

RESEARCH ARTICLE

Bayesian estimation of Lassa virus epidemiological parameters: Implications for spillover prevention using wildlife vaccination

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Data Availability Statement: Source code is available as a public repository on GitHub (<https://github.com/snuismer/LaMOUSE.git>). Rodent time series data is now included. All relevant data from animal studies used to inform prior distributions is included within the manuscript.

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Abstract

Lassa virus is a significant burden on human health throughout its endemic region in West Africa, with most human infections the result of spillover from the primary rodent reservoir of the virus, the natal multimammate mouse, *M. natalensis*. Here we develop a Bayesian methodology for estimating epidemiological parameters of Lassa virus within its rodent reservoir and for generating probabilistic predictions for the efficacy of rodent vaccination programs. Our approach uses Approximate Bayesian Computation (ABC) to integrate mechanistic mathematical models, remotely-sensed precipitation data, and Lassa virus surveillance data from rodent populations. Using simulated data, we show that our method accurately estimates key model parameters, even when surveillance data are available from only a relatively small number of points in space and time. Applying our method to previously published data from two villages in Guinea estimates the time-averaged R_0 of Lassa virus to be 1.74 and 1.54 for rodent populations in the villages of Bantou and Tanganya, respectively. Using the posterior distribution for model parameters derived from these Guinean populations, we evaluate the likely efficacy of vaccination programs relying on distribution of vaccine-laced baits. Our results demonstrate that effective and durable reductions in the risk of Lassa virus spillover into the human population will require repeated distribution of large quantities of vaccine.

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Author summary

Lassa virus is a chronic source of illness throughout West Africa, and is considered to be a threat for widespread emergence. Because most human infections result from contact with infected rodents, interventions that reduce the number of rodents infected with Lassa virus represent promising opportunities for reducing the public health burden of this disease. Evaluating how well alternative interventions are likely to perform is complicated by our relatively poor understanding of viral epidemiology within the reservoir population. Here we develop a novel statistical approach that couples mathematical models and viral surveillance data from rodent populations to robustly estimate key epidemiological parameters. Applying our method to existing data from Guinea yields well-resolved parameter estimates and allows us to simulate a variety of rodent vaccination programs. Together, our results demonstrate that rodent vaccination alone is unlikely to be an effective tool for reducing the public health burden of Lassa fever within West Africa.

Introduction

Lassa virus is a zoonotic pathogen endemic to West Africa where it poses a significant burden on human health [1]. Although only a relatively small proportion of human cases result in severe symptoms and mortality, human infection is common, with 8–52% of the human population within Sierra Leone seropositive [2–4], indicative of past infection by Lassa virus. In addition to being a chronic source of illness throughout West Africa, Lassa virus is considered to be a threat for widespread emergence and is recognized by the World Health Organization as a priority pathogen [5].

Human infection with Lassa virus occurs primarily through contact with excretions of the primary reservoir species, the natal multimammate mouse, *M. natalensis* [2]. Within Lassa endemic regions of West Africa, *M. natalensis* frequently inhabit human dwellings and trapping studies have demonstrated that up to 30% of *M. natalensis* individuals can be PCR positive for Lassa virus [6, 7]. Recent modeling and genetic studies have confirmed the primary importance of zoonotic transmission, providing evidence that human to human transmission is rare outside of hospital settings [8–10]. Because most human infections result from contact with infected rodents, strategies for reducing human infection have focused on reducing human contact with the reservoir species, *M. natalensis*, reducing the reservoir population as a whole through trapping or poisoning, or reducing the proportion of infected rodents through vaccination [11–13].

Recent studies investigating the efficacy of rodent removal using annual application of a rodenticide in Guinea demonstrated poisoning could yield substantial transient reductions in the density of *M. natalensis* [13]. Specifically, this study applied rodenticide during the dry season over a four-year period and evaluated trapping success at the beginning and end of each application period. Although trapping success (and presumably rodent density) declined by the end of each application period, populations rapidly rebounded to their pre-treatment levels in all but the fourth year. Thus, the extent to which rodenticide application can yield durable reductions in rodent density remains unclear. In contrast to rodent removal, no experimental studies examining the impact of rodent vaccination exist because vaccines targeting Lassa virus in the reservoir population are under development, but not yet available. As a consequence, efforts to predict how well vaccination campaigns might work have relied on computer simulations [e.g., 12]. Using individual based simulations to predict the effectiveness of culling and vaccination, Marien et al. (2019) found that Lassa virus could be eliminated from

its reservoir population only through continuous rodent control or vaccination. Because these conclusions rest on informal model parameterization, do not integrate seasonal variation in reproduction, and investigate only a small range of possible vaccination strategies, their generality remains unclear.

Here we develop a robust Bayesian methodology for estimating key epidemiological parameters of Lassa virus within its natural reservoir, the natal multimammate mouse, *Mastomys natalensis*, that couples mechanistic mathematical models, remotely sensed precipitation data, and rodent capture data from two villages in Guinea using Approximate Bayesian Computation (ABC). We use this Bayesian approach to estimate individual model parameters as well as the time-averaged R_0 for Lassa virus within two villages in Guinea for which time-series data is available [6, 14]. The time-averaged value of R_0 measures the average number of new Lassa virus infections produced by an infected rodent if it were introduced into an entirely susceptible population. Repeated sampling from the posterior distribution allowed us to generate probabilistic predictions for the efficacy of vaccination campaigns and to identify the optimal timing of vaccine distribution.

Methods

Ethics statement

In vivo studies were approved by the Institutional Animal Care and Use Committee of the RML. Animal work was conducted adhering to the institution's guidelines for animal use, and followed the guidelines and basic principles in the United States Public Health Service Policy on Humane Care and Use of Laboratory Animals, and the Guide for the Care and Use of Laboratory Animals by certified staff in an Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International accredited facility. Protocol numbers are 2014–001 and 2014–031.

Biosafety

All work with infectious LASV and potentially infectious materials derived from animals was conducted in a Biosafety Level 4 (BSL 4) laboratory in the Integrated Research Facility of the Rocky Mountain Laboratories (RML), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH). Sample inactivation and removal was performed according to standard operating protocols approved by the local Institutional Biosafety Committee.

Mathematical model

We model the coupled ecological and epidemiological dynamics of *M. natalensis* and Lassa virus in a metapopulation consisting of a set of \mathcal{P} populations connected by migration. We assume the age structure of the reservoir population, *M. natalensis*, can be well-described by three discrete life stages: pup, pre-reproductive juvenile, and reproductive adult. The epidemiological dynamics of Lassa virus are assumed to follow an SIR model where individual rodents are either susceptible to Lassa infection (S), currently infected by Lassa virus and infectious to other rodents (I), or recovered from Lassa virus infection and immune to further infection (R). We do not include the complication of modeling an exposed class [e.g., 12] because viral shedding may commence rapidly (2–3 days) after exposure. Our model allows for horizontal transmission of Lassa virus among classes as well as vertical transmission from mother to offspring and transmission of protective maternal antibodies. We include the possibility of vertical transmission and maternal antibody transfer because both have been demonstrated in related

arenaviruses and included in previous models exploring the efficacy of Lassa control measures [12]. Within a location, x , we assume individuals encounter one another at random and that juveniles and adults move at random from location x to location y at per capita rates $m_{J,x,y}$ and $m_{A,x,y}$, respectively. Both density-dependent and density-independent mortality are included as both have been demonstrated to be important in *M. natalensis* population dynamics [15]. Although not previously demonstrated for this system, for completeness, we also include the possibility of density-dependent birth rates. Together, these assumptions lead to the following system of differential equations describing the dynamics of Lassa virus infection within a single geographic location, x :

$$\dot{S}_{P,x} = b_x(1 - \varphi_x N_x)(S_{A,x} + (1 - V)I_{A,x} + (1 - M)R_{A,x}) - (\alpha_{PJ} + d_p + k_x N_x + \sum_{i \in \mathcal{A}} \beta_{P-i} I_{i,x}) S_{P,x} \tag{1A}$$

$$\dot{S}_{J,x} = \alpha_{PJ} S_{P,x} - (\alpha_{JA} + d_j + k_x N_x + \sum_{i \in \mathcal{A}} \beta_{J-i} I_{i,x}) S_{J,x} + \sum_{y \in \mathcal{P}} m_{J,x,y} (S_{J,y} - S_{J,x}) \tag{1B}$$

$$\dot{S}_{A,x} = \alpha_{JA} S_{J,x} - (d_A + k_x N_x + \sum_{i \in \mathcal{A}} \beta_{A-i} I_{i,x}) S_{A,x} + \sum_{y \in \mathcal{P}} m_{A,x,y} (S_{A,y} - S_{A,x}) \tag{1C}$$

$$\dot{I}_{P,x} = b_x(1 - \varphi_x N_x) V I_{A,x} + S_{P,x} \sum_{i \in \mathcal{A}} \beta_{P-i} I_{i,x} - (\gamma + \alpha_{PJ} + d_p + k_x N_x) I_{P,x} \tag{1D}$$

$$\dot{I}_{J,x} = \alpha_{PJ} I_{P,x} + S_{J,x} \sum_{i \in \mathcal{A}} \beta_{J-i} I_{i,x} - (\gamma + \alpha_{JA} + d_j + k_x N_x) I_{J,x} + \sum_{y \in \mathcal{P}} m_{J,x,y} (I_{J,y} - I_{J,x}) \tag{1E}$$

$$\dot{I}_{A,x} = \alpha_{JA} I_{J,x} + S_{A,x} \sum_{i \in \mathcal{A}} \beta_{A-i} I_{i,x} - (\gamma + d_A + k_x N_x) I_{A,x} + \sum_{y \in \mathcal{P}} m_{A,x,y} (I_{A,y} - I_{A,x}) \tag{1F}$$

$$\dot{R}_{P,x} = b_x(1 - \varphi_x N_x) M R_{A,x} + \gamma I_{P,x} - (\alpha_{PJ} + d_p + k_x N_x) R_{P,x} \tag{1G}$$

$$\dot{R}_{J,x} = \alpha_{PJ} R_{P,x} + \gamma I_{J,x} - (\alpha_{JA} + d_j + k_x N_x) R_{J,x} + \sum_{y \in \mathcal{P}} m_{J,x,y} (R_{J,y} - R_{J,x}) \tag{1H}$$

$$\dot{R}_{A,x} = \alpha_{JA} R_{J,x} + \gamma I_{A,x} - (d_A + k_x N_x) R_{A,x} + \sum_{y \in \mathcal{P}} m_{A,x,y} (R_{A,y} - R_{A,x}) \tag{1I}$$

where all parameter and variables are described in Table 1.

Because seasonal patterns of rainfall are known to influence reproduction in at least some *M. natalensis* populations [e.g., 16], as well as populations of other rodents [17], our model allows the birth rate to fluctuate in response to precipitation. Specifically, we assume that the current birth rate of a population at location x depends on the average precipitation that has fallen at the location over the previous 30 days, \bar{P}_x . Allowing the sensitivity of current birth rate to average precipitation to be tuned by the parameter ρ yields the following function describing the birth rate at location x and time t :

$$b_x(t) = \frac{b_M \bar{P}_x}{\rho + \bar{P}_x} \tag{2}$$

where \bar{P}_x for each location x is calculated by averaging daily precipitation values provided by the CHIRPS 2.0 database [18] for the 0.05 degree grid square in which the latitude and longitude of the location x fall.

Although our model is sufficiently general to allow for both density dependent mortality and birth, different rates of transmission between age classes, and an arbitrary number of populations connected by variable rates of movement, our analyses focus on two simplified

Table 1. Model variables and parameters.

Variables/ Parameters	Biological interpretation
\mathcal{A}	The set of all age classes
\mathcal{P}	The set of all populations
N_x	The total number/density of <i>M. natalensis</i> juveniles and adults in location x
$S_{i,x}$	The number/density of Lassa virus susceptible <i>M. natalensis</i> in age class i at location x (PCR-/Sero-)
$I_{i,x}$	The number/density of Lassa virus infected <i>M. natalensis</i> in age class i at location x (PCR+/Sero- and PCR+/Sero+)
$R_{i,x}$	The number/density of Lassa virus recovered/resistant <i>M. natalensis</i> in age class i and location x (PCR-/Sero+)
$b_x(t)$	<i>M. natalensis</i> birth rate at location x and time t
φ_x	Density dependent reduction in birth rate at location x
b_M	Maximum possible per capita birth rate for <i>M. natalensis</i>
ρ	The sensitivity of <i>M. natalensis</i> birth rate to precipitation
\bar{p}_x	Average precipitation at location x over the preceding ω days
k_x	Density dependent death rate of <i>M. natalensis</i> at location x
d_i	Density independent death rate of <i>M. natalensis</i> in age class i
α_{ij}	Maturation rate from age class i to age class j
$\beta_{i \rightarrow j}$	Transmission rate of Lassa virus from individuals in age class j to individuals in age class i . Horizontal transmission is assumed to occur only among juveniles and adults.
V	Probability of vertical transmission of Lassa virus infection
M	Probability of maternal antibody transfer
γ	Recovery rate from Lassa virus infection
$m_{i,x,y}$	Rate of movement between populations x and y for age class i
τ_i	Rate at which individuals in age class i are trapped

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scenarios. Specifically, we consider only density dependent mortality in the results reported in the main text as this is best supported by previous work in this system [16]. Key results for a model with density dependent birth are reported in the supplemental material. In addition, we assume horizontal transmission occurs only among juveniles and adults at a constant rate and focus on only a single pair of populations. These simplifications were made to reduce model complexity and improve inference in light of the limited data available for model parameterization. The project source code remains general, however, allowing any of these assumptions to be easily relaxed in future investigations.

Rodent capture data

We focus our inference procedure on data collected from a multi-year rodent trapping study conducted in Guinea between 2002 and 2005 [6, 14]. Rodents were trapped in two villages, Bantou and Tanganya, which are located in the prefecture of Faranah in Upper Guinea. These villages are separated by approximately 50 km, and were inhabited by around 1000 and 600 people respectively in 2003. The houses are round, made with mud and covered by a thatched roof. Rodents can easily enter into the houses through the roofs and openings at the base of the walls in which they dig burrows. Inside, they can be active both diurnally and nocturnally, when the houses are closed, independently of the presence of the owners [19]. Each captured rodent was identified, aged using eye lens weight, sexed, and screened for LASV infection using both PCR and Serology with details as previously described [6, 14]. We translated the original data into our SIR modeling framework by classifying individuals as juvenile if age

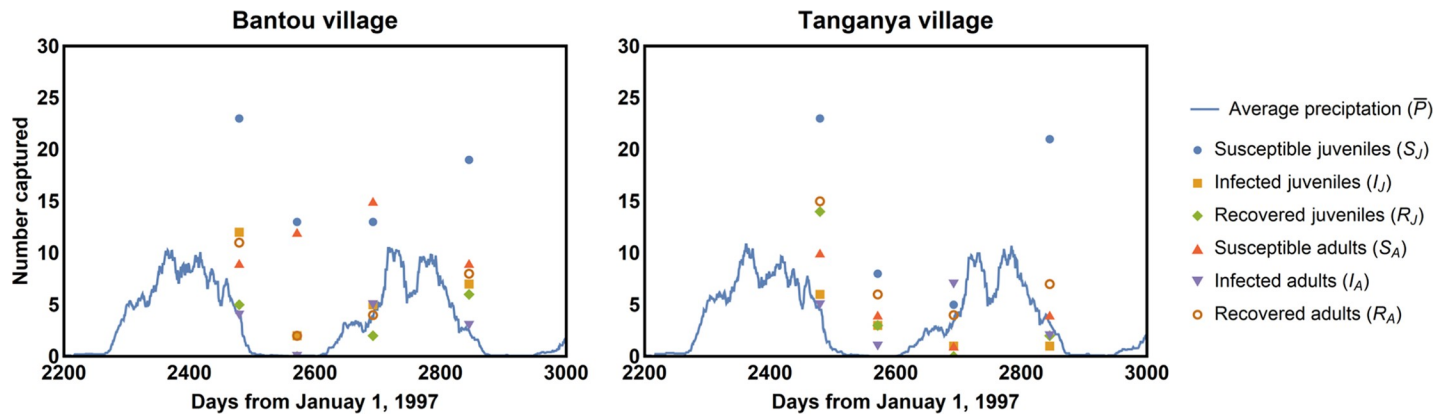


Fig 1. Time series data for the number of *M. natalensis* individuals captured within two villages in Guinea over four trapping sessions occurring between 2002–2005 (colored symbols). The blue lines indicate the 30-day average precipitation values for each village. *M. natalensis* capture data comes from the study described in [6, 14] and precipitation data comes from the CHIRPS 2.0 database. Although the original rodent trapping study included two additional dates, one of these is not shown because complete data on all classes was absent and the other is not shown and was not used due to a substantially reduced trapping effort we believed could compromise results.

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estimated from eye lens weight was less than 131.74 days and adult if estimated age was equal or greater than 131.74 days. We chose 131.74 days as the threshold because this is the average age of first reproduction for female *M. natalensis* within a captive colony of *M. natalensis* originally captured in Mali and housed at Rocky Mountain Laboratories (S1 Table). Changing this threshold ± 10 days had no substantive impact on results. No pups (pre-weaning life stage) were captured so data on this age class are unavailable. Individuals were classified as susceptible (S) if they were PCR and serologically negative for Lassa virus, infected (I) if they were PCR positive for Lassa virus, and recovered/resistant if they were PCR negative for Lassa virus but serologically positive. Using these definitions to translate the data into our modeling framework results in a time series for each village describing the number of juvenile and adult *M. natalensis* that are susceptible, infectious, or recovered at each sampling time point (Fig 1). The numerical data underpinning this figure can be found in S2 Table.

Approximate Bayesian computation

Because our model is too complex to solve analytically and does not allow expressions for the likelihood of observed time-series data to be explicitly formulated, we developed an Approximate Bayesian approach. Specifically, our mechanistic model is parameterized using Approximate Bayesian Computation (ABC). In brief, ABC works by: 1) drawing parameters at random from prior distributions informed by existing data, 2) simulating data under the model (i.e., a time series of *M. natalensis* abundance and infection status), and 3) placing the randomly drawn parameters into the posterior distribution only if the simulated data is sufficiently close to the real data. Repeating this process ultimately results in an approximate posterior distribution for model parameters [20–22]

Our implementation of ABC relies on simulating the model (1–2) using parameters drawn from the prior distributions shown in Table 2 and daily precipitation data for each geographic location downloaded from the CHIRPS 2.0 database [18]. We used the Gillespie algorithm [23] to stochastically simulate the analogous continuous-time Markov chain version of Eqs (1–2), with simulations initiated 2479 days prior to the start of rodent sampling to allow ecological and epidemiological dynamics to burn into a stationary distribution prior to comparing simulated and real data. To compare simulated values of rodent abundances to real data on

Table 2. Prior distributions for model parameters.

Parameter	Prior	Biological Justification
b_M	Gamma with mode 0.2148 and shape 50.0	The mode was selected to match the maximum rate of offspring production in a captive colony from Mali where females can produce an average of 10.74 pups every 25 days (S1 Table).
ρ	Uniform on [0.0, 0.5]	The range was selected to reproduce <i>M. natalensis</i> population dynamics ranging from mild seasonality as observed in Guinea [24] to strong seasonality as observed in Tanzania [15]
k_x	Uniform on $[6.0 \times 10^{-6}, 3.8 \times 10^{-5}]$	Chosen to yield biological plausible rodent population sizes of ≈ 600 –2,000 animals per location/village
d_p	Gamma with mode 0.001 and shape 20.0	Chosen to span the estimate used in [12]
d_j	Gamma with mode 0.003 and shape 3.0	Chosen to span the estimate used in [12]
d_A	Gamma with mode 0.005 and shape 3.0	Chosen to span the estimate used in [12]
α_{pj}	Gamma with mode 0.05 and shape 30.0	Modal value corresponds to weaning occurring 20 days after birth, on average. This is the average date of weaning in a captive colony from Mali (S1 Table).
α_{jA}	Gamma with mode 0.009 and shape 20.0	Modal value corresponds to reproductive maturity occurring 131.74 days after birth, on average. This is the average date of first reproduction in a captive colony derived from Mali (S1 Table).
β	Uniform on $[3.0 \times 10^{-5}, 3.0 \times 10^{-4}]$	Corresponds to time averaged R_0 values ranging between ≈ 1.0 –4.0
V	Exponential with expected value 0.01	No data available for Lassa virus. Prior reflects biological plausibility.
M	Exponential with expected value 0.01	No data available for Lassa virus. Prior reflects biological plausibility.
γ	Gamma with mode 0.0476 and shape 20.0	Acute infection and viral shedding lasts, on average, for 21 days. Consistent with, estimates for related Morogoro virus [25], and rate assumed by [12]
$m_{i,x,y}$	Exponential with expected value 0.001	Spans single available estimate from Senegal [26].
τ_i	Gamma with mode 3.5×10^{-5} and shape 5.0	Set to yield trapping success rates consistent with those in the Guinean data set with biologically plausible rodent population sizes of ≈ 600 –2,000 animals per location/village

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numbers of rodents captured using traps, we implemented simulated rodent trapping experiments at each time point for which data was available. These simulated rodent capture experiments proceeded by drawing a random number from a binomial distribution for each rodent age/infectious class with the number of trials set to the number of trap nights in the trapping session and the probability of capture, p , set to the value:

$$p = 1 - \exp(-\tau_i C) \quad (3)$$

where τ_i is the rate at which rodents in age class i are trapped and C is the simulated population density of the class. Thus, the greater the population density of a particular class, the more likely individuals of this class are to be captured by a trap over the course of an individual trap night.

For each simulation, simulated trapping data and real trapping data were compared, and parameter combinations yielding simulated trapping data sufficiently close to the real trapping data were included in the posterior distribution. Specifically, parameter combinations were added to the posterior if two criteria were met. First, the total number of juvenile and adult animals captured in the simulated data must be within 25% of its true value, on average, across all trapping sessions and locations. Second, the sum of the absolute distance between frequencies of captured individuals belonging to infected juvenile (I_j), infected adult (I_A), juvenile recovered (R_j), and adult recovered (R_A) classes in the simulated and real data must be less than 0.5, on average, across all trapping sessions and locations.

Before applying our ABC method to real data, we evaluated its performance by testing on simulated data sets. Details of simulation testing of our ABC methodology and calculation of

the time-averaged R_0 are described in the supporting online material. These analyses demonstrated that our method generates 95% credible intervals that include the true value of all parameters in $\geq 90\%$ of simulated data sets and $\geq 95\%$ of simulated data sets for the majority of parameters as desired and expected. For only a subset of model parameters, however, does our method reveal a significant positive relationship between the point estimate for the parameter and its true value in the simulated data. Specifically, the correlation between estimated and simulated parameter values exceeds 0.5 for only the following parameters: 1) the rate of horizontal transmission (β), 2) the rate of recovery from viral infection (γ), 3) the strength of density dependent mortality (k_X), and 4) the sensitivity of birth rates to past precipitation (ρ). In addition, testing against simulated data revealed that our method accurately estimates the time-averaged value of the composite epidemiological parameter R_0 , which measures the average number of new infections produced by a single infected individual (Fig 2).

Animal studies

To make prior distributions for model parameters as accurate as possible, we supplemented information available from published studies with information derived from ongoing studies of a captive colony of *M. natalensis*. Specifically, unpublished data from a captive colony derived from Mali and housed at Rocky Mountain National Laboratories (RML) was used to refine prior distributions for maximum possible birth rate, b_M , age at weaning, α_{PJ} , age at first reproduction, α_{JA} , and duration of viral shedding, γ .

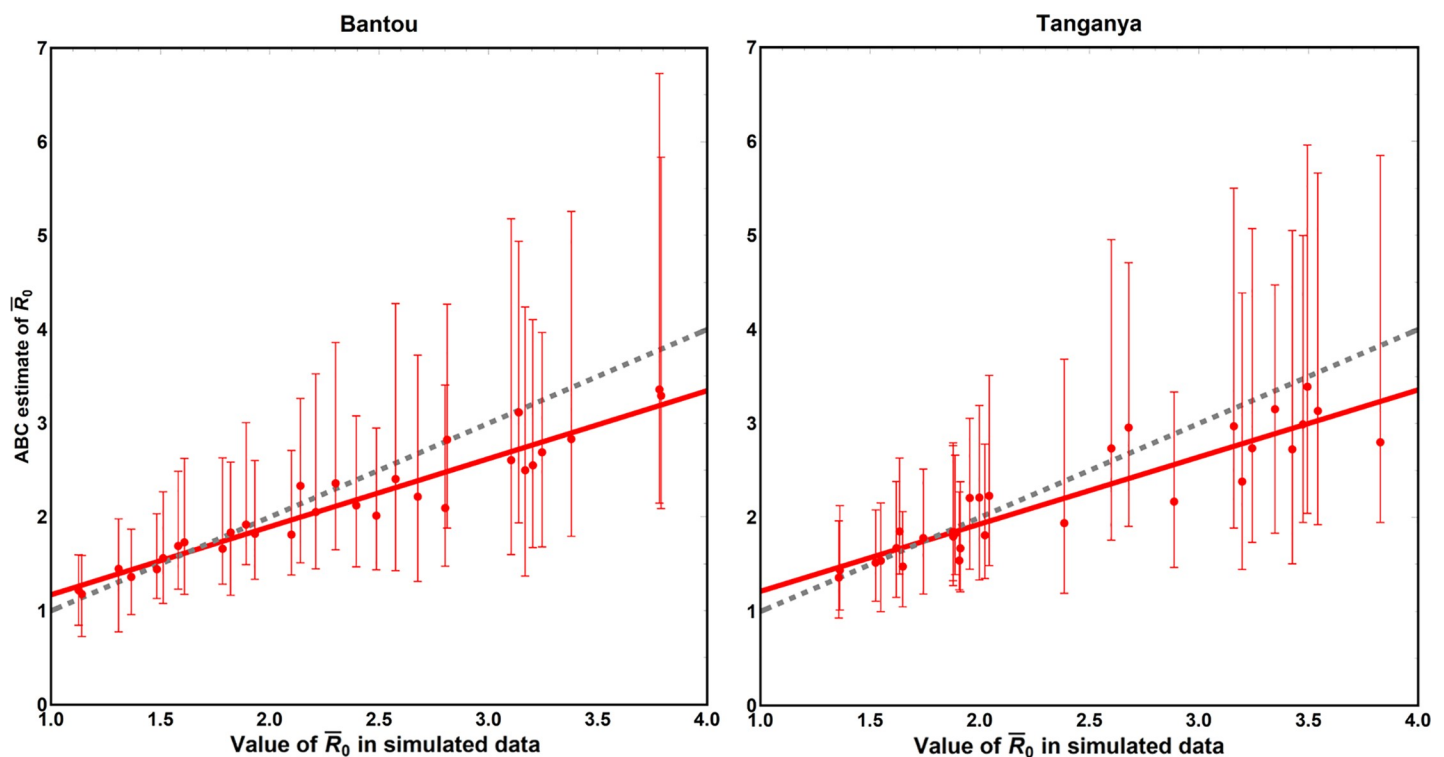


Fig 2. Comparison of time average values of R_0 in simulated data sets (x axes) and the values of time averaged R_0 estimated by our ABC approach (y-axes) when applied to the simulated data sets. The red dots indicate individual simulations, the red line the best fit to the dots, and the gray dashed line is the expected 1:1 relationship for a perfect fit. The equation for the line of best fit was given by $y = 0.447 + 0.725x$ for Bantou and by $y = 0.501 + 0.714x$ Tanganya where y is the value estimated by our ABC method and x is the true value in the simulated data set.

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Mastomys

All mice were bred and maintained under pathogen-free conditions at an American Association for the Accreditation of Laboratory Animal Care accredited animal facility at RML and housed in accordance with the procedures outlined in the Guide for the Care and Use of Laboratory Animals under an animal study proposal approved by the RML Animal Care and Use Committee. *Mastomys natalensis* are placed in breeding pairs between 5–6 weeks of age. Animals are health checked at least once daily and new litters are recorded on the cage card. At the identification of a new litter, the pups are counted and recorded on the cage card. The date of birth is recorded for each animal which allows for an accurate determination of age at first litter (reproduction). Weaning occurs when pups are able to eat normal feed, usually around day 21. Since cages are checked daily for litters, the inter-litter interval is easily determined for each individual dam. Life history data for this colony is available in [S1 Table](#).

Simulating reservoir vaccination campaigns

When applied to the time-series data on rodent captures from the villages of Bantou and Tanganya in Guinea, our ABC approach results in a multi-dimensional posterior distribution describing the probability of various parameter combinations. Drawing parameter combinations from this posterior probability distribution and simulating forward in time while implementing vaccination allowed us to generate probabilistic predictions for the impact of different vaccination regimes. Specifically, we considered vaccination campaigns that rely on distributing vaccine-laced baits into both Bantou and Tanganya villages. We assume baits are distributed randomly at a daily rate, σ , and consumed by juvenile and adult rodents; pups do not consume vaccine baits prior to weaning. Pups can, however, be immunized through maternal transfer of protective antibodies with probability M , if born to a vaccinated mother. For simplicity, we assume consumption of a vaccine bait results in immediate, lifelong, complete immunity to Lassa virus. Because we assume baits are consumed by rodents at random, our model captures the reality that some proportion of vaccine bait is wasted on animals that are already infected with Lassa virus or recovered from prior Lassa infection and thus already immune. Specifically, the rate at which susceptible rodents of age class i (juvenile or adult) consume vaccine bait and become immune is given by:

$$\mathcal{V}_i = \sigma \frac{S_i}{S_J + S_A + I_J + I_A + R_J + R_A} \quad (4)$$

where the denominator is the total number of actively foraging rodents. The quantity \mathcal{V}_i was capped at the number of susceptible individuals in class i .

We considered vaccination regimes that distributed between 500–10,000 individual baits annually over a period ranging from 7–168 days. In addition, we evaluated vaccination campaigns that began distributing bait in November (wet to dry transition) and those that began distributing bait in May (dry to wet transition). These temporal patterns were chosen because our ABC analysis revealed that reproduction in the *M. natalensis* population is maximal in November and minimal in May, and because previous work has demonstrated that the effectiveness of wildlife vaccination campaigns can be improved by focusing vaccination on periods of high reproduction [27]. For each combination of bait number, baiting duration, and timing of bait distribution, we calculated the probability that Lassa virus was eliminated from both study villages (Bantou and Tanganya), and the average number of Lassa infected rodents over 100 replicate stochastic simulations.

Results

Parameter estimation for the Lassa virus pathosystem

We applied our ABC method to the rodent trapping data collected from the villages of Tanganyika and Bantou in Guinea until the posterior distribution accumulated 19,992 points. Univariate analysis of marginal posterior distributions allowed us to calculate modal values and credible intervals for all model parameters (Table 3). Our analysis of simulated data revealed that only a subset of model parameters can be accurately and reliably estimated from the data, and accordingly, we focused on this subset of parameters here. Modal values for the remaining parameters differed little, if any, from the modal values of their prior distributions, consistent with our analyses of simulated data showing that little signal exists in the data for the value of these parameters (S1 Text).

Posterior distributions for those parameters reliably estimable from the data were generally well-resolved. For instance, the rate of horizontal transmission of Lassa virus among juvenile and adult *M. natalensis* showed a well-defined peak at $\beta = 1.45 \times 10^{-4}$ and the strength of density dependent mortality had clear univariate modes at $k = 1.455 \times 10^{-5}$ in Bantou and $k = 1.96 \times 10^{-5}$ in Tanganyika (Fig 3). Similarly, the posterior distribution for the parameter ρ that quantifies the sensitivity of *M. natalensis* birth rates to past precipitation had a clear mode near zero ($\rho = 0.008$), suggesting only weak seasonality (Fig 4). To better understand the consequences of the full multi-dimensional posterior distribution for the population and epidemiological dynamics of the system, and to compare these predicted dynamics to the original data from Bantou and Tanganyika, we repeatedly sampled from the posterior distribution and simulated model dynamics using precipitation data for each village from the CHIRPS 2.0 database. This analysis demonstrated that seasonal fluctuations are significant (although modest relative to those observed for *M. natalensis* in other well-studied populations in East Africa) and that our 95% prediction intervals include 87.5% of the original data points (Fig 5).

To gain further insight into the epidemiological dynamics of Lassa virus within these villages, we generated posterior distributions for the time average value of R_0 within each village

Table 3. Univariate modes and 95% credible intervals (highest posterior density) for model parameters.

Parameter	Mode	95% Credible interval
b_M	0.222	{0.152, 0.266}
ρ	0.008	{0, 0.400}
k_{Bantou}	1.455×10^{-5}	$\{6.32 \times 10^{-6}, 2.78 \times 10^{-5}\}$
$k_{Tanganyika}$	1.96×10^{-5}	$\{8.86 \times 10^{-6}, 3.29 \times 10^{-5}\}$
d_P	0.0010	{0.0005, 0.0014}
d_J	0.0028	{0.000, 0.0089}
d_A	0.0037	{0.000, 0.0127}
α_{PJ}	0.0523	{0.0337, 0.0675}
α_{JA}	0.0103	{0.0064, 0.0142}
β	1.45×10^{-4}	$\{6.00 \times 10^{-5}, 2.50 \times 10^{-4}\}$
V	0.0017	{0, 0.0297}
M	0.0014	{0.0, 0.0287}
γ	0.0457	{0.0283, 0.0631}
m_J	1.91×10^{-4}	{0, 0.003}
m_A	1.90×10^{-4}	{0, 0.003}
τ_J	4.36×10^{-5}	$\{1.38 \times 10^{-5}, 7.81 \times 10^{-5}\}$
τ_A	5.24×10^{-5}	$\{1.85 \times 10^{-5}, 9.25 \times 10^{-5}\}$

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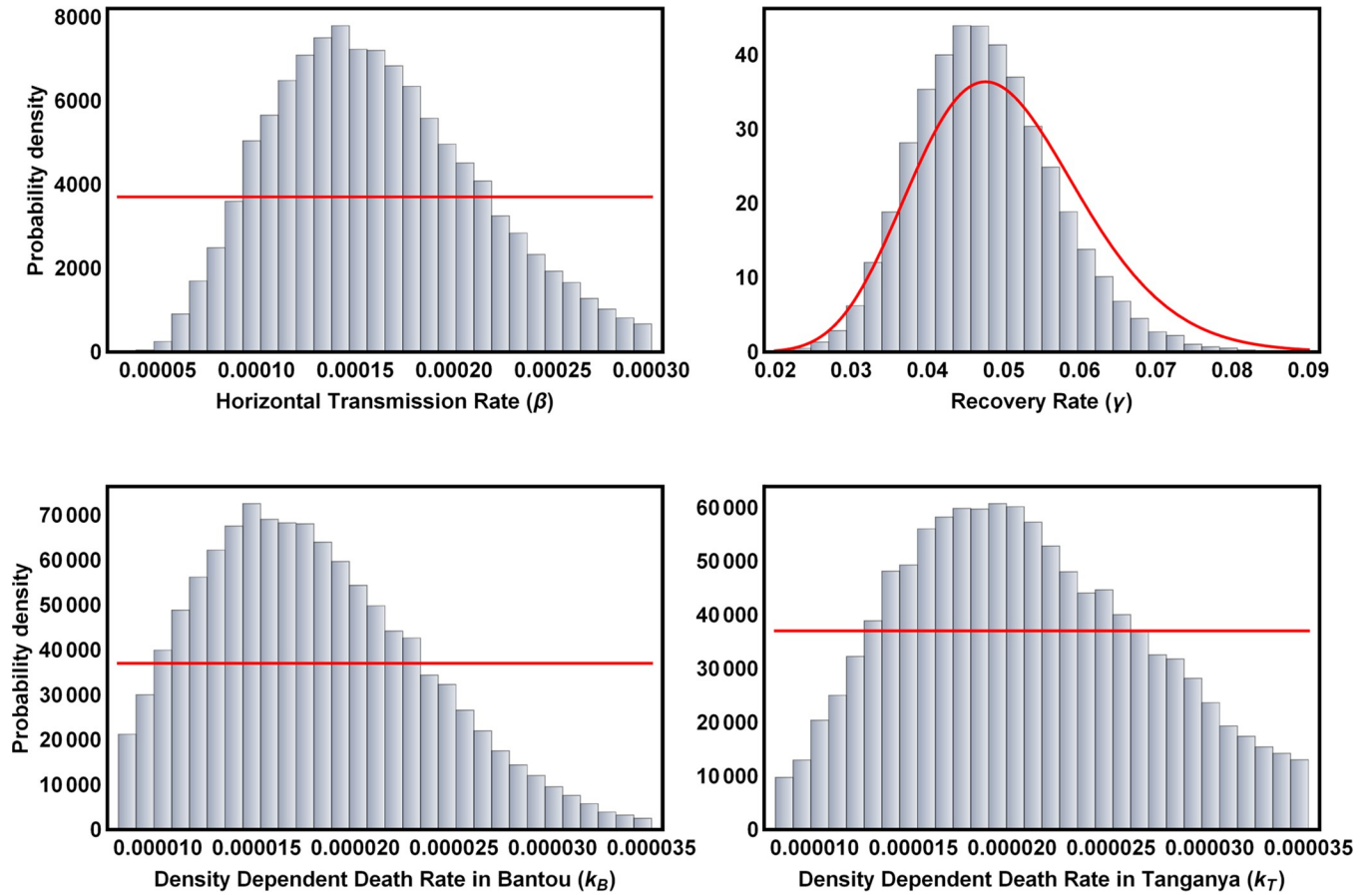


Fig 3. Posterior distributions for key model parameters estimated by our ABC method when applied to time series data from the villages of Bantou and Tanganya. The red lines show the prior distribution for each parameter and the bars the posterior probability density.

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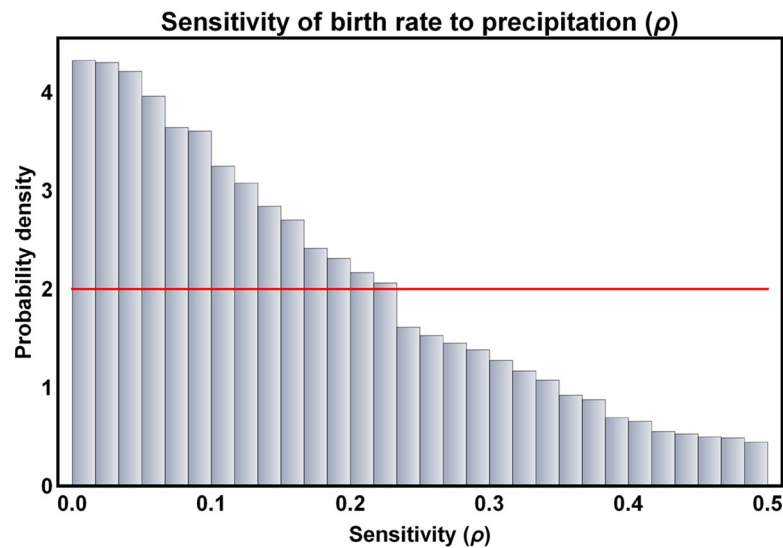


Fig 4. Posterior distribution for the sensitivity of birth rate to average precipitation over the preceding 30 day interval (ρ). The red line shows the prior distribution and the bars indicate the posterior probability density.

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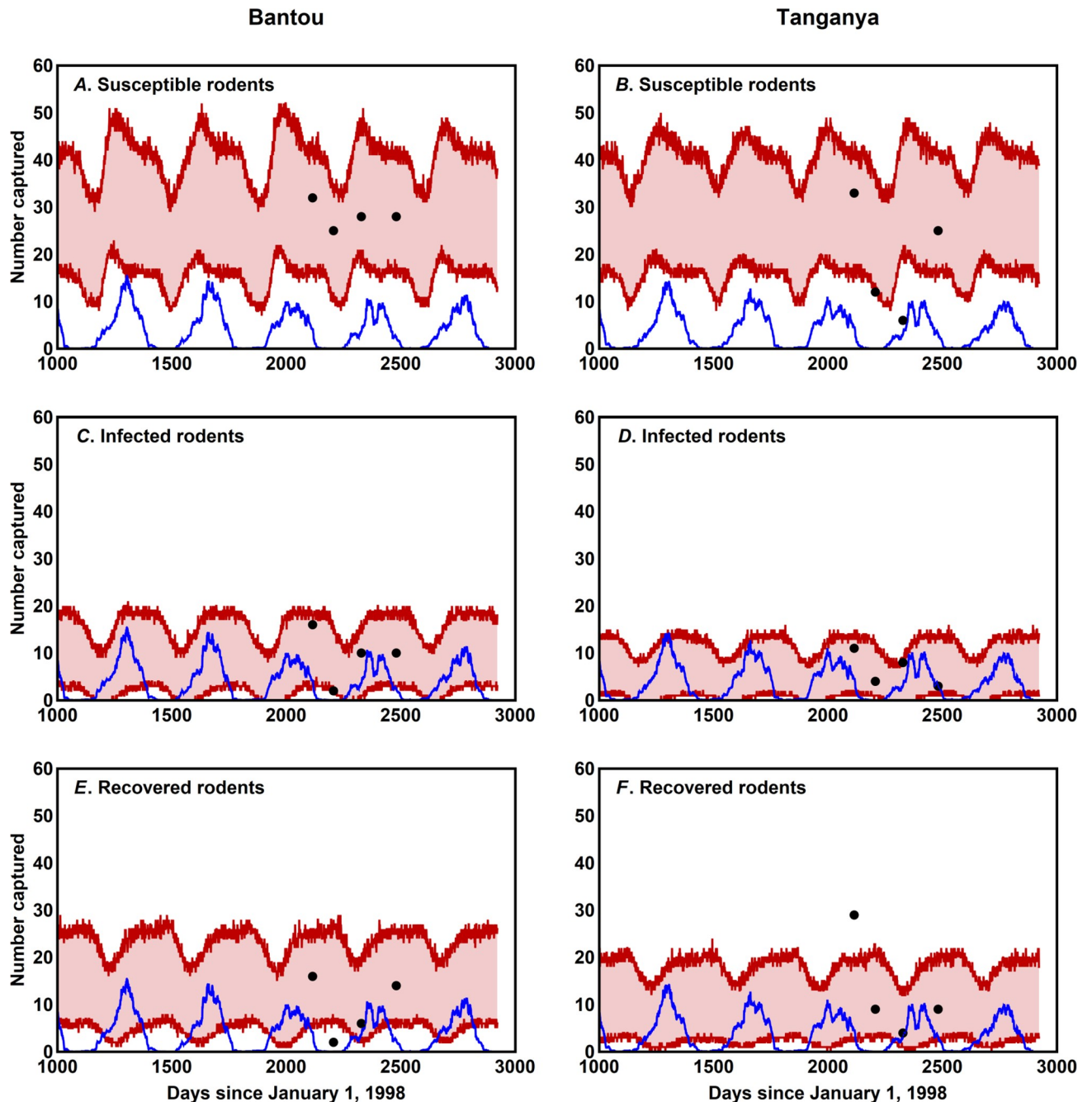


Fig 5. The predicted population and epidemiological dynamics of *M. natalensis* and Lassa virus within the villages of Bantou and Tanganya over a period spanning the original field study. The first row shows the prediction interval (pink area between red lines) for the number of captured rodents in the S class with black dots indicating capture data from the original study and the blue line average rainfall over the preceding thirty days. The second row shows the same quantities but for rodents in the I class, and the third row for rodents in the R class. Prediction intervals were generated by: 1) drawing parameter vectors at random from the posterior distribution, 2) Simulating dynamics forward in time using precipitation data for each village from the CHIRPS 2.0 database, 3) Conducting daily simulated rodent trapping experiments, 4) repeating this procedure for 200 random draws from the posterior distribution, and 5) calculating 95% prediction interval for each day by eliminating the upper and lower 2.5% of simulated captures.

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(Fig 6). The modal values and credible intervals for R_0 varied somewhat across villages, with modal values of 1.74 and 1.54 and credible intervals of {1.33, 2.32} and {1.17, 1.90} in Bantou and Tanganya, respectively. Using a classical result from epidemiological theory [28], these

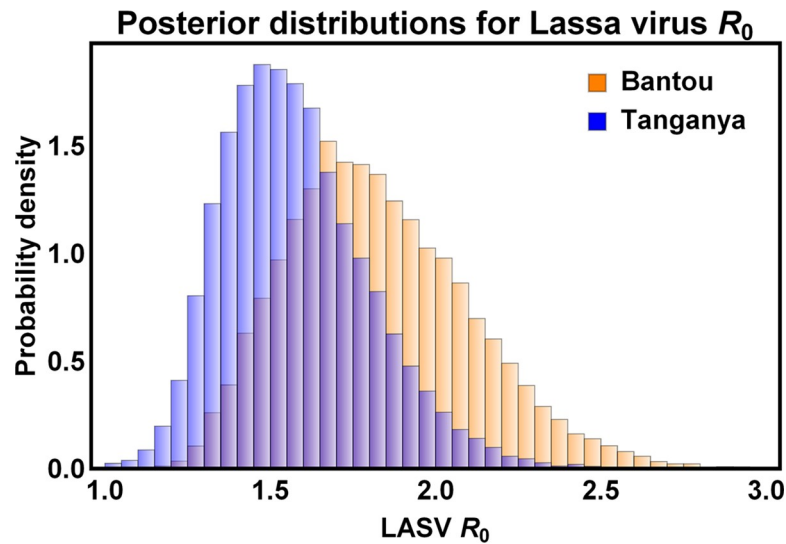


Fig 6. Posterior distributions for the time averaged value of R_0 inferred by our ABC method for the villages of Bantou (orange) and Tanganya (blue). The modal values and credible intervals for R_0 varied somewhat across villages, with modal values of 1.74 and 1.54 and credible intervals of {1.32, 2.32} and {1.17, 1.90} in Bantou and Tanganya, respectively.

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values of R_0 suggest that vaccination thresholds of 42.5% in Bantou and 35.1% in Tanganya would be sufficient for local elimination of Lassa virus from the reservoir population. Although these values suggest the feasibility of rodent vaccination, they rest on several important assumptions, including being able to vaccinate individuals prior to exposure by Lassa virus and population dynamics that are at a steady state. In contrast, vaccinating individuals prior to Lassa exposure is challenging and *M. natalensis* population dynamics are unlikely to be at a steady state. To explore how these features of the system influence the vulnerability of Lassa virus to rodent vaccination campaigns, we simulated reservoir vaccination campaigns using our mathematical model parameterized with the multi-dimensional posterior distribution derived from the villages of Bantou and Tanganya.

Simulating reservoir vaccination campaigns

Results of simulated vaccination experiments with parameters drawn repeatedly from the posterior distributions demonstrate that eliminating Lassa virus from both villages by distributing conventional vaccine baits is extremely challenging and requires a level of bait distribution greatly in excess of existing wildlife vaccination programs. Specifically, our results show that the probability of eliminating Lassa virus from both Bantou and Tanganya villages is negligible when modest numbers of baits are distributed in each village every year (Fig 7). Only when thousands of baits are distributed annually over at least several weeks does the elimination of Lassa virus become a possibility (Fig 7). Results for reductions in the number of infected rodents are more encouraging, at least over the short term, with an appreciable reduction in the number of Lassa virus infected rodents achievable with distribution of one thousand or so baits per village per year (Fig 8). Notably, these reductions in the number of infected rodents were transient, with infections returning to near pre-vaccination campaign levels within 180 days following the end of the vaccination campaign (Fig 8, compare across rows). Comparing the results of vaccination campaigns that distribute baits when birth rates are at their peak (November) with vaccination campaigns that distribute baits when birth rates are at their

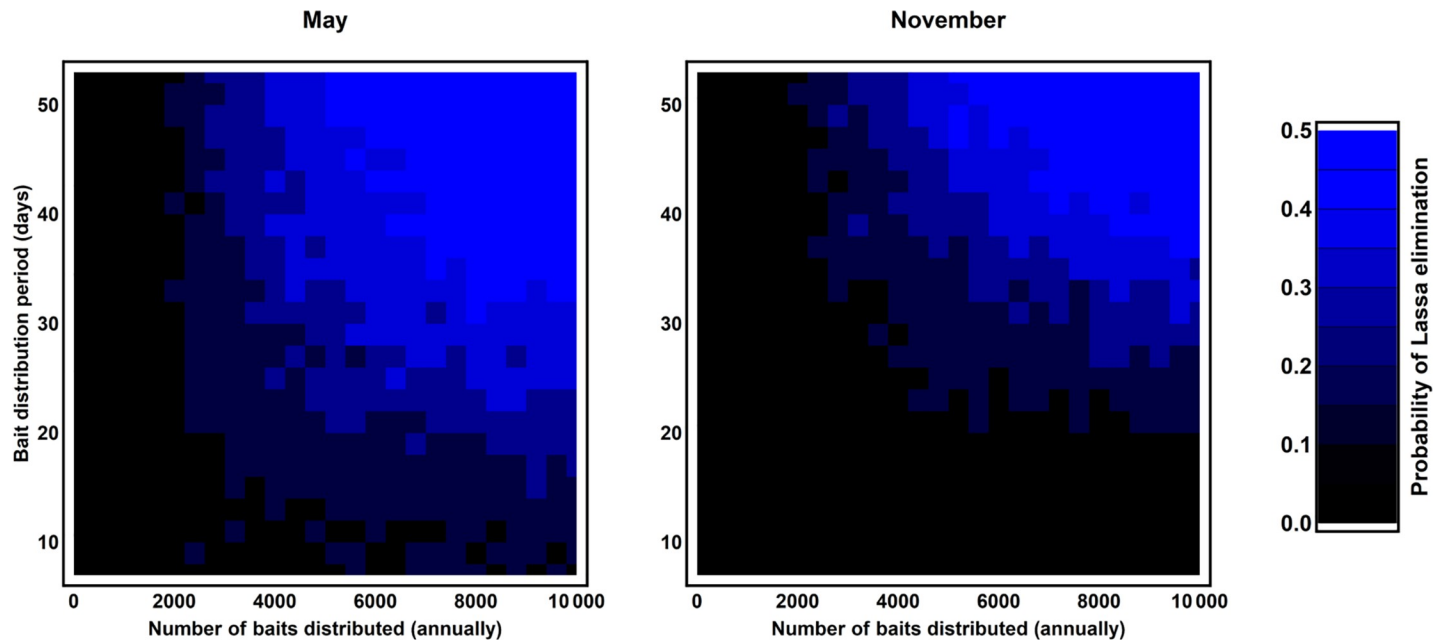


Fig 7. The proportion of simulated vaccination campaigns resulting in the simultaneous elimination of Lassa virus from the villages of Bantou and Tanganya as a function of the number of vaccine-laced baits distributed per year (x axis) and the duration of bait distribution (y axis). The left-hand column shows results for campaigns where vaccination occurs in May when birth rates are minimized (bait distribution begins May 1 of each year), and the right hand column campaigns where vaccination occurs in November when birth rates are maximized (bait distribution begins November 1 of each year).

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minimum (May) suggests there may be slight benefits to distributing baits during November in terms of reductions in density of infected rodents but slight benefits to distributing baits during May in terms of increasing the probability of local pathogen elimination (Figs 7 and 8, compare left and right hand columns). If density regulation operates on birth rates, rather than death rates as we have assumed here, control of Lassa virus using vaccine laced baits becomes more feasible. Specifically, results presented in the Supporting Online Material show that local pathogen elimination can then be achieved by distributing hundreds, rather than thousands, of baits within each village and year (S1 Fig). This result emphasizes the importance of understanding basic mechanisms of population regulation for planning and implementing wildlife vaccination campaigns.

Discussion

We have developed an Approximate Bayesian Computation (ABC) approach for estimating demographic and epidemiological parameters of Lassa virus and its natural reservoir *M. natalensis* using time-series data on rodent captures. Extensive testing of our approach using simulated data sets demonstrates accurate estimation of key parameters such as the rate of horizontal transmission, the strength of density dependent mortality, and the sensitivity of birth rates to seasonal patterns of precipitation. In addition, our approach allows accurate estimation of the time-averaged value of the composite parameter R_0 , quantifying the average number of new Lassa virus infections produced by a Lassa infected rodent introduced into an entirely susceptible population. Applying our approach to previously published data collected from two villages in Guinea [6, 14] allowed us to develop estimates for epidemiological and demographic parameters, including robust estimates for the average R_0 of Lassa virus within its animal reservoir ($R_0 = 1.74$ in Bantou and $R_0 = 1.54$ in Tanganya). Although these estimates

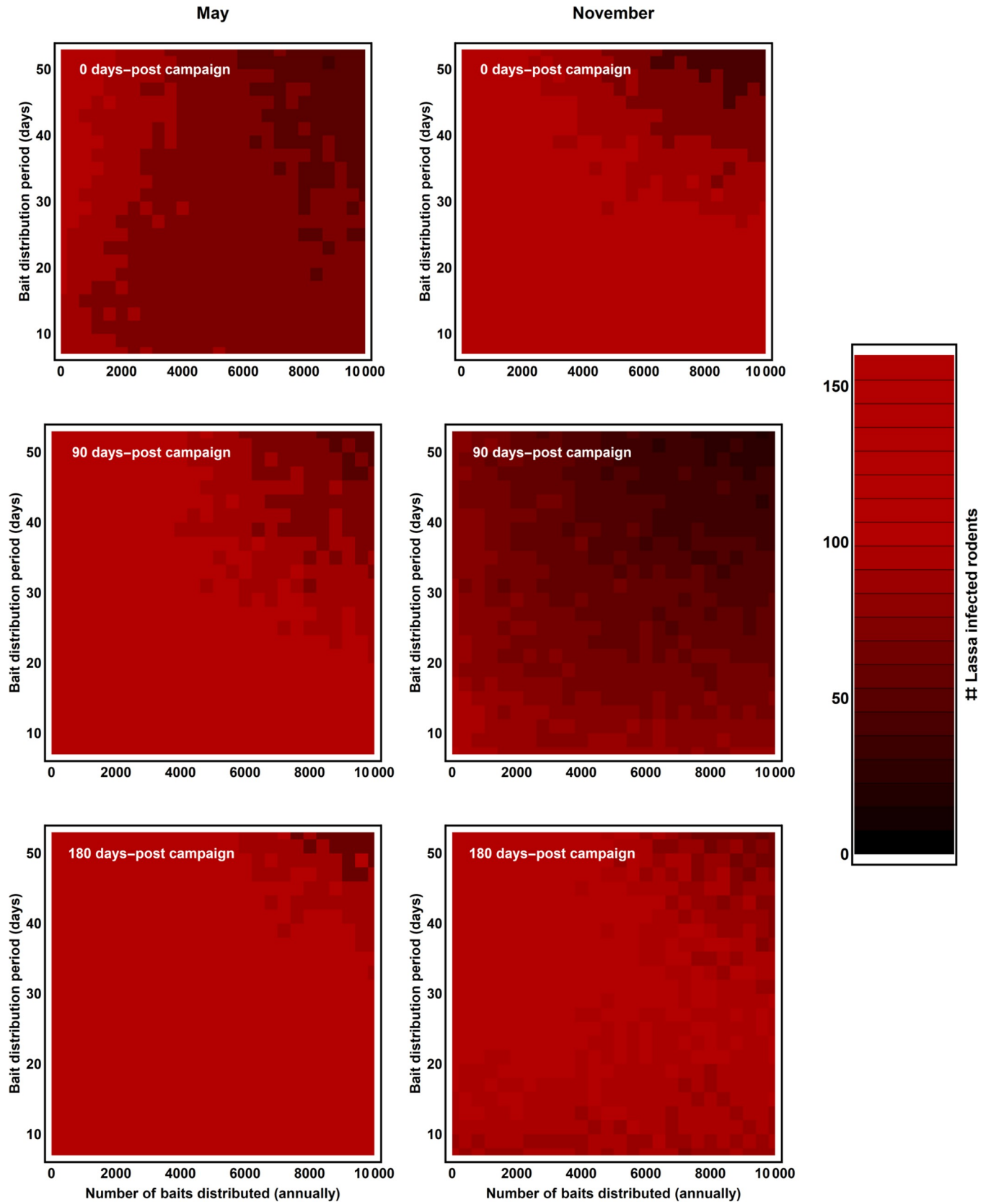


Fig 8. The number of *M. natalensis* infected with Lassa virus 0, 90, and 180 days after the end of simulated vaccination campaigns (rows) as a function of the number of vaccine laced baits distributed per year (x axis) and the duration of bait distribution (y axis). The left-hand column shows results for campaigns where vaccination occurs in May when birth rates are minimized (bait distribution begins May 1 of each year), and the right hand column campaigns where vaccination occurs in November when birth rates are maximized (bait distribution begins November 1 of each year). Reductions in Lassa virus infection within the reservoir population accomplished by vaccination dissipate rapidly, with only modest reductions remaining 180 days after even the most intense vaccination campaigns cease.

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of R_0 suggest Lassa virus may be vulnerable to vaccination campaigns targeting the rodent reservoir, *M. natalensis*, extensive simulated vaccination campaigns suggest distribution of conventional vaccine as bait may be ineffective unless an extremely high number of baits were regularly distributed.

There are at least two reasons reservoir vaccination is ineffective in our simulated vaccination campaigns. First, relatively large proportions of *M. natalensis* individuals within Guinea are known to be infected with Lassa virus or previously infected and recovered (9.1%–66.7% in the villages of Bantou and Tanganya). As a consequence, a large fraction of vaccine-laced baits will be consumed by rodents that are already infected by, or immune to, Lassa virus. Thus, to the extent that immunity to Lassa virus is lifelong as we have assumed here, only a relatively small fraction of distributed vaccine finds its way to its intended target. This contrasts with the case of rabies where relatively few animals are actively infected and high virulence prevents previously infected and immune animals from accumulating within the population [29]. Second, the extremely high birth rate of the *M. natalensis* reservoir population causes immunity to wash out of the population very rapidly, with our simulations demonstrating that the impact of vaccine distribution generally lasts for less than 120 days once vaccine distribution ceases. If density dependence acts on birth rates rather than death rates as we have assumed here, the outlook for vaccination improves due to a reduction in birth rate (S1 Fig). Recent work using a different modeling framework and alternative assumptions came to a slightly more optimistic conclusion [12], most likely because direct vaccination of only susceptible individuals was assumed rather than the more realistic model of random bait consumption considered here.

At least two alternatives to the random distribution of vaccine laced baits could be promising: 1) coupling rodent removal through poisoning or trapping with distribution of conventional vaccine laced baits, or 2) vaccination through the use of transmissible vaccines. In the first, the impact of rodent vaccination may be enhanced by coupling the distribution of vaccine laced baits with intensive rodent culling. Although culling alone is insufficient to eliminate Lassa virus within *M. natalensis* [12], by reducing the number of foraging rodents it may substantially reduce the number of vaccine baits required to reduce or eliminate pathogen infection, at least over the short term [e.g., 30]. In some cases where culling has been employed and studied, however, it has been shown to have potentially counter-intuitive impacts, potentially increasing the prevalence of the target pathogen [31, 32]. A second alternative to conventional vaccination relies on the use of transmissible vaccines capable of transmitting infectiousness within the target population [33–35]. Transmissible vaccines have been shown to substantially improve the likelihood of eliminating infectious disease in theoretical studies, but have been explored empirically in only a small number of cases [33, 34, 36, 37]. A transmissible vaccine targeting Lassa virus could potentially overcome the significant hurdles confronting traditional vaccination in this system. For instance, using formula derived in [35] along with the estimates for the time-averaged value of R_0 in the Guinean populations we have derived here, shows that even a weakly transmissible vaccine with an $R_0 = 1.0$ could reduce the number of baits that must be distributed by 57% in Bantou and 65% in Tanganya. A more strongly transmissible vaccine with an R_0 in excess of 1.74 could allow Lassa virus to be autonomously eliminated from these populations.

Although our ABC approach allowed us to robustly estimate some epidemiological and demographic parameters, other parameters proved to be more challenging to estimate. Fortunately, most of these have been independently estimated in other studies (see Table 2), allowing their prior distributions to be defined with a relatively high degree of confidence. However, a number of parameters that our method is unable to estimate accurately have not been independently estimated (e.g., rates of Lassa virus vertical transmission) or have been estimated, but only in distant locations with substantial differences in rodent ecology (e.g., Tanzania)[15, 38]. Because of these limitations, there is some inevitable uncertainty in our estimates for model parameters. By generating our predictions for the efficacy of vaccination programs by repeatedly drawing parameters at random from the posterior distribution, however, this uncertainty is faithfully represented in predicted outcomes. In addition to assumptions about the likely values of a few poorly understood model parameters, our approach relies on a mathematical model that simplifies population age structure, assumes density-dependent infection and spatially-homogenous transmission rates. Relaxing these assumptions could, in principle, alter our quantitative estimates for some model parameters [39]. Finally, our estimates of parameters are based on data collected over 14 years ago, creating the possibility that ecological, sociological, or evolutionary change in Lassa virus, the reservoir *M. natalensis*, or human populations with which the reservoir is commensal have caused values of important parameters to change.

Lassa virus is among the highest priority zoonotic pathogens identified by the World Health Organization and is a key emerging threat to human health [40]. Curtailing this significant threat to public health will likely require a combination of synergistic efforts including reservoir vaccination, targeted rodent control, reducing risky human behavior, and human vaccination campaigns. The ABC approach we have developed here provides a robust method for estimating key epidemiological parameters of Lassa virus and for predicting the likely effectiveness of these various types of intervention both individually and in combination. As additional field and experimental studies accrue, our ABC approach can be used to update and refine parameter estimates and predictions for intervention impacts within Guinea, and also to develop predictions for other regions with substantial differences in rodent ecology. Only through rigorous evidence-based analyses and investigations of the impacts of all potential control options can global resources be effectively leveraged to combat this and other high-consequence threats to global health security.

Supporting information

S1 Table. Summary statistics for *M. natalensis* life history traits calculated for 18 breeding groups in a captive colony from Mali.

(PDF)

S2 Table. Rodent capture data stratified by age class and infection status. Rows do not always sum to totals due to gaps in viral diagnostics that prevented individuals from being assigned to a category.

(PDF)

S1 Text. Evaluating the performance of ABC using simulated data, calculating time averaged R_0 , and results for density dependent birth.

(DOCX)

S1 Fig. The proportion of simulated vaccination campaigns resulting in the simultaneous elimination of Lassa virus from the villages of Bantou and Tanganya as a function of the number of vaccine laced baits distributed per year (x axis) and the duration of bait distribution (y

axis). The left-hand column shows results for campaigns where vaccination occurs in May when birth rates are minimized (bait distribution begins May 1 of each year), and the right hand column campaigns where vaccination occurs in November when birth rates are maximized (bait distribution begins November 1 of each year). The model used to generate this figure assumed density dependence acts on birth rather than death as in the main text. (TIF)

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