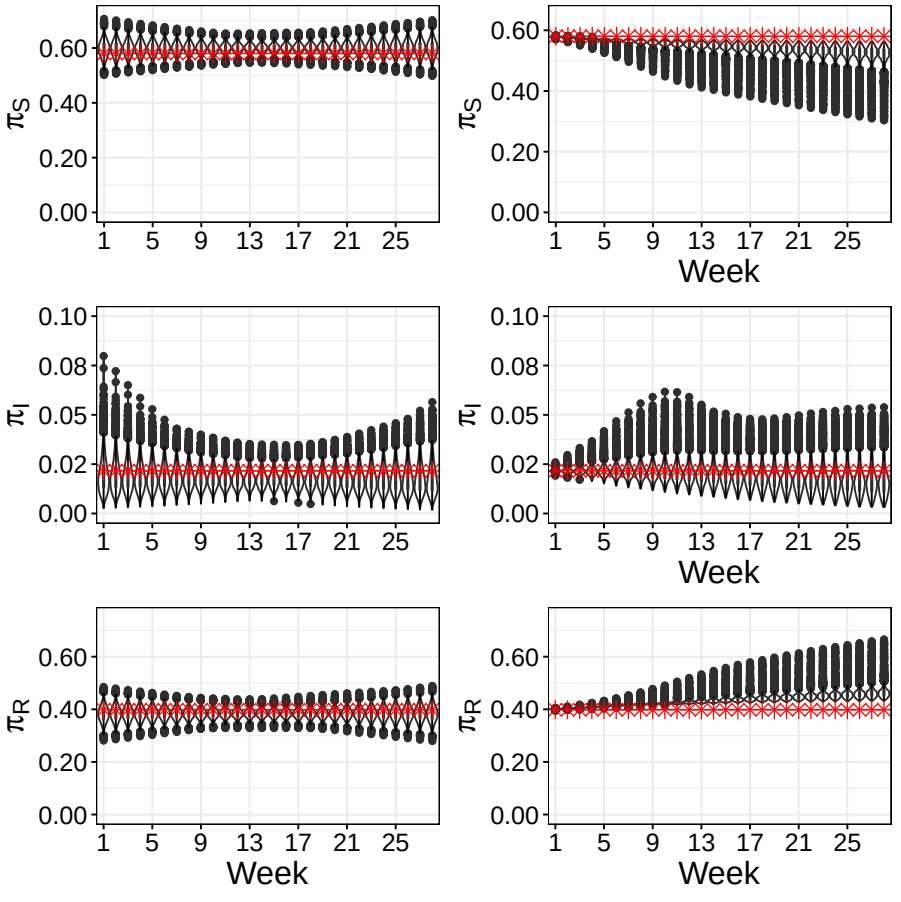

Figure 1. Posterior predictive probabilities resulting from fitting multinomial-generated data with constant proportions across time using multinomial logistic regression (left) and the compartmental model (right). Known proportions are shown as red stars. The multinomial logistic regression model results in tight intervals around the truth, whereas the compartmental modeling approach gets close to the truth, but under-predicts and over-predicts in the $\mathcal{S}$ and $\mathcal{R}$ classes, respectively. Distributions were based on 5000 simulations at each week.

sample size was chosen because it is the average number of observations made each week in the *L. infantum* infection data set we study in this paper. The latter was chosen to examine model performance for a larger sample size. The data sets then were fit assuming multinomial logistic regression and assuming the compartmental model structure, resulting in four model fits. Distributions for posterior predictive probabilities were generated for each of the four model-data combinations and compared to the true proportions for each category at each time. Reported results correspond to the scenario where $n = 35$ at each week. Results are consistent for $n = 100$; this should persist for larger sample sizes.

Figure 1 shows the resulting posterior predictive probability distributions for each of the two models using the multinomial-generated data with constant proportions across time. The multinomial logistic regression model captures the constant proportions well; distributions are concentrated around the truth. The compartmental model comes close to capturing the truth; the bulk of the distribution is generally at or close to the true

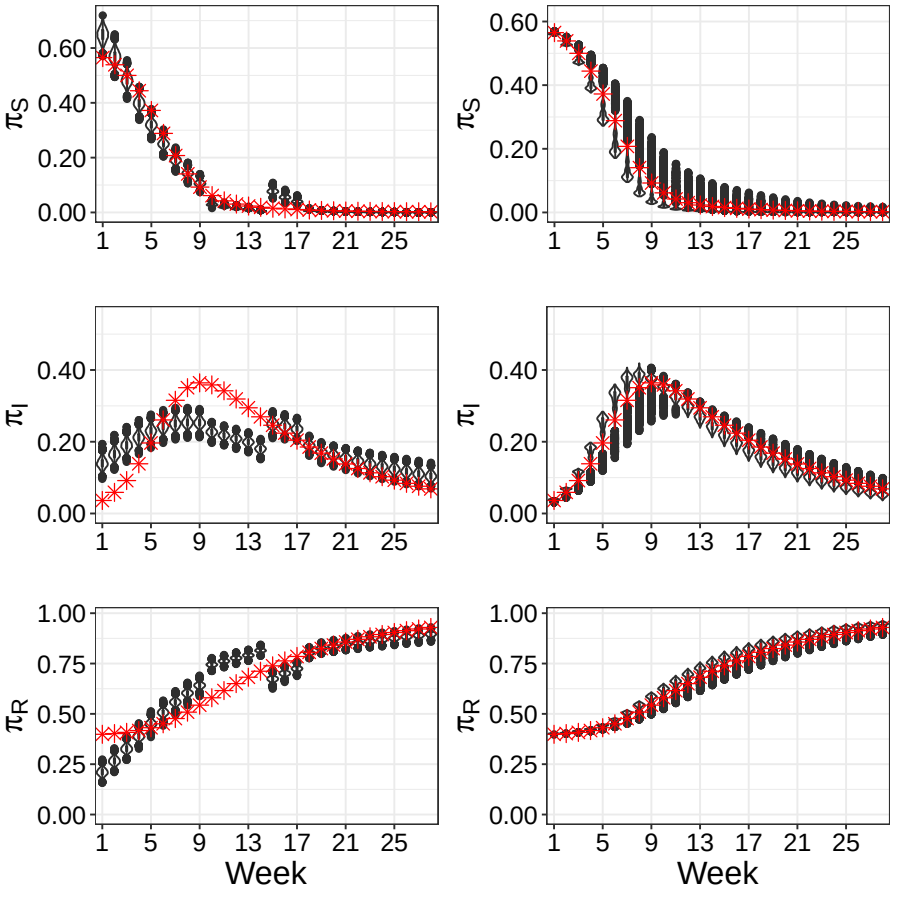

Figure 2. Posterior predictive probabilities resulting from fitting multinomial-generated data with a compartmental model structure on the proportions across time using multinomial logistic regression (left) and the compartmental model (right). Known proportions are shown as red stars. The multinomial logistic regression model missed nuances in the shape of the data, particularly at early time points. In contrast, the compartmental model captures the changes over time well for all compartments.

proportion for each of the compartments. The parameter estimates and 95% credible intervals for each of the two models in Figure 1 are shown in Table 2. The Bayes factor for the multinomial logistic regression model versus the compartmental model was 1.55 (BF_{12}) when Euclidean distance was employed. According to the interpretation guidelines set forth by Toni *et al.* and adapted from Kass and Raftery, this is very weak evidence in favor of the multinomial logistic regression model [21,41]. This result supports the assertion that the compartmental model is flexible enough to capture the constant proportions well. The results were consistent for Manhattan and Chebyshev distance metrics; there was no convincing evidence to favor one model over the other.

Figure 2 shows the resulting posterior predictive probability distributions for each of the two models using the compartmental model-generated data with a compartmental model structure on the proportions across time. The multinomial logistic regression model misses the nuances of the shape of the data, particularly in the $\mathcal{I}$ category, but also in the early

Table 3. Parameter estimates and symmetric 95% credible intervals for multinomial logistic regression and compartmental models fit to data simulated from compartmental model with variability over time. Here we see the significance of time in the multinomial logistic regression model.

	Multinomial Logistic Regression			
	$\mathcal{S}/\mathcal{R}$		$\mathcal{I}/\mathcal{R}$	
	Estimate	95% Credible Interval	Estimate	95% Credible Interval
Intercept	1.459	(1.040, 1.889)	−0.389	(−0.734, −0.038)
Week	−0.353	(−0.419, −0.294)	−0.055	(−0.077, −0.033)

	Compartmental Model	
	Estimate	95% Credible Interval
Intercept	0.324	(0.253, 0.376)
Week	−1.409	(−3.348, 0.609)
$\pi^{(\mathcal{IR})}$	0.101	(0.089, 0.115)

weeks for both the $\mathcal{S}$ and $\mathcal{R}$ categories. In contrast, the SIR model captures the simulated data well. The parameter estimates and 95% credible intervals for each of the two models in Figure 1 are shown in Table 3. The Bayes factor for the SIR model versus the multinomial logistic regression model is larger than 150 (BF_{21}), which indicates very strong evidence in favor of the compartmental model [21,41]. Again, the results were consistent for Manhattan and Chebyshev distance metrics.

4. Results of *L. infantum* infection analysis

4.1. Posterior estimates and model convergence

For both models, the Raftery and Lewis diagnostic test was used to inform the number of iterations to be used for burn-in when using the Geweke diagnostic, which was used as a measure of convergence [16,35]. Both diagnostic tests were implemented using the `coda` package in R [34].

The multinomial logistic regression model was run for 150,000 iterations; every 10th iteration was saved to address minor auto-correlation. A burn-in of 120 saved iterations was used for all parameters based on the Raftery and Lewis diagnostic test. All twelve parameters had test statistics from the Geweke diagnostic test with absolute values less than 1.96, so there was no evidence of lack of convergence for this model. Posterior parameter estimates are included in Table 4. Note, sampling methods like Hamiltonian Monte Carlo, which are designed to reduce autocorrelation by more efficiently exploring the parameter space, can be employed in this scenario [31]. However, since the autocorrelation is not severe, and there is no evidence of lack of convergence, we did not employ one of these sampling schemes.

The compartmental model was run for two million iterations to ensure convergence; every 500th iteration was saved because auto-correlation was high in this model. Note, sampling methods like Hamiltonian Monte Carlo are difficult to apply in this setting due to the discrete nature of compartment membership counts. Such an approach would require the introduction of continuous likelihood approximations, which may not be a good fit. Four separate MCMC chains were run in parallel. A burn-in of 334 saved iterations was

Table 4. Bayesian multinomial logistic regression posterior estimates for outcome with three categories. The baseline disease category was removed, and the baseline area category was rural.

	$\mathcal{S}/\mathcal{R}$		$\mathcal{I}/\mathcal{R}$	
	Estimate	95% Credible Interval	Estimate	95% Credible Interval
Intercept	−0.104	(−0.999, 0.961)	−0.112	(−1.642, 0.727)
Area: Urban	0.093	(−0.573, 0.760)	0.303	(−0.425, 1.038)
Area: Periurban	0.410	(−0.274, 1.093)	−0.387	(−1.376, 0.542)
Sex: Male	−0.523	(−1.077, 0.022)	−0.870	(−1.626, −0.160)
Age $>$ 35	−0.827	(−1.364, −0.304)	−0.225	(−0.886, 0.438)
Week	0.046	(0.016, 0.076)	−0.029	(−0.077, 0.016)

used. The resulting Geweke test statistics for β_0 and β_1 were −0.2458 and 1.2989, respectively, so there was no significant evidence against convergence. The test statistics for the γ's were −0.5996, −0.6083, −0.6276, 0.6098, respectively, so similarly there was no significant evidence against convergence for these parameters. The test statistic for $\pi^{(\mathcal{IR})}$ was −0.9536. These parameters form a sufficient basis for simulation and drive epidemic behavior. Therefore, in the high dimensional context of compartmental models, these results are indicative of overall model convergence.

4.2. Model comparisons for L.infantum infection analysis

The multinomial logistic regression and the compartmental model were compared using posterior predictive counts, as described in the Model Comparisons section. The distributions of counts across time for each disease state and each model are shown in Figure 3. The stars represent the observed counts at each week. The tails of the posterior predictive distributions from the multinomial logistic regression approach generally capture the observed data. This model appears to perform particularly badly for the $\mathcal{I}$ compartment. The SIR model seems to be a more reasonable mechanism for generating the observed counts than the multinomial logistic regression model. The Bayes factor for the SIR model versus the multinomial logistic regression model is larger than 150 (BF_{21}), which is very strong evidence in favor of the SIR model [41].

One potential criticism of these comparisons is that in fitting the multinomial logistic regression model, vague priors were put on the regression coefficients, whereas in the compartmental model, informative priors were put on the initial compartments, S_0 and I_0, and on the transition probability $\pi^{(\mathcal{IR})}$. While this is an understandable concern, there are several points that should be considered. First, the compartmental model simulates a biological process, and it is critical to start with biologically plausible priors in order to obtain meaningful results. For example, non-informative priors on the initial compartments, S_0 and I_0, can easily result in counts that do not resemble the population. Similarly, the prior for $\pi^{(\mathcal{IR})}$ needs to be biologically plausible; it can be made vaguer, but it needs be centered in a reasonable location. As described in Section 2.2.3.2, we have good prior information from surveys and case studies to establish plausible priors for these three parameters. Second, there is little known about what the impact of the covariates considered in the multinomial logistic regression should be, so there is not enough information to include informative prior information about them. In fact, the data used in this analysis were originally collected to study the importance of these covariates for each infection

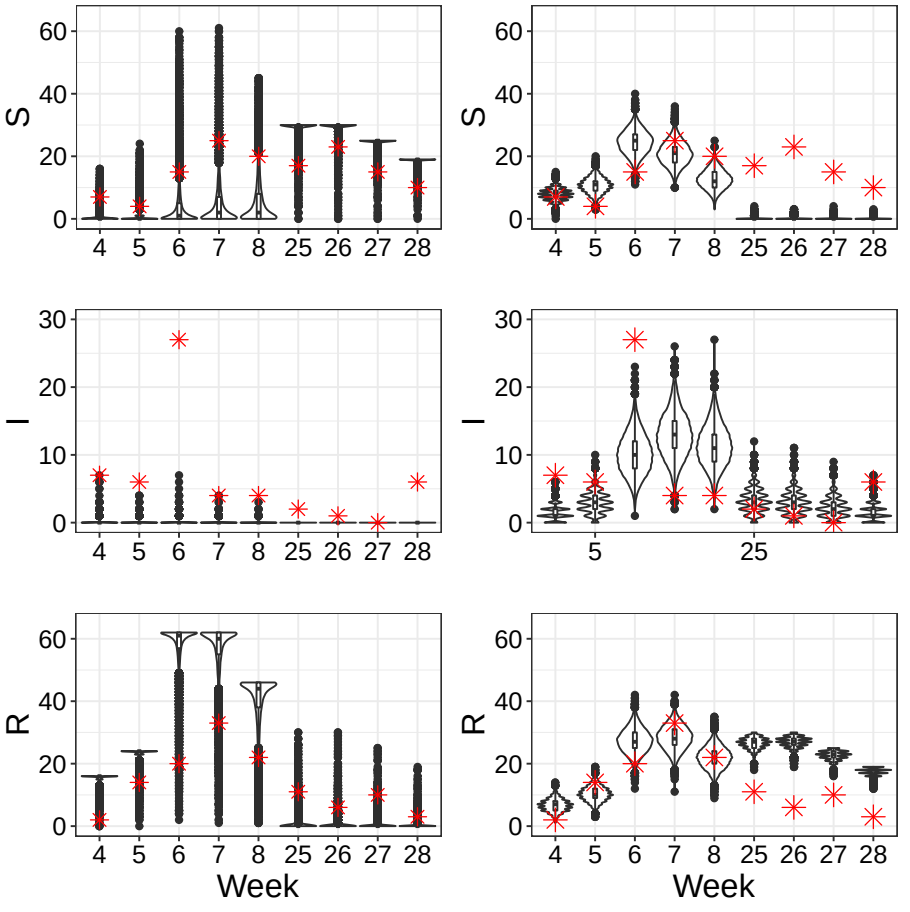

Figure 3. Comparison of posterior predictive counts from multinomial logistic regression (left) and the compartmental model (right) to observed counts (red stars) for each compartment at each week. At each week, 5000 counts were generated from the posterior predictive distribution; the distributions are represented using violin plots. The compartmental model allows for more variability in the posterior predictive counts and as a consequence does a better job of capturing the observed counts, particularly for the infectious state, where the counts are generally small.

category. Also, there is no guarantee that these are all the individual-level covariates that should be included. In contrast, the framework for the compartmental model allows us to easily incorporate known information about the dynamics of VL; the framework for the compartmental model is better suited to incorporating known information about the infection process. Since we have good information about the biological process at hand, we can leverage the compartmental model framework to gain a better understanding of the population level dynamics of *L. infantum* infection than we can get with the multinomial logistic regression model.

Another potential criticism is that time is not modeled carefully enough in the logistic regression model; there are more complex ways in which time could be incorporated into the model than a linear time component, which might provide a more reasonable fit to the data. It is true that various treatments of time could be considered, but it would likely

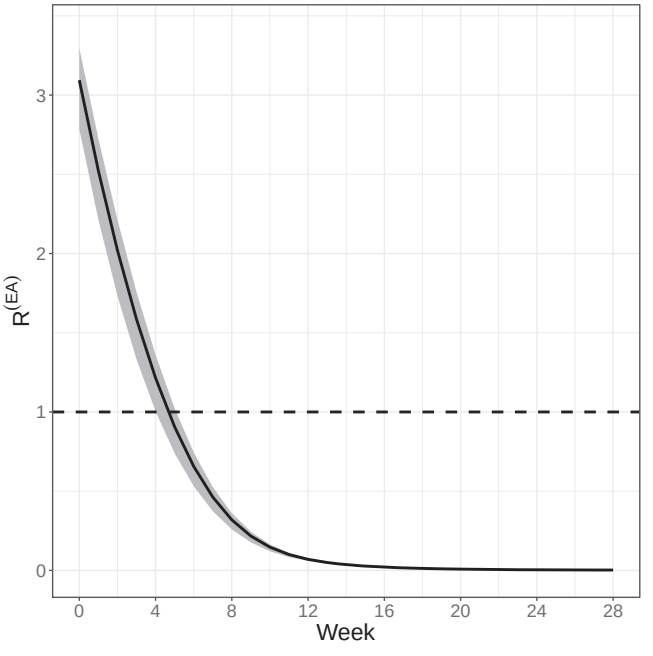

Figure 4. Empirically-adjusted reproductive number over time. Symmetric 95% credible intervals are in grey. In the first four weeks of the year, on average, an infectious individual infects more than 1 person, but this number drops below 1 after Week 4. This is due to the seasonality of the infection, rather than because the infection has died out.

require a great deal of data to identify the appropriate structure for time without overfitting. In contrast, the stochastic compartmental model allows us to consider fairly simple treatments of time (it is treated as linear in the model for the real data) while still fitting the data well. The compartmental model provides a more convenient framework for incorporating time.

4.3. Reproductive number

An added advantage of using the SIR framework to model this infection data is that we can easily calculate point estimates and credible intervals for the empirically-adjusted reproductive number, $\mathcal{R}^{(EA)}$, at each time point, t. These estimates and credible intervals are shown in Figure 4. In the first 4 weeks, $\mathcal{R}^{(EA)}$ is greater than 1, indicating that on average, an infectious individual infects more than 1 person. After 4 weeks, this number drops below 1. This change is due to the seasonality of the infection; it does not indicate that the infection will no longer be present in the population.

5. Conclusions

In this paper, we compared the performances of the Bayesian multinomial logistic regression and SIR models for fitting both simulated and real VL data. We introduced a novel way to estimate Bayes factors using an SMC-ABC-inspired approach when the models are fit

using MCMC rather than ABC, as is commonly done in practice. Specifically, we discussed how to choose the tolerance, ϵ, in the algorithm using acceptance ratios from Metropolis Hastings. This method allowed us to estimate Bayes factors when the model likelihoods are non-normal and when parameter spaces are high-dimensional. We were able to show that the stochastic compartmental model was a better approach for determining infection state proportions than multinomial regression was. We also adapted the empirically-adjusted reproductive number introduced by Brown *et al.* to obtain estimates and credible intervals for the reproductive number for VL [8].

When the simulated data arose from a multinomial likelihood, the Bayes factor showed that there was very weak evidence in favor of the multinomial logistic regression model. In contrast, when the simulated data arose from a compartmental model, the Bayes factor demonstrated that there was very strong evidence in favor of the SIR model [21,41]. We expect some variation due to seasonality, interventions, or natural host-vector-pathogen dynamics. The compartmental modeling approach assumes that this variability exists and offers a convenient framework for including it in the model [22].

Analysis of data from the *L. infantum* endemic region supports the conclusion that the compartmental model is a more reasonable modeling choice for this dynamic endemic site when the objective is to estimate the proportion of individuals in the population in each infection state over time. The compartmental model captures the observed counts better than the multinomial logistic regression model. The Bayes factor provides very strong evidence in favor of the SIR model for the VL data. The framework of the SIR model also allows us to easily compute estimates for the empirically-adjusted reproductive number at each time point, along with credible intervals. As shown in Figure 4, $\mathcal{R}^{(EA)}$ is larger than 1 in the first four weeks of the year and drops below 1 after the fourth week.

Multinomial logistic regression has two implementation advantages over the compartmental modeling approach. First, there are several R packages that implement the model, both in the frequentist and Bayesian frameworks. Second, the model runs quickly for reasonably small sample sizes. For our simulation study, for example, there were a total of 2800 observations (100 observations at each of 28 time points). The multinomial logistic regression model took 43.46 seconds to run for 100,000 iterations using the *MCMCmnl* function from the `MCMCpack` package [26]. In contrast, the compartmental model took 919.19 seconds to run under the same conditions. The code for the compartmental model was written by the authors and is available in the supplementary materials, but it has not yet been optimized. Since the code for the compartmental model has not been fully optimized yet, it may be possible to fit the model more efficiently. While some readers may be concerned about the computation time needed to fit the SIR model, the time required is still neglible relative to the length of study. It should be noted that the R package `pomp` can be used to fit compartmental epidemiological models as well.

In spite of these advantages, we have demonstrated, both through simulation studies and real data analysis, that multinomial logistic regression does not perform as well as the compartmental model when the objective is to estimate the proportion of individuals in various states of infection across time. The Bayes factors show that there is decisive evidence in favor of the SIR model, both in the simulation when the simulated data arise from an SIR model, and in the analysis of the data from the *L. infantum* endemic region. We can also quantify a reproductive number for the infection.

This compartmental modeling approach may be applicable to other infectious diseases besides VL that have known seasonality, established/experimental interventions, or other host-vector-pathogen dynamics. Infectious diseases like Lyme disease and dengue hemorrhagic fever may benefit from analysis using this approach because of seasonality, for example [32,36]. However, this modeling approach may be ill-suited to infectious diseases that may have many potential sources of infection, like sepsis, because it is difficult to determine what form the transition probabilities should take. Furthermore, if we do not have good information about the biology/dynamics of a particular disease or infection, the compartmental model may not provide sensible results.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

Research reported in this publication was supported by the Fogarty International Center of the National Institutes of Health under Award Number R01TW010500 and by the National Institute of Allergy and Infectious Diseases under Award Number P50 AI30639. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ORCID

Marie V. Ozanne http://orcid.org/0000-0001-5020-8529

References

[1] E. Agyingi, D. Ross, and K. Bathena, *A model of the transmission dynamics of leishmaniasis*, J. Biol. Syst. 19 (2011), pp. 237–250.
[2] J. Alvar, I.D. Vé lez, C. Bern,M. Herrero, P. Desjeux, J. Cano, J. Jannin, M. den Boer, and M. Kirk, *Leishmaniasis worldwide and global estimates of its incidence*, PLoS ONE 7 (2012), pp. e35671.
[3] H. Andersson and T. Britton, *Stochastic Epidemic Models and Their Statistical Analysis*, Springer-Verlag, New York, 2000.
[4] M. Beaumont, *Approximate Bayesian computation in evolution and ecology*, Annu. Rev. Ecol. Evol. Syst. 41 (2010), pp. 379–406.
[5] M. Beaumont, W. Zhang, and D. Balding, *Approximate Bayesian computation in population genetics*, Genetics 162 (2002), pp. 2025–2035.
[6] B. Bonsu and M. Harper, *Differentiating acute bacterial meningitis from acute viral meningitis among children with cerebrospinal fluid pleosytosis: A multivariable regression model*, Pediatr. Infect. Dis. J. 23 (2004), pp. 511–517.
[7] R. Braz, E. Nascimento, D. Martins, M.E. Wilson, R.D. Pearson, S.G. Reed, and S.M.B. Jeronimo, *The sensitivity and specificity of leishmania chagasi recombinant k39 antigen in the diagnosis of American visceral leishmaniasis and in differentiating active from subclinical infection*, Am J Trop Med Hyg 67 (2002), pp. 344–348.
[8] G.D. Brown, J.J. Oleson, and A.T. Porter, *An empirically adjusted approach to reproductive number estimation for stochastic compartmental models: A case study of two ebola outbreaks*, Biometrics 72 (2016), pp. 335–343.
[9] G. Celeux, F. Forbes, C.P. Robert and D.M. Titterington, *Rejoinder to discussion of deviance information criteria for missing data models*, Bayesian Anal. 1 (2006), pp. 701– 705.

[10] D. Chadwick, B. Arch, A. Wilder-Smith, and N. Paton, *Distinguishing dengue fever from other infections on the basis of simple clinical and laboratory features: Application of logistic regression analysis*, J. Clin. Virol. 35 (2006), pp. 147–153.
[11] C. Costa, H. Pereira, and M. Araújo, *Visceral leishmaniasis epidemic in the state of Piaui, Brazil, 1980–1986*, Revista de saúde pública 24 (1990), pp. 361–372.
[12] C. Dye and D. Wolpert, *Earthquakes, influenza and cycles of Indian kala-azar*, Trans. R. Soc. Trop. Med. Hyg. 82 (1988), pp. 843–850.
[13] C.R. Franke, M. Ziller, C. Staubach, and M. Latif, *Impact of el niño/southern oscillation on visceral leishmaniasis, Brazil*, Emerg Infect Dis 8 (2002), pp. 914–917.
[14] J.R. Fried, R.V. Gibbons, S. Kalayanarooj, S.J. Thomas, A. Srikiatkhachorn, I.-K. Yoon, R.G. Jarman, S. Green, A.L. Rothman, D.A.T. Cummings, and S.B. Halstead, *Serotype-specific differences in the risk of dengue hemorrhagic fever: An analysis of data collected in Bangkok, Thailand from 1994 to 2006*, PLOS Negl. Trop. Dis. 4 (2010), p. e617.
[15] O. Genaro, C.A. da Costa, P. Williams, J.E. Silva, N.M. Rocha, S.L. Lima, and W. Mayrink, *Occurrence of kala-azar in the urban area of Grande Belo Horizonte, Minas Gerais*, Revista da Sociedade Brasileria de Medicina Tropical 23 (1989), p. 121.
[16] J. Geweke, *Evaluating the accuracy of sampling-based approaches to the calculation of posterior moments*, Bayesian Statist. 4 (1992), pp. 169–193.
[17] G. Hasibeder, C. Dye, and J. Carpenter, *Mathematical modelling and theory for estimating the basic reproduction number of canine leishmaniasis*, Parasitology 105 (1992), pp. 43–53.
[18] B.L. Herwaldt, *Laboratory-acquired parasitic infections from accidental exposures*, Clin. Microbiol. Rev. 14 (2001), pp. 659–688.
[19] S.M.B. Jeronimo, P. Duggal, R.F.S. Braz, C. Cheng, G.R.G Monteiro, E.T. Nascimento, D.R.A. Martins, T.M. Karplus, M.F.F.M. Ximenes, C.C.G. Oliveira, V.G. Pinheiro, W. Pereira, J.M. Peralta, J.M.A. Sousa, I. M. Medeiros, R.D. Pearson, T.L. Burns, E.W. Pugh, and M.E. Wilson, *An emerging per-urban pattern of infection in northeast brazil*, Scand. J. Infect. Dis. 36 (2004), pp. 443–449.
[20] S.M.B. Jeronimo, R.M. Oliveira, S. Mackay, R.M. Costa, J. Sweet, E.T. Nascimento, K.G. Luz, M.Z. Fernandes, J. Jernigan, and R.D. Pearson, *An urban outbreak of visceral leishmaniasis in Natal, Brazil*, Trans. R. Soc. Trop. Med. Hyg. 88 (1994), pp. 386–388.
[21] R.E. Kass and A.E. Raftery, *Bayes factors*, J. Am. Stat. Assoc. 90 (1995), pp. 773–795.
[22] P.E. Lekone and B.F. Finkenstädt, *Statistical inference in a stochastic epidemic SEIR model with control intervention: Ebola as a case study*, Biometrics 62 (2006), pp. 1170–1177.
[23] M. Levy and M. Yiengst, *Kala-azar: Report of a case showing unusual leukocyte response and prolonged incubation period*, J. Am. Med. Assoc. 136 (1948), pp. 81–84.
[24] I.D. Lima, J.W. Queiroz, H.D. Lacerda, N.N. Pontes, P.V.S. Queiroz, R.D. Pearson, J.L. Weirather, S.M. B. Jeronimo, D.R. Martins, J.D.A. Barbosa, and M.E. Wilson, *Leishmania infantum chagasi in northeastern Brazil: Asymptomatic infection at the urban perimeter*, Am. J. Trop. Med. Hyg. 86 (2012), pp. 99–107.
[25] A.N.S. Maia-Elkhoury, W.A. Alves, M.L. de Sousa-Gomes, J.M. de Sena, and E.A. Luna, *Visceral leishmaniasis in Brazil: Trends and challenges*, Cadernos de Saúde Pública 24 (2008), pp. 2941–2947.
[26] A.D. Martin, K.M. Quinn, and J.H. Park, *MCMCpack: Markov chain Monte Carlo in R*, J. Stat. Softw. 42 (2011), p. 22.
[27] M.C.A. Marzochi, K.B.F. Marzochi, and R.W. Carvalho, *Visceral leishmaniasis in Rio de Janeiro*, Parasitol. Today 10 (1994), pp. 37–40.
[28] L. Moral, E.M. Rubio, and M. Moya, *A leishmanin skin test survey in the human population of l'Alacantí region (Spain): Implications for the epidemiology of Leishmania infantum infection in southern Europe*, Trans. R. Soc. Trop. Med. Hyg. 96 (2002), pp. 129–132.
[29] A.C. Morrison, C. Ferro, R. Pardo, M. Torres, B. Devlin, M.L. Wilson, and R.B. Tesh, *Seasonal abundance of lutzomyia longipalpis (dipteral psychodidae) at an endemic focus of visceral leishmaniasis in Colombia*, J. Med. Entomol. 32 (1995), pp. 538–548.
[30] K.E. Mott, P. Desjeux, A. Moncayo, P. Ranque, and P. de Raadt, *Parasitic diseases and urban development*, Bull. World Health Organ. 68 (1990), pp. 691–698.

[31] R. Neal, *MCMC using Hamiltonian dynamics*, in *Handbook of Markov Chain Monte Carlo*, S. Brooks, A. Gelman, G. Jones, and X. Meng, eds., Chap. 5, Chapman & Hall, Boca Raton, 2011.
[32] J. Piesman, T.N. Mather, G.J. Dammin, S.R. Telford, C.C. Lastavica, and A. Spielman, *Seasonal variation of transmission risk of lyme disease and human babesiosis*, Am. J. Epidemiol. 126 (1987), p. 1187–1189.
[33] M. Plummer, *Penalized loss functions for bayesian model comparison*, Biostatistics 9 (2008), pp. 523–539.
[34] M. Plummer, N. Best, K. Cowles, and K. Vines, *Coda: Convergence diagnosis and output analysis for MCMC*, R News 6 (2006), pp. 7–11.
[35] A. Raftery and S. Lewis, *How many iterations in the gibbs sampler?*, Bayesian Statist. 4 (1992), pp. 763–773.
[36] E. Schwartz, L.H. Weld, A. Wilder-Smith, F. von Sonnenburg, J.S. Keystone, K.C. Kain, J. Torresi, and D.O. Freedman, *Seasonality, annual trends, and characteristics of dengue among ill returned travelers, 1997–2006*, Emerg. Infect. Dis. 14 (2008), pp. 1081–1088.
[37] H. Shimozako, J. Wu, and E. Massad, *Mathematical modelling for zoonotic visceral leishmaniasis dynamics: A new analysis considering updated parameters and notified human Brazilian data*, Inf. Dis. Mod. 2 (2017), pp. 143–160.
[38] O.P. Singh, E. Hasker, D. Sacks, M. Boelaert, and S. Sundar, *Asymptomatic leishmania infection: A new challenge for leishmania control*, Clin. Infect. Dis. 58 (2014), pp. 1424–1429.
[39] D.J. Spiegelhalter, N.G. Best, B.P. Carlin, and A. van der Linde, *Bayesian measures of model complexity and fit*, J Royal Stat Soc B 64 (2002), pp. 583–639.
[40] A. Stauch, R.R. Sarkar, A. Picado, B. Ostyn, S. Sundar, S. Rijal, M. Boelaert, J.-C. Dujardin, H.-P. Duerr, and A.P. Galvani, *Visceral leishmaniasis in the Indian subcontinent: Modelling epidemiology and control*, PLOS Negl. Trop. Dis. 5 (2011), pp. 1–12.
[41] T. Toni, D. Welch, N. Strelkowa, A. Ipsen, and M.P.H Stumpf, *Approximate Bayesian computation scheme for parameter inference and model selection in dynamical systems*, J. R. Soc. Interface 6 (2009), pp. 187–202.
[42] W. Venables and B. Ripley, *Modern Applied Statistics with S*, 4th ed., Springer, New York, 2002.
[43] G.L. Werneck, M.S. Batista, J.R.B. Gomes, D.L. Costa, and C.H. Costa, *Prognostic factors for death from visceral leishmaniasis in Teresina, Brazil*, Infection 31 (2003), pp. 174–177.
[44] M.E. Wilson, S.M.B. Jeronimo, and R.D. Pearson, *Immunopathogenesis of infection with the visceralizing leishmania species*, Microb. Pathog. 38 (2005), pp. 147–160.

Appendix 1. Full conditionals, compartmental model

(1) $p(S_0 \mid \cdot) \propto p(\mathbf{y} \mid \mathbf{S}, \mathbf{I}, \mathbf{R}, \boldsymbol{\gamma}) p(\mathbf{I}^{(\mathcal{SI})} \mid \mathbf{S}, \boldsymbol{\beta}) p(S_0 \mid \pi^{(S_0)})$
(2) $p(I_0 \mid \cdot) \propto p(\mathbf{y} \mid \mathbf{S}, \mathbf{I}, \mathbf{R}, \boldsymbol{\gamma}) p(\mathbf{R}^{(\mathcal{IR})} \mid \mathbf{I}, \pi^{(\mathcal{IR})}) p(I_0 \mid \pi^{(I_0)})$
(3) $p(\boldsymbol{\beta} \mid \cdot) \propto p(\mathbf{y} \mid \mathbf{S}, \mathbf{I}, \mathbf{R}, \boldsymbol{\gamma}) p(S_0 \mid \pi^{(S_0)}) p(\mathbf{I}^{(\mathcal{SI})} \mid \mathbf{S}, \boldsymbol{\beta}) p(\boldsymbol{\beta})$
(4) $p(\boldsymbol{\gamma} \mid \cdot) \propto p(\mathbf{y} \mid \mathbf{S}, \mathbf{I}, \mathbf{R}, \boldsymbol{\gamma}) p(\boldsymbol{\gamma})$
(5) $p(\mathbf{I}^{(\mathcal{SI})} \mid \cdot) \propto p(\mathbf{y} \mid \mathbf{S}, \mathbf{I}, \mathbf{R}, \boldsymbol{\gamma}) p(S_0 \mid \pi^{(S_0)}) p(\mathbf{I}^{(\mathcal{SI})} \mid \mathbf{S}, \boldsymbol{\beta})$
(6) $p(\mathbf{R}^{(\mathcal{IR})} \mid \cdot) \propto p(\mathbf{y} \mid \mathbf{S}, \mathbf{I}, \mathbf{R}, \boldsymbol{\gamma}) p(I_0 \mid \pi^{(I_0)}) p(\mathbf{R}^{(\mathcal{IR})} \mid \mathbf{I}, \pi^{(\mathcal{IR})})$
(7) $p(\pi^{(\mathcal{IR})} \mid \cdot) \propto p(\mathbf{R}^{(\mathcal{IR})} \mid \mathbf{I}, \pi^{(\mathcal{IR})}) p(\pi^{(\mathcal{IR})})$
Note: $p(\pi^{(\mathcal{IR})} \mid \cdot) \propto [\pi^{(\mathcal{IR})}]^{\sum_{t \in \mathcal{T}} R_t^{(\mathcal{IR})} + \alpha^{(\mathcal{IR})} - 1} [1 - \pi^{(\mathcal{IR})}]^{\sum_{t \in \mathcal{T}} (I_{t-1} - R_t^{(\mathcal{IR})} + \beta^{(\mathcal{IR})} - 1)}$

Appendix 2. Outline of Markov Chain Monte Carlo algorithm, compartmental model

(1) Initialize all values.
(2) Update initial values S_0, I_0, and R_0.
(3) Update $\boldsymbol{\beta}$ using Metropolis Hastings via a Gaussian random walk.
(4) Calculate the deterministic vector $\boldsymbol{\pi}^{(\mathcal{SI})}$.
(5) Update $\boldsymbol{\gamma}$ using Metropolis Hastings via a Gaussian random walk.
(6) Update $\mathbf{I}^{(\mathcal{SI})}$ using Metropolis Hastings.

(7) Calculate the deterministic vectors $\mathbf{S}, \mathbf{I}, \mathbf{R}$.
(8) Calculate the deterministic vector $\boldsymbol{\pi}^{(\mathcal{SI})}$.
(9) Update $\mathbf{R}^{(\mathcal{IR})}$ using Metropolis Hastings.
(10) Calculate the deterministic vectors $\mathbf{I}, \mathbf{R}$.
(11) Update $\pi^{(\mathcal{IR})}$ using Gibbs.