

Quantifying spillover risk with an integrated bat-rabies dynamic modeling framework

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Abstract

Vampire bat-transmitted rabies has recently become the leading cause of rabies mortality in both humans and livestock in Latin America. Evaluating risk of transmission from bats to other animal species has thus become a priority in the region. An integrated bat-rabies dynamic modeling framework quantifying spillover risk to cattle farms was developed. The model is spatially explicit, and is calibrated to the state of São Paulo, using real roost and farm locations. Roosts and farms characteristics, as well as environmental data through ecological niche model, are used to modulate rabies transmission. Interventions in roosts (such as culling or vaccination) and in farms (vaccination) were considered as control strategies implemented to reduce risk. Both interventions significantly reduce the number of outbreaks in farms and disease spread (based on distance from source), with control in roosts being a significantly better intervention. High risk areas were also identified, which can support ongoing programs, leading to more effective control interventions.

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Summary

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keywords: bat rabies, infectious disease transmission, mathematical model, spillover

Introduction

Bats have long been associated with highly pathogenic zoonoses affecting domestic animal and human hosts (van Brussel and Holmes, 2022). Despite attempts to understand cross-species pathogen transmission from reservoir hosts to recipient hosts, there are still gaps in knowledge regarding the environmental conditions and mechanisms necessary for spillover events to occur (Ruiz-Averna et al., 2021).

In Latin America, vampire-bat-driven rabies (VBR) has come to attention as both an underappreciated and growing threat (Benavides et al., 2016), and is now the leading cause of both human and livestock rabies mortality in Latin America (Benavides et al., 2020; Horta et al., 2022). VBR is responsible for substantial agricultural and subsequent monetary losses, disproportionately affecting resource-poor farming communities that depend on agricultural economy (Benavides et al., 2017). It has been recently estimated that tens of thousands of livestock die of VBR annually, corresponding to financial losses between 30 to 50 million USD in the region (Benavides et al., 2020; Bakker et al., 2019). VBR is a member of the *Lyssavirus* genus; and similar to other lyssaviruses, disease pathology is marked by acute fatal encephalitis (Banyard et al., 2011; Rupprecht et al., 2017). Of the three species of hematophagous bats, *Desmodus rotundus* (Chiroptera: Phyllostomidae) is the most abundant and prefers to feed on livestock blood (Kuzmin & Rupprecht, 2015; Horta et al., 2022); this preference displays the species ability to adapt to anthropogenic ecological changes as it is believed during the pre-Columbian era *D. rotundus* fed upon large terrestrial mammals (Rocha et al. 2020). Instead of being negatively impacted by urbanization, deforestation, and a resultant decrease in wild prey, *D. rotundus* adapted to the new food sources resulting in an artificially high population (Delpietro et al. 1992; Rocha et al., 2020). The population changes might have implications for disease dynamics.

Mathematical modeling has been used extensively to understand spread dynamics and improve surveillance and control strategies for many infectious diseases (Grassly and Fraser, 2008; Chowell et al., 2016; Dorratoltaj et al., 2017; Bornaa et al., 2020). Several frameworks have been proposed to model the dynamics of rabies transmission, approaching the problem from different perspectives (Dimitrov et al., 2007; Blackwood et al., 2013; Ruan, 2017; Gentles et al., 2020; Dias and Ulloa-Stanojlovic, 2021). Here we present a stochastic network model designed to capture the spatial heterogeneity of VBR transmission between known bat roosts in the state of São Paulo, Brazil, and spillover events into the local cattle farms. We explore the effect of different combinations of current reactive interventions, namely vaccination of cattle in confirmed VBR positive farms and other nearby farms, and vampire bat roost control in surrounding areas (Rocha and Dias, 2020). Currently, as a roost control, Warfarin is applied on the back of the captured vampire bats as anticoagulant paste that is spread between bats by themselves during socializing and grooming, they subsequently die of hemorrhage (Rocha et al., 2020). Both ethical and scientific arguments exist against bat culling (Olival, 2016). Moreover, indiscriminate culling may lead to social disruptions in the roosts, which facilitates pathogen spread (Benavides et al., 2020; Rocha and Dias, 2020). As a less controversial alternative and arguably more effective, spreadable vaccine may be administered in a similar manner (Standing et al., 2017; Bakker et al., 2019; Griffiths et al., 2022). Risk maps for each combination of current control measures used in the area of interest, the state of São Paulo, Brazil, are provided.

Materials and methods

Study area and databases

A mathematical modeling framework was developed that broadly represents disease dynamics of VBR transmitted between *D. rotundus* roosts and cattle farms within the state of São Paulo, Brazil. Data on bats and roosts ecology, have been generated from long-term studies carried out in the state of São Paulo, Brazil, for the past 20 years (Rocha et al., 2020; Rocha and Dias, 2020). The data on roosts and farms used in this study were collated from the surveillance survey carried out in 2017-2018 by the Coordenadoria de Defesa Agropecuária (CDA), the São Paulo State animal health service. The data contain information such as location (municipality, latitude and longitude coordinates, elevation), information about the farms (number of cattle), and roosts specifications (roost types with information about population demographics) on 132,787 farms and 5,170 roosts in São Paulo. The roosts were categorized as either “harems”, if occupied mostly by females and pups; “bachelor”, if dominated by young males; “overnight” if it is only a transit location to rest during foraging and digestion; and “empty” if the location is never occupied by vampire bats (Rocha and Dias, 2020). Cattle farm locations were obtained from the Ministry of Agriculture and Livestock. The farms with no cattle (50,556 farms), as well as empty and overnight roosts (971 roosts), were removed from the data set, as this study focuses on infection spillover exclusively to cattle and it is believed that the empty and overnight roosts contribute negligibly to rabies transmission. After data cleaning and data quality control checks (i.e. correcting longitude/latitude entry errors where possible, and removing data where it is not possible to correct the entry errors, along with removing of duplicated or incomplete records; 6,956 farms and 32 roosts removed), our modeling simulations were carried out on 4,167 bat roosts (2,186 bachelors and 1,981 harems) and 75,275 cattle farms (Figure 1).

Model description

We have developed a stochastic network two-species metapopulation model, linking bat populations (roosts) to cattle populations (farms), through a discrete-time state-based Markov-chain model. The state of each population (roost or farm) changes at every discrete daily time step in a probabilistic manner according to a set of rules, see Model details in Supporting Information.

We consider two possible states for the roosts, and three possible states for the farms, Figure 2A. A roost is defined as susceptible, S^R , when rabies is not present and infectious, I^R , otherwise, i.e. when there is at least one infectious bat in the roost, hence the infection spread from the roost is possible. Susceptible roosts become infectious by interacting with an infectious roost and can recover (i.e. become susceptible again) after a period of time (Table 1 and Recovery in Supporting Information). Similarly, a farm is susceptible, S^F , if there is no infected cattle animal with rabies. Farms where an animal is infected by a bat from an infectious roost become exposed, E^F , with infection present, but undetected. The detection time period is drawn from *lognormal* distribution for the farm once its status changed from susceptible to exposed. After this time to detection has past, the infection can be detected in the farm, and thus the farm will be considered infected, I^F (Table 1, Detection time period in farms in Supporting Information, and Supporting Information Figure S1). A farm with a detected infection can recover and become susceptible again (Figure 2A, Table 1, and Recovery in Supporting Information).

Roosts can be composed of young males (i.e. a bachelor roost, R_B) or be female dominated (i.e. a harem roost, R_H). We assume the driver of rabies transmission are the bachelor roosts, such that bachelors can transmit and acquire the infection from other roosts (bachelor or harem), while the harems can only acquire and transmit the infection to bachelors, as male bats are generally the ones traveling between bachelors and harems (Streicker et al., 2016; Becker et al., 2020). The recovery rate differ between bachelor and harem as the longevity of male and female bats differ (Figure 2B, Table 1 and Recovery in Supporting Information). Roost sizes are assumed to be fixed and relatively small (20 individuals in bachelor roosts, 100 in harems), in line with the data collected in the region (Rocha et al., 2020).

The populations, roosts and farms, are connected through a distance based contact network, assumed to be time-invariant (Rocha and Dias, 2020). Only contacts that could lead to disease transmission are considered,

such as interactions between two roosts representing males competing for access to females or to roosts with females, i.e. male-driven transmission, or between a roost and a farm representing bats feeding on cattle, expressed by the edges in the network. The transmission is limited up to 10 kilometers flight distance (Benavides et al., 2016). The bats are expected to feed only in farms at a lower altitude than their roost (Rocha et al., 2020), thus spillover events are limited by this in the model as well. Contacts between two farms were not considered, transmission usually occurs via a bite or scratch of an infected bat, consequently, rabies transmission between farms via movement of infected animals is highly unlikely (Network in Supporting Information, and Supporting Information Figure S2).

The risk of rabies virus transmission depends on spatial interactions subjected to a gravity model. The probability of bat movement decreases with longer distance to minimize spent energy, however increases with higher number of bats within the roost, harems in our model, as they may fly to further distance due to increased competition, and the roosts with more individuals attract more bats contacts (Spatial interaction in Supporting Information). Within-population dynamics are not considered. We assume that the between-roost transmission risk is further modified according to the environmental drivers of location suitability of both roosts; vegetation, elevation, temperature, precipitation, and night time light. These environmental data on roosts were used to calculate suitability indexes by ecological niche model (ENM) (Ecological niche model in Supporting Information, and Supporting Information Figure S3) (Anderson, 2013; Owens et al., 2013; Soberón and Peterson, 2005). The more suitable locations of roosts are expected to attract more bats. The edges in the network are weighted by the risk of rabies virus transmission and between two roosts also by their average environment suitability, where the edges does not exist as described above, i.e. the risk of transmission is negligible, it is expressed as zero weight of the edge (Network weights in Supporting Information). The network weights drive the probability of transmission. The probability of a susceptible population to become infectious or exposed, if it is a roost or a farm, respectively, depends on the sum of the weights of all edges connecting the population with an infectious roost (Probability of status changes due to bats behavior in Supporting Information).

We considered two possible rabies interventions in the model: A reactive vaccination of animals in the infected premise, and all surrounding farms in a 10 km radius; and/or a reactive roost control in the surrounding area within a 10 km radius from the infected premise, see Supporting Information Figure S4 for model schematic for the transmission of bat rabies virus between bat roosts and cattle farms including both interventions.

The reactive vaccination of farms is modeled as providing immunity to all farms vaccinated for a year (viz., 365 days). During this time, the vaccinated farms cannot be infected. After a year, the farm loses the immunity, it will likely be susceptible, however, if the farm was vaccinated while already exposed to infection, but not detected, the farm might be still exposed or infected. If there is a new outbreak in 10 km radius from the vaccinated farm, and it is more than a half of year (viz., 182 days) since last vaccination, the animals on the farm are re-vaccinated.

The roost control is currently based on the administration of a warfarin paste in the back of the captured vampire bats so that during social grooming conspecifics ingest the paste and indistinctly die of hemorrhage (Rocha et al., 2020; Rocha and Dias, 2020). Such roost control results in the death of nearly all vampire bats in the roost (Linhart et al., 1972), hence we assume that it leads to an empty roost, which likely will not be repopulated for a long time, and will not contribute to the virus transmission until is repopulated. Under the assumption of at least one year of immunity, and as a result, prevention of the roost to contribute to transmission, the spreadable vaccine can be considered as a roost control as well (Standing et al., 2017; Bakker et al., 2019). Consequently, for the purposes of modeling the roost control for one year, we assume that if a roost receives an intervention (culling or vaccination), all transmission ceases. To account for a reduced infection pressure when roosts are controlled, we assumed an increased recovery rate for farms when the roost control is carried out (Table 1).

Table 1 Summary of model parameters.

Parameter	Value	References
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Roost recovery rate, γ_{RH} and γ_{RB}	$1.71 \cdot 10^{-4}$ and $1.61 \cdot 10^{-4}$	[Delpietro et al., 2017]
Detection time in farm, τ_i	\sim lognormal ($\mu = 3.14$, $\sigma = 1.24$), shifted by 25	[Sartwell, 1966; Nishiura, 2007; Tojinbara et al., 2016]
Farm recovery rate, γ_F	$16.44 \cdot 10^{-3}$ (if roost control performed); $5.48 \cdot 10^{-3}$ (if roost control not performed)	Discussion with local experts
Roost-to-roost transmission rate, β_{PP}	$8.99 \cdot 10^{-2} - 13.36^1$; see Figure S5 in SI ² for posterior distribution	Calibrated
Roost-to-farm transmission rate, $\beta_{P\Phi}$	$154.37 - 693.80^1$; see Figure S5 in SI ² for posterior distribution	Calibrated

Notes:¹Calibrated with distances in meters.²SI stands for Supporting Information.

Model calibration

The model was calibrated to the data available from the region of São Paulo acquired in 2017-2018 when vaccination of farms, but no roost control, was performed in the area. Two model parameters, the roost-to-roost transmission rate, β_{PP} , and the roost-to-farm transmission rate, $\beta_{P\Phi}$, were fitted (see below); the remaining parameters were extracted from the literature (Table 1).

Model fitting was carried out using a regression-based conditional density Approximate Bayesian Computation algorithm, such as implemented in Prada et al. (2014), following Beaumont et al. (2002) and Lopes and Beaumont (2010). Briefly, summary statistics were calculated from the 2017-2018 data, and we ran a total of 7,800 simulations to calibrate the roost-to-roost and roost-to-farm transmission rates, β_{RR} and β_{RF} , respectively. Due to the high number of nodes in the network, the fitting process was carried out in two phases. First, the roost-to-roost transmission rate parameter was calibrated to reach 1% prevalence across all roosts in the network by simulation of 100 of years of transmission between roosts. The spillover to farms was not considered in this phase, therefore, no intervention was allowed. Second, the roost-to-farm transmission rate parameter was fitted to generate 226 outbreaks in farms across a five-year period, as we calibrated the parameters using the data collected in 2017-2018 when only farm vaccination was performed, only this intervention was allowed in the second phase of calibration, see Model calibration in Supporting Information for more details.

Bat-rabies control scenarios

Using the calibrated model, we explored several VBR control scenarios, assessing the effect over the spread of VBR from a single introduction in a randomly selected roost. We considered three initial settings of suitability environments, depending on whether the single initial introduction was in either a high, middle, or low suitability environment (limited to roosts connected to at least five other roosts, to ensure simulations are not initiated in isolated locations). We define these three initial sets of roosts, so that the roosts with the suitability index, calculated through the ENM (Anderson, 2013; Owens et al., 2013; Soberón and Peterson, 2005), within upper decile (after excluding isolated locations) form a set of roosts in high suitability environment, roosts with the suitability index of $\pm 5\%$ around the median form the middle, and within bottom decile form the low suitability environment sets of roosts (Supporting Information Figure S6).

In each initial setting, in response to VBR being detected in farms, we consider all combinations of two reactive interventions included in the model: a combination of roost control and farm vaccination, each intervention alone, or no intervention. Consequently, we simulate 12 different control scenarios (three initial settings of suitability environment with four different intervention strategies, Figure 3). This enables a comparison of the impact of environmental suitability on virus transmission and intervention effectiveness.

With the model calibration, we selected the best posterior draws (107 selected), and we ran 50 simulations with each posterior, 5,350 simulations in total per control scenario.

We assessed two different outcomes: (i) the number of detected outbreaks in farms, and (ii) the distance of virus spread from initial infection in a roost to a farm in one year, for the different control scenarios. We determined whether there are any statistically significant differences between the means of the outcomes for different intervention strategies by the Welch’s one-way heteroscedastic F test, an alternative to ANOVA robust to the violation of variance homogeneity assumption, which we observed for both outcomes. The Welch’s test has one of the highest adjusted power among one-way tests for positively skewed data, which we observed for the numbers of outbreaks, and for approximately normally distributed data, that we observed for the distances (Dag et al., 2018). Since we do not confirm the hypotheses of equal means, we perform the Games-Howell post-hoc tests to recognize which pairs of intervention strategies significantly differ, assessed through the Holm-corrected p -values. Tests and visualization are performed using the *ggstatsplot* package of R (Patil, 2021).

Areas at persistently high risk of VBR transmission and spillover in the state of São Paulo after random introductions can be highlighted by mapping spillover events. We divided the state of São Paulo into squares of $3'$ latitude times $3'$ longitude (30km^2). Spillover risk of farms was calculated as a proportion of (detected and undetected) infections among all simulations of a particular scenario.

Results

The average number of detected outbreaks in farms in a year, from a single introduction, is decreased significantly when an intervention strategy is implemented (being either cattle vaccination, roost control, or both), across all three suitability environments considered (Figure 4A-C). The maximal distances of virus spread from a single infection in a roost to a farm in one year, for the different intervention strategies are shown in Figure 4D-F.

The F statistics and the p -values of Welch’s F test are summarized for each comparison in Table S3 in Supporting Information, with all p -values close to zero, i.e. for both outcomes, across all three initial suitability settings, we do not confirm the hypothesis of equal means in the four intervention strategies. The Games-Howell post-hoc tests identify which pairs of intervention strategies significantly differ. The Holm-corrected p -values indicate that the outcomes for the combination of farm vaccination and roost control, versus roost control alone, are not significantly different, Figure 4A-F. Additionally, when infection starts in a low suitability environment, the number of outbreaks in farms do not significantly differ between the combination of farm vaccination and roost control, versus farm vaccination alone, Figure 4C.

The most ecologically suitable areas for bats, and thus where spread is likely to be higher, are concentrated in the east side of São Paulo state. The infection risk decreases dramatically with any intervention (whether it is farm vaccination, roost control, or both); the probability of an outbreak occurring in farms, after a single introduction, can be as high as 3.81% of the simulations ran without intervention and 1.02% of the simulations with the roost control, the most effective intervention strategy (Figure 5). High infection risk probabilities in farms were also observed in the middle and low suitability environments, which could be as high as 7.12% (Supporting Information Figure S7).

Discussion

The aim of this study was to explore the spatio-temporal dynamics of vampire-bat-driven rabies (VBR) in São Paulo, Brazil, and identify high-risk areas of spillover to cattle farms. This was achieved through the development of a novel stochastic network two-species metapopulation model. The model was used to explore the impact of current interventions, ring vaccination of farms and/or ring roost control (either bat culling or bat vaccination) around a positive farm. Our results suggest that either strategy can prevent substantial number of on-farm outbreaks, as well as significantly reduce the geographical spread of the virus. However, roost control alone or combined with farm vaccination in general leads to more significant control results than cattle vaccination alone. Interestingly, combination of both intervention did not provide a significant

benefit comparable to roost control alone. We also found areas of consistently high infection risk in high roost suitability environments, and in middle and low suitability environments for bat roosting.

As possibly, the most diverse, abundant, and geographically dispersed vertebrate, bats are unique in their ability to fly, long lifespans, migratory patterns, and in hosting a diverse suite of pathogens including rabies virus (Calisher et al., 2006; Luis et al., 2013). Some of these factors contribute towards the efficacy of bats as zoonosis transmitters, but also towards the lack of data about pathogen circulation, in particular their high level of mobility and vast geographic ranges, as field data are often collected from a subset of a species geographic range over a small timescale (Benavides et al., 2016). While keeping the model relatively simple in terms of bat demography, we reproduce several important environmental drivers of disease transmission, such as elevation driving the explicit range of contact between roosts and farms, male-driven transmission between bat roosts, flight distance and environmental suitability. This is key to generate useful risk maps that can support policy implementation. For example, Benavides et al. (2020) highlighted the challenge of applying bat vaccines across many roosts, which could be mitigated by focusing efforts on the areas estimated by the model to be at higher risk, which could in addition reduce cross-species exposure while reducing the impact on bat communities.

Bat culling remains a controversial approach to VBR control (Streicker et al, 2012). Alternatively, a spreadable vaccine may be administered similar as the vampiricide. Laboratory and model results showed that the oral vaccination could be effective (Standing et al., 2017; Bakker et al., 2019). In the model we considered the implementation of a roost control, which can either represent bat culling or bat vaccination. Either way, it is modeled so that if a roost receives the intervention, all transmission ceases for at least one year. In the case of culling, the spread of the poison due to intensive grooming leads to an empty roost (Linhart et al, 1972), which would likely be repopulated in the future, but this could potentially take a long time and has dangerous ecological implications. Furthermore, it was suggested that culling may increase recruitment of susceptible juveniles into the system, making the intervention ineffective or counterproductive, therefore, the efficacy simulated here is likely overestimated in case of culling (Streicker et al., 2012; Gentles et al., 2020). To study this in more detail, model would need to be modified to include within roost dynamics. Bat vaccination, being spread the same way, will lead to the entire roost population immune, arguably for at least one year. This type of control would not change the population structure within the roost, on the other hand, it will not reduce the impacts of bats as pests causing harm to animals by bat bites independently of rabies, including skin damage, anemia, loss of vision, loss of weight and productivity, and predisposition to other infection (Delpietro et al., 2021).

Nevertheless, cattle vaccination has also achieved considerable reduction in on-farm outbreaks and geographical spread of infection across the three initial suitability environments. Either way, a spatial mathematical model simulating the impact of these interventions, for example extending the one presented here, could be used before hand to evaluate the consequences of their introduction, and identify the most suitable locations to cover with the campaign for the successfully control, or even eradication, of the virus. As concluded by Blackwood et al. (2013), who developed several stochastic SEIR models examining viral persistence, bat population migration, and the effects of bat population culling; the mechanisms to reduce spillover via viral elimination, likely need to be spatially coordinated to be effective as we demonstrated here.

In the model we considered the minimum delay in the detection of outbreaks in the cattle farms to be 25 days, with a mean detection time around 75 days, and the most frequently observed delay (mode) of 30 days. We assumed a relatively over dispersed distribution to capture both the latency period and delay in detection. As the interventions simulated here are reactive, reducing the delay in detection could generate significant gains in reducing transmission. Alternatively, the farm or roost control could be administered in a prospective manner, for example focusing on high-risk areas. The challenge would be to justify the investment to stakeholders (whether it is the farmers paying for the cattle vaccine, or the government paying for either farm or roost control), when the risk might not be perceived.

We followed prior work made in the region (Rocha et al., 2020; Rocha and Dias, 2020), building a similar contact network as in Rocha and Dias (2020), with a consistent assumption of up to 10 km flight distance

(Benavides et al., 2016), and dependence of bat foraging migration pattern on altitude (Rocha et al., 2020). How far within the 10 km distance the bats fly is determined by the number of individuals in the roost, since individuals may fly to more distant feeding sources and/or roosts to minimize competition with conspecifics (Kunz and Fenton, 2003; Rocha et al., 2020). We address these spatial interactions by utilizing a gravity model. In addition, we incorporate knowledge of favorable conditions for bats using the roost locations and an ecological niche model to capture the environmental suitability (Ecological niche model in Supporting Information). Our approach has however a number of limitations; the contact network is assumed to be time-invariant and we are examining outbreaks over a one year time-period from a single introduction. Assuming a unique infected roost at random (potentially in the middle of the region) as a starting point is unrealistic, however it allows us to better capture the expected spatial spread from a single point. The model focuses only on spillover to cattle, however, other animals are in risk (e.g. horses), and since rabies virus is zoonosis also spillover to humans occurs.

The reactive interventions depend on reports from the producers which is influenced by many socio-ecological factors, similarly adherence to intervention and thus vaccination of the animals when infection nearby is reported might be conditioned by various factors (Benavides et al., 2017). The behavior effects on intervention needs to be accounted for in model if we want more realistic predictions. Furthermore, the intervention strategies effective to reach programmatic goals needs to be evaluated in economic manner as the government and farmers financial sources are limited (Janoušková et al., 2022). For example, anemia from bat bites may reduce livestock productivity (Bakker et al., 2019), hence making a difference in bat culling compare to bat vaccination. The roost control might be more cost-efficient to the official service since a smaller number of locations should be visited and vaccine delivery (for example as a paste) is more straight-forward than cattle vaccination. The model presented here, does not evaluate the economic implications, therefore distinguish only between susceptible, exposed, and infected farms, ignoring how many number of animals and to which extent are affected by bites and/or infection. The cumulative losses due to bites if no culling is performed, and even deaths if no roost control is in place might markedly change the cost-effectiveness. Last, but not least, the trust, support and commitment of stakeholders and involved institutions is necessary to reach the expected results (Janoušková et al., 2022). For instance, vaccination of vampire bats without population reduction will be unacceptable to some stakeholders since uncontrolled bat depredation sustains exposures to non-rabies pathogens (Bakker et al., 2019). The stakeholder's preferences have to be taken into account when assessing the sustainability of the interventions.

Conclusion

We have developed a novel stochastic network two-species metapopulation model, that captures transmission of VBR between bat roost, as well as spillover events to cattle farms. After exploring two alternative control strategies, namely reactive ring roost control (i.e. bat culling or bat vaccination) and reactive ring cattle farm vaccination, we found no large differences in their expected efficacy, however interventions in roosts were statistically significantly better in all settings considered across both outcomes (number of outbreaks and spatial spread from initial introduction). Such mathematical frameworks can prove useful to inform control interventions, particularly identifying high-risk areas where prospective vaccination, either in cattle or in bats, could take place. This will support ongoing programs, leading to more effective control. Nonetheless, to reach long-term strategies and sustainability that could move beyond control to potential local elimination and eradication, human behavior, for example, in context of interventions uptake and response to VBR infection in farms, needs to be incorporated in model to get more accurate predictions. In addition to assessing intervention strategies effectiveness and high-risk areas such as provided in this study, economic evaluation is essential before decision is made on interventions.

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Data availability statement

The data that support the findings of this study are not publicly available and are protected by confidential

agreements, therefore, are not available.

Ethics statement

The authors confirm the ethical policies of the journal, as noted on the journal’s author guidelines page. Since this work did not involve animal sampling nor questionnaire data collection by the researchers, there was no need for ethics permits.

Statement of contribution EJ, JMP and GM conceived the study. EJ, JMP, RAD and GM participated in the design of the study. RAD and GM gathered the necessary farm and root data. EJ conducted data processing, and cleaning, and designed the model. Computing simulating scenarios was led by EJ with the assistance of JMP and GM. EJ conducted the formal coding. EJ, JMP and GM wrote and edited the manuscript. All authors discussed the results and critically reviewed the manuscript. GM and JMP secured the funding.

Conflict of interest

The authors declare that there is no conflict of interest.

References

- Anderson, R. P. (2013). A framework for using niche models to estimate impacts of climate change on species distributions. *Annals of the New York Academy of Sciences* , 1297 , 8–28.
<https://doi.org/10.1111/nyas.12264>
- Bakker, K. M., Rocke, T. E., Osorio, J. E., Abbott, R. C., Tello, C., Carrera, J. E., Valderrama, W., Shiva, C., Falcon, N., & Streicker, D. G. (2019). Fluorescent biomarkers demonstrate prospects for spreadable vaccines to control disease transmission in wild bats. *Nature Ecology & Evolution* , 3 (12), 1697–1704.
<https://doi.org/10.1038/s41559-019-1032-x>
- Banyard, A. C., Hayman, D., Johnson, N., McElhinney, L., & Fooks, A. R. (2011). Chapter 12—Bats and Lyssaviruses. In A. C. Jackson, *Advances in Virus Research* (Vol. 79, pp. 239–289). Academic Press.
<https://doi.org/10.1016/B978-0-12-387040-7.00012-3>
- Beaumont, M. A., Zhang, W., & Balding, D. J. (2002). Approximate Bayesian Computation in Population Genetics. *Genetics* , 162 (4), 2025–2035. <https://doi.org/10.1093/genetics/162.4.2025>
- Becker, D. J., Broos, A., Bergner, L. M., Meza, D. K., Simmons, N. B., Fenton, M. B., Altizer, S., & Streicker, D. G. (2020). Temporal patterns of vampire bat rabies and host connectivity in Belize. *Transboundary and Emerging Diseases* , 00 , 1–10. <https://doi.org/10.1111/tbed.13754>
- Benavides, J. A., Paniagua, E. R., Hampson, K., Valderrama, W., & Streicker, D. G. (2017). Quantifying the burden of vampire bat rabies in Peruvian livestock. *PLOS Neglected Tropical Diseases* , 11 (12), e0006105. <https://doi.org/10.1371/journal.pntd.0006105>
- Benavides, J. A., Valderrama, W., Recuenco, S., Uieda, W., Suzán, G., Avila-Flores, R., Velasco-Villa, A., Almeida, M., Andrade, F. A. G. de, Molina-Flores, B., Vigilato, M. A. N., Pompei, J. C. A., Tizzani, P., Carrera, J. E., Ibanez, D., & Streicker, D. G. (2020). Defining New Pathways to Manage the Ongoing Emergence of Bat Rabies in Latin America. *Viruses* , 12 (9), 1002. <https://doi.org/10.3390/v12091002>
- Benavides, J. A., Valderrama, W., & Streicker, D. G. (2016). Spatial expansions and travelling waves of rabies in vampire bats. *Proceedings of the Royal Society B: Biological Sciences* , 283 (1832), 20160328. <https://doi.org/10.1098/rspb.2016.0328>
- Blackwood, J. C., Streicker, D. G., Altizer, S., & Rohani, P. (2013). Resolving the roles of immunity, pathogenesis, and immigration for rabies persistence in vampire bats. *Proceedings of the National Academy of Sciences* , 110 (51), 20837–20842. <https://doi.org/10.1073/pnas.1308817110>

- Bornaa, C. S., Seidu, B., & Daabo, M. I. (2020). Mathematical Analysis of Rabies Infection. *Journal of Applied Mathematics* , 2020 , e1804270. <https://doi.org/10.1155/2020/1804270>
- Chowell, G., Sattenspiel, L., Bansal, S., & Viboud, C. (2016). Mathematical models to characterize early epidemic growth: A review. *Physics of Life Reviews* , 18 , 66–97. <https://doi.org/10.1016/j.plrev.2016.07.005>
- Dag, O., Dolgun, N. A., & Konar, N. (2018). onewaytests: An R Package for One-Way Tests in Independent Groups Designs. *The R Journal* , 10 , 175–199. <https://doi.org/10.32614/RJ-2018-022>
- Delpietro, H. A., Marchevsky, N., & Simonetti, E. (1992). Relative population densities and predation of the common vampire bat (*Desmodus rotundus*) in natural and cattle-raising areas in north-east Argentina. *Preventive Veterinary Medicine* , 14 , 13–20. [https://doi.org/10.1016/0167-5877\(92\)90080-Y](https://doi.org/10.1016/0167-5877(92)90080-Y)
- Delpietro, H. A., Russo, R. G., Carter, G. G., Lord, R. D., & Delpetrio, G. L. (2017). Reproductive seasonality, sex ratio and philopatry in Argentina’s common vampire bats. *Royal Society Open Science* , 4 , 160959. <https://doi.org/10.1098/rsos.160959>
- Delpietro, H. A., Russo, R. G., Rupprecht, C. E., & Delpietro, G. L. (2021). Towards Development of an Anti-Vampire Bat Vaccine for Rabies Management: Inoculation of Vampire Bat Saliva Induces Immune-Mediated Resistance. *Viruses* , 13 (3), 515. <https://doi.org/10.3390/v13030515>
- Dias, R. A., & Ulloa-Stanojlovic, F. M. (2021). Predictive risk model of livestock rabies occurrence in Peru. *Brazilian Journal of Veterinary Research and Animal Science* , 58 , e183270. <https://doi.org/10.11606/issn.1678-4456.bjvras.2021.183270>
- Dimitrov, D. T., Hallam, T. G., Rupprecht, C. E., Turmelle, A. S., & McCracken, G. F. (2007). Integrative models of bat rabies immunology, epizootiology and disease demography. *Journal of Theoretical Biology* , 245 (3), 498–509. <https://doi.org/10.1016/j.jtbi.2006.11.001>
- Dorratoltaj, N., Nikin-Beers, R., Ciupe, S. M., Eubank, S. G., & Abbas, K. M. (2017). Multi-scale immunological modeling of within-host and between-host HIV dynamics: Systematic review of mathematical models. *PeerJ* , 5 , e3877. <https://doi.org/10.7717/peerj.3877>
- Gentles, A. D., Guth, S., Rozins, C., & Brook, C. E. (2020). A review of mechanistic models of viral dynamics in bat reservoirs for zoonotic disease. *Pathogens and Global Health* , 114 (8), 407–425. <https://doi.org/10.1080/20477724.2020.1833161>
- Grassly, N. C., & Fraser, C. (2008). Mathematical models of infectious disease transmission. *Nature Reviews Microbiology* , 6 , 477–487. <https://doi.org/10.1038/nrmicro1845>
- Griffiths, M. E., Broos, A., Bergner, L. M., Meza, D. K., Suarez, N. M., Filipe, A. da S., Tello, C., Becker, D. J., & Streicker, D. G. (2022). Longitudinal deep sequencing informs vector selection and future deployment strategies for transmissible vaccines. *PLOS Biology* , 20 (4), e3001580. <https://doi.org/10.1371/journal.pbio.3001580>
- Horta, M. A., Ledesma, L. A., Moura, W. C., & Lemos, E. R. S. (2022). From dogs to bats: Concerns regarding vampire bat-borne rabies in Brazil. *PLOS Neglected Tropical Diseases* , 16 (3), e0010160. <https://doi.org/10.1371/journal.pntd.0010160>
- Janoušková, E., Clark, J., Kajero, O., Alonso, S., Lamberton, P. H. L., Betson, M., & Prada, J. M. (2022). Public health policy pillars for the sustainable elimination of zoonotic schistosomiasis. *Frontiers in Tropical Diseases* , 3 , 826501. <https://doi.org/10.3389/ftd.2022.826501>
- Kunz, T. H., & Fenton, M. B. (2003). *Bat Ecology* . University of Chicago Press.
- Kuzmin, I. V., & Rupprecht, C. E. (2015). Bat Lyssaviruses. In L.-F. Wang & C. Cowled, *Bats and Viruses: A New Frontier of Emerging Infectious Diseases* (pp. 47–97). John Wiley & Sons. <https://doi.org/10.1002/9781118818824>

- Linhart, S. B., Flores Crespo, R., & Mitchell, G. C. (1972). Control of vampire bats by topical application of an anticoagulant, chlorophacinone. *Boletín de La Oficina Sanitaria Panamericana (OSP) English Edition* , 6 (2).
- Lopes, J. S., & Beaumont, M. A. (2010). ABC: A useful Bayesian tool for the analysis of population data. *Infection, Genetics and Evolution* , 10 (6), 825–832. <https://doi.org/10.1016/j.meegid.2009.10.010>
- Luis, A. D., Hayman, D. T. S., O’Shea, T. J., Cryan, P. M., Gilbert, A. T., Pulliam, J. R. C., Mills, J. N., Timonin, M. E., Willis, C. K. R., Cunningham, A. A., Fooks, A. R., Rupprecht, C. E., Wood, J. L. N., & Webb, C. T. (2013). A comparison of bats and rodents as reservoirs of zoonotic viruses: Are bats special? *Proceedings of the Royal Society B: Biological Sciences* , 280 (1756), 20122753. <https://doi.org/10.1098/rspb.2012.2753>
- Nishiura, H. (2007). Early efforts in modeling the incubation period of infectious diseases with an acute course of illness. *Emerging Themes in Epidemiology* , 4 , 2. <https://doi.org/10.1186/1742-7622-4-2>
- Olival, K. J. (2016). To Cull, Or Not To Cull, Bat is the Question. *EcoHealth* , 13 , 6–8.
- Owens, H. L., Campbell, L. P., Dornak, L. L., Saupe, E. E., Barve, N., Soberón, J., Ingenloff, K., Lira-Noriega, A., Hensz, C. M., Myers, C. E., & Peterson, A. T. (2013). Constraints on interpretation of ecological niche models by limited environmental ranges on calibration areas. *Ecological Modelling* , 263 , 10–18. <https://doi.org/10.1016/j.ecolmodel.2013.04.011>
- Patil, I. (2021). Visualizations with statistical details: The “ggstatsplot” approach. *Journal of Open Source Software* , 6 (61), 3167. <https://doi.org/10.21105/joss.03167>
- Prada Jiménez de Cisneros, J., Stear, M. J., Mair, C., Singleton, D., Stefan, T., Stear, A., Marion, G., & Matthews, L. (2014). An explicit immunogenetic model of gastrointestinal nematode infection in sheep. *Journal of The Royal Society Interface* , 11 (99), 20140416. <https://doi.org/10.1098/rsif.2014.0416>
- Rocha, F., & Dias, R. A. (2020). The common vampire bat *Desmodus rotundus* (Chiroptera: Phyllostomidae) and the transmission of the rabies virus to livestock: A contact network approach and recommendations for surveillance and control. *Preventive Veterinary Medicine* , 174 , 104809. <https://doi.org/10.1016/j.prevetmed.2019.104809>
- Rocha, F., Ulloa-Stanojlovic, F. M., Rabaquim, V. C. V., Fadil, P., Pompei, J. C., Brandão, P. E., & Dias, R. A. (2020). Relations between topography, feeding sites, and foraging behavior of the vampire bat, *Desmodus rotundus* . *Journal of Mammalogy* , 101 (1), 164–171. <https://doi.org/10.1093/jmammal/gyz177>
- Ruan, S. (2017). Spatiotemporal epidemic models for rabies among animals. *Infectious Disease Modelling* , 2 (3), 277–287. <https://doi.org/10.1016/j.idm.2017.06.001>
- Ruiz-Aravena, M., McKee, C., Gamble, A., Lunn, T., Morris, A., Snedden, C. E., Yinda, C. K., Port, J. R., Buchholz, D. W., Yeo, Y. Y., Faust, C., Jax, E., Dee, L., Jones, D. N., Kessler, M. K., Falvo, C., Crowley, D., Bharti, N., Brook, C. E., ... Plowright, R. K. (2021). Ecology, evolution and spillover of coronaviruses from bats. *Nature Reviews Microbiology* , 1–16. <https://doi.org/10.1038/s41579-021-00652-2>
- Rupprecht, C., Kuzmin, I., & Meslin, F. (2017). Lyssaviruses and rabies: Current conundrums, concerns, contradictions and controversies. *F1000Research* , 6 , 184. <https://doi.org/10.12688/f1000research.10416.1>
- Sartwell, P. E. (1966). The incubation period and the dynamics of infectious disease. *American Journal of Epidemiology* , 83 (2), 204–216.
- Soberón, J., & Peterson, A. T. (2005). Interpretation of Models of Fundamental Ecological Niches and Species’ Distributional Areas. *Biodiversity Informatics* , 2 , 1–10. <https://doi.org/10.17161/bi.v2i0.4>

Stading, B., Ellison, J. A., Carson, W. C., Satheshkumar, P. S., Roche, T. E., & Osorio, J. E. (2017). Protection of bats (*Eptesicus fuscus*) against rabies following topical or oronasal exposure to a recombinant raccoon poxvirus vaccine. *PLOS Neglected Tropical Diseases*, 11 (10), e0005958. <https://doi.org/10.1371/journal.pntd.0005958>

Streicker, D. G., Recuenco, S., Valderrama, W., Gomez Benavides, J., Vargas, I., Pacheco, V., Condori Condori, R. E., Montgomery, J., Rupprecht, C. E., Rohani, P., & Altizer, S. (2012). Ecological and anthropogenic drivers of rabies exposure in vampire bats: Implications for transmission and control. *Proceedings of the Royal Society B: Biological Sciences*, 279 (1742), 3384–3392. <https://doi.org/10.1098/rspb.2012.0538>

Streicker, D. G., Winternitz, J. C., Satterfield, D. A., Condori-Condori, R. E., Broos, A., Tello, C., Recuenco, S., Velasco-Villa, A., Altizer, S., & Valderrama, W. (2016). Host–pathogen evolutionary signatures reveal dynamics and future invasions of vampire bat rabies. *Proceedings of the National Academy of Sciences*, 113 (39), 10926–10931. <https://doi.org/10.1073/pnas.1606587113>

Tojinbara, K., Sugiura, K., Yamada, A., Kakitani, I., Kwan, N. C. L., & Sugiura, K. (2016). Estimating the probability distribution of the incubation period for rabies using data from the 1948–1954 rabies epidemic in Tokyo. *Preventive Veterinary Medicine*, 123, 102–105. <https://doi.org/10.1016/j.prevetmed.2015.11.018>

van Brussel, K., & Holmes, E. C. (2022). Zoonotic disease and virome diversity in bats. *Current Opinion in Virology*, 52, 192–202. <https://doi.org/10.1016/j.coviro.2021.12.008>

Figure legends

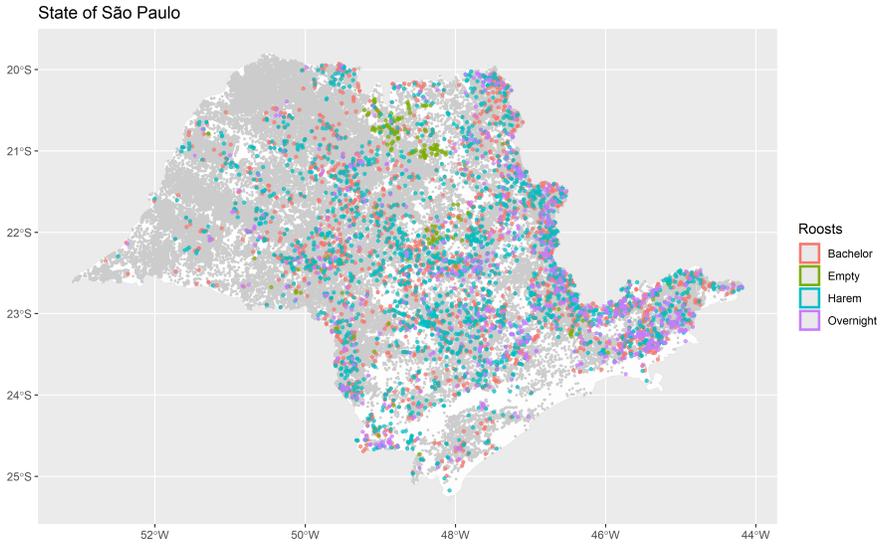
Figure 1 Geographic location of bat roosts visited in 2017–2018, colored by roost type, and cattle farms, gray dots, in the state of São Paulo.

Figure 2 (A) Model schematic for the transmission of bat rabies virus between bat roosts and cattle farms. **(B)** Detailed between roost dynamics schematic. The state changes between epidemiological classes are shown by solid arrows. The parameters affecting the state changes are displayed, see also Table 1. Dashed arrows represent virus transmission. No interventions are included in these diagrams.

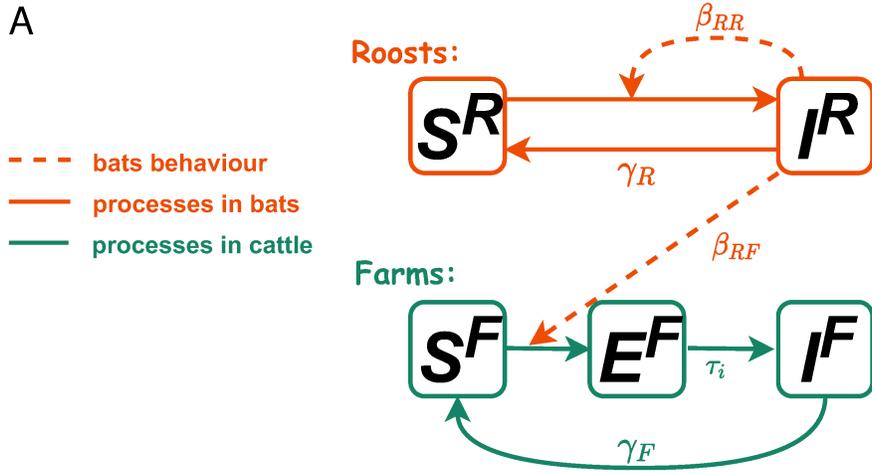
Figure 3 Diagram of the different reactive intervention strategies, summarizing which farm and/or roost will be controlled. An intervention would be implemented in farms and/or roosts within 10 km distance from a detected positive farm (large light gray circle). The only exceptions would be farms recently vaccinated (subindex V) that will not be re-vaccinated again until 6 months have passed since last vaccination, and controlled roosts (C). Four different intervention strategies were modeled **(A)** farm vaccination and roost control, **(B)** farm vaccination, **(C)** roost control, **(D)** no intervention.

Figure 4 (Top: A–C) Distribution of the number of outbreaks (i.e. infection detections) in farms for different combinations of interventions. **(Bottom: D–F)** Distribution of maximal distances of virus spread from a single initial infection in a roost to a farm in one year in kilometers, including no virus spillovers to farms, i.e. zero distances; for different combinations of interventions. The initial suitability environment of a first infected roost is either **(Left: A, D)** high (90–100th percentile), **(Middle: B, E)** middle (45–55th percentile), or **(Right: C, F)** low (0–10th percentile). For Welch’s F test statistics and p -values for each comparison (A–F) to test the hypothesis of equal means in the four intervention strategies, see Table S3 in Supporting Information.

Figure 5 Spillover risk to farms measured as the probability of detected and undetected infections, among all simulations with initial infection in high suitability environment, for each intervention strategy. The value per pixel shown is the average across the farms within the pixel (square 3’ latitude times 3’ longitude, i.e. approx. 30 km²).



A



B

