Climate-driven changes in zoonotic risk of arenaviral hemorrhagic fevers in South America

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# Main

Climate change has been found to exacerbate 58% of human infectious diseases 1. Moreover, long-term changes in climate and adverse weather events have well-documented effects on the spread of vector-borne diseases2–4. Indeed, localized endemic neglected tropical diseases are being increasingly reported in neighboring, previously unaffected, areas 3. Similar to vector-borne diseases, rodent-borne diseases are also expected to be affected by climate change 2,3,5. It is estimated that, globally, more than 3000 mammalian species, including rodents, are expected to change habitats by 2070 6. This could have devastating impacts on disease spread. Guterres and de Lemos (2018) demonstrated that zoonotic outbreaks of rodent-borne hantaviral infections can be predicted with reasonable accuracy by tracking changes in the environmental and climatic conditions 7. Particularly, the risk of high consequence *mammarenaviral* infections in humans, such as Lassa fever (caused by Lassa fever virus) and Argentine hemorrhagic fever (caused by Junin virus), which have been selected as prototype viruses for pandemic preparedness, will be affected given the expected changes in climate and the environment in the coming two to five decades 8–11.

Arenavirus spillover into humans is strongly affected by human-rodent contact and the distribution of rodent reservoirs. The main routes of disease transmission among rodents and humans include fomites, dried droppings, and urine through the oral route and, less frequently, through non-oral routes via breathing, scratches, and biting from reservoir hosts 12,13. The likelihood of human-rodent contact is determined by anthropogenic factors like deforestation, human movement, changing agricultural patterns, as well as the increasing domestic/peri-domestic presence of rodent species 14. Drastic shifts in the habitats of rodent reservoirs of these zoonotic arenaviruses driven by changes in food availability, climate suitability, human population dynamics, and increasing human–rodent interactions are expected. In our previous study, we estimated that the ecological habitat of *Calomys musculinus*—the rodent reservoir of Junin virus (JUNV), which causes Argentine Hemorrhagic Fever (AHF)—will undergo substantial changes in the future as a response to climate change 2,9.

In the case of South America, New World Arenaviruses (NWAs), such as Guanarito virus (GTOV) in Venezuela and Colombia, Machupo virus (MACV) in Bolivia and Paraguay, and JUNV in Argentina, have caused multiple human outbreaks, with case fatality rates ranging from 5% to 30% 15. Old World Arenaviruses (OWAs) such as Lassa fever virus in Africa have been extensively studied and modeled in terms of disease dynamics and spillover risk 11,16,17. Despite being currently included in the viral list of priority pathogens for biodefense and emerging infectious diseases by institutions such as National Institute of Allergy and Infectious Diseases (NIAID), the US Centers for Disease control and Prevention (CDC), the disease dynamics and reservoir distributions of GTOV, MACV, and JUNV have not been modeled, to our knowledge 18. Furthermore, the impact of climate change on the disease dynamics and spillover of NWAs from rodents to humans remains poorly understood.

The surface temperature in South American countries is expected to rise between 0.92 to 6.14 °C by the end of the 21st century, based on the Shared Socio-economic Pathways (SSPs) 19. Moreover, precipitation followed by prolonged droughts may increase wildfire risk and become prominent 20. These climatic conditions as well as anthropogenic land use changes might have extreme effects on rodent populations, subsequently increasing risks of rodent-borne arenaviral zoonoses 21. Rodent species that are known hosts of New World arenaviruses are one of the first species to repopulate after fires in burned areas, which has been associated with an increased risk of human cases 22. Similarly, temperature, rainfall, and land-use changes are all presumed to influence rodent populations in South America 20. Therefore, it follows that the human risk of NWAs in South America might shift in response to changes in the habitat of their rodent reservoirs.

We hypothesized that the zoonotic risk of rodent-borne NWAs is strongly dependent on the eco-habitat of their rodent reservoirs, and that, given the forecasted climatic changes in South America, this may facilitate their spread to previously non-endemic areas. Therefore, we expect climate driven environmental changes to be predictive of changes in the zoonotic risk of NWAs spillover to humans. In this study, we estimated the zoonotic spillover risk of NWAs in South America by quantifying the force-of-infection (FOI) to humans (probability of successful zoonotic transmission) based on human-rodent interactions under different climate change scenarios. FOI estimates were mechanistically modeled based on the species distribution patterns and estimated population density of six known rodent reservoir species for NWAs: *Zygodontomys brevicauda* (GTOV), *Sigmodon alstoni* (GTOV), *Calomys callosus* (MACV), *Calomys musculinus* (JUNV), *Calomys laucha* (JUNV) and *Oligoryzomys flavescens* (JUNV). This integrated approach of combining species distribution modeling (SDMs) and mechanistic FOI models was applied to three climate scenarios: (i) the current climate, and two future climate scenarios based on 23 , namely, (ii) SSP 2-4.5 (Moderate Climate Change Scenario) and (iii) SSP 5-8.5 (Extreme Climate Change Scenario) of years 2041-2060.

# Hotspots for spillover risk of New World Arenaviruses will increase in the future

Projected spatial risk profiles of NWAs for the two future climate change scenarios (SSP 2-4.5 and SSP 5-8.5) showed a more widespread and increased risk of transmission compared to the current scenario for all three modeled NWAs (Figure 1). We also predicted a higher risk (increased FOI) of all three NWAs in some of their currently endemic regions (Figure 1). Overall, when compared with each other, the two future climate change scenarios of SSP 2-4.5 and SSP 5-8.5 did not show markedly different projected FOI patterns. When compared with the current climate scenario, the differences in FOI with SSP 2-4.5 were more prominent than with SSP 5-8.5 (Figure 1 and Figure 2).

In both climate change scenarios, the risk of GTOV transmission was estimated to be more widespread. Non-endemic areas in the countries of Guyana, Suriname and Brazil, showed a positive change in projected risk compared to the currently endemic zones in Venezuela (Figure 1A). In contrast, the endemic regions along the northern seashore of Venezuela projected reduced FOI estimates for both climate change scenarios. The FOI remained unchanged in the interior region within the habitats of the GTOV reservoirs (Figure 1A) for both climate change scenarios. For some of the endemic regions near the northern coast of Venezuela, the risk remained unchanged in SSP 2-4.5 but was slightly lower for SSP 5-8.5 scenario compared to the current climate (for details, see Supplementary Figure S1.4). For MACV, the model predicted overall FOI was higher for both climate change scenarios compared to the current estimates. The endemic zones along the eastern foothills of the Bolivian Andes mountains had reduced FOI, whereas the non-endemic zones of interior grasslands in Bolivia and Paraguay showed an increase in FOI compared to the current estimates (Figure 1B). Similarly, for JUNV, the spillover risk in the endemic regions of the Pampas grasslands of central Argentina for AHF was predicted to be lower in both climate change scenarios and higher for the surrounding non-endemic zones. SSP 2-4.5 showed less pronounced changes compared to SSP 5-8.5, and some of the FOI estimates remained unchanged for certain endemic areas in Buenos Aires province but increased around the capital region of Buenos Aires (Figure 1C). The non-endemic regions around the borders between Argentina, Paraguay and Bolivia were also estimated to have higher disease risk in both future scenarios. These high-risk zones overlap with the higher risk zones for MACV in the two climate change scenarios (Figures 1 B-C).

For all three NWAs, the average spillover risk was higher for the SSP 2-4.5 and SSP 5-8.5 scenarios compared with the current scenario. For GTOV and MACV, the increase in spillover risk was higher in eastern tropical parts of the reservoir habitats compared to the dryer western parts separated by the Andes and other mountain ranges (Figure 2A). For MACV, due to the shift in risk based on the FOI from the Andean foothills to the interior grasslands, the average change in FOI was higher in eastern Bolivia compared to the higher altitude western regions (Figure 2A). The spillover risk of GTOV had a median increase of 0.05 and 0.08 for SSP 2-4.5 and SSP 5-8.5 respectively (Figure 2B (i)) compared to the current scenario. For JUNV, the risk in terms of FOI increased by a median value of 0.03 for both climate change scenarios (Figure 2C (ii)). For MACV, the median increase in FOI was 0.19 and 0.18 for SSP 2-4.5 and SSP 5-8.5, respectively (Figure 2B (iii)). We predicted that potential hotspots for NWA spillover in the current scenario remained persistent in both moderate and extreme climate change scenarios (see supplementary Figure S1.3).

# Changes in the risk for NWA spillover showed strong association with the climate and land use changes in the reservoir habitats

At the virus level, increase in spillover risk (represented by FOI) under both future climate change scenarios, for all three NWAs, corresponded to (i) positive changes (increase) in temperature- based features such as annual range, seasonality, etc., (ii) negative changes (decrease) in precipitation-based features such as precipitation in warmest quarter or in wettest quarter, (iii) positive changes (expansion) in urban and crop land (iv) and negative changes (contraction) in forested land (Figure 3A).

For GTOV, changes in FOI from the current to the future scenario were found to be more sensitive to the features related to temperature, such as its annual range and seasonality (Figure 3A). For the top three features in the SSP 2-4.5 scenario model, the estimated increase in FOI corresponded with an increase in temperature seasonality and the presence of crop land. We theorize that anthropogenic activities that lead to land use changes such as the expansion of arable land and deforestation might be the primary reason for increased risk of GTOV in agriculture crop areas 24. In contrast, the estimated change in FOI decreased with an increase in precipitation of the wettest quarter of the year (Figure 3B). For the SSP 5-8.5, the predicted change in FOI had a positive relationship with both the changes in the annual range and the seasonal patterns of the temperature. In contrast, the increase in presence of forested land corresponded with a decrease in FOI (Figure 3B). Considering that both GTOV reservoirs (*Z. brevicauda, S. alstoni)* can be found in shrub and grassland areas with wet conditions, the sensitivity to seasonality in temperature, precipitation, and host range was expected 25.

For MACV, the changes in FOI were sensitive to changes in the precipitation and temperature features. Considering the top three features for the SSP 2-4.5 scenario, the increase in FOI corresponded to a decrease in isothermality as well as annual mean temperature, and a slight increase in the minimum temperature of the coldest month (Figure 3A). For the SSP 5-8.5 scenario, the relationship between the changes in FOI and precipitation of the wettest quarter showed a positive trend. FOI decreased with a decrease in the mean temperature of the wettest quarter. We theorize that the sensitivity to changes in temperature and precipitation might be ascribed to the habitat preferences of C. callosus, along with the expected increase in human migration towards non-urban areas, since C. callosus is known to inhabit areas with dry, semi-arid climate conditions with open vegetation 26,27.

For JUNV, the FOI changes corresponded to changes in temperature, precipitation and presence of urban or crop lands for both scenarios (Figure 3A). In the SSP 2-4.5 model, the relationship between FOI and changes in temperature seasonality was negative with a flat slope, positive for increase in urban land and negative for precipitation in the warmest quarter (Figure 3B). For the SSP 5-8.5, changes in precipitation of the wettest quarter, mean temperature of the coldest quarter, and presence of urban land had a slight negative, negative, and positive relationship, respectively (Figure 3B). These sensitivities signaled a shift in contact pattern between the rodent species away from urban environments towards more rural/ semi-rural environments. These findings are in line with prior studies showing that shifts in the habitat of rodent reservoirs of JUNV intersect with areas of human activity 9,28.

# Shifts in species distribution patterns of NWA rodent reservoirs predicted

We predicted the species distribution patterns for the six rodent reservoirs of the three NWAs for (i) the current time, and the future in years 2041-2060 represented by (ii) SSP 2-4.5 scenario and (iii) SSP 5-8.5 scenario, using a Species Distribution Modeling (SDM) framework. In general, the projected future species distributions showed different spatial patterns as well as different magnitudes of probabilities of presence in each spatial unit for all the rodent reservoir species compared to the current distributions, predicting a radical change in the habitats of these rodent reservoirs in the future. However, the differences in the probabilities of presence between the SSP 2-4.5 and SSP 5-8.5 scenarios, were more subtle (Figure 4). We also predicted more widespread habitats for the NWA rodent reservoirs, shifting away from currently high human population density areas toward yet untransformed areas.

We projected the species distribution of *Z. brevicauda* to shift inland and away from the Caribbean coast and towards the forested and rural inland areas (Figure 4A). Our models predicted lower probabilities in existing metropolitan and highly populated areas, thereby demonstrating a migration of the rodent species to a larger and more widespread area. We also projected a westward shift for the species distribution patterns of *S.alstoni*  in the years 2041-2060 for both SSP 2-4.5 and 5-8.5 scenarios. Our models did not predict similar shifts for the species distribution of *C.callosus*. We projected minor changes for *C.callosus,* where the probability of species presence increased for northern parts of Paraguay and western Brazil, with lower probabilities in central Bolivia and northern Argentina (Figure 4B). We predicted a decrease in probabilities of presence in the central region of Argentina for *C.musculinus* (Figure 4C). Conversely, we predicted increased probabilities *for C.laucha* and *O.flavescens* in the same region, thereby showing changes in the rodent species inhabiting this region (Figure 4C). We projected the presence of *O.flavescens* to shift northward, whereas that of *C.musculinus* to shift southward. The presence of *C.laucha* was projected to shift inland into the central region. Specific geographical changes for each species distribution can be seen in Supplementary Table S2.3.

In terms of features that were important for prediction of species distribution patterns, our models predicted varying features for different rodent reservoir species (comprehensive results in Supplementary Table S2.2). This variability indicated that each rodent species was sensitive to different climate and environmental conditions. In general, the most important features for *Z.brevicauda* were crop land and temperature seasonality. For *S.alstoni* the most important features were precipitation and temperature seasonality. For *C.callosus*, the annual and the diurnal temperature range were found to be most important. For *C.musculinus*, the most important features were presence of urban land, and the annual precipitation. For *C.laucha*, crop land and maximum temperature in the warm period (month and quarter, equally) were found to be the most important features. For *O.flavescens*, crop and urban land were equally important followed by annual precipitation.

# Discussion

Our models predicted that NWAs could theoretically emerge and cause larger scale outbreaks in non-endemic areas that fall within the expanding habitats of the reservoir species due to climate change impacts. We used an epidemiological perspective to link the habitat patterns of NWA rodent reservoirs to the possibility of a spillover outbreak in humans. A higher FOI (representing the spillover risk) was interpreted as a higher probability of the reservoirs’ presence as well as a higher probability of spillover from an infectious reservoir animal to the human(s) it encounters. This interpretation was not unlike multiple prior studies that used species distribution models in determining habitat suitability for disease vectors and reservoirs 29.

Besides emergence in non-endemic regions, we predicted overlapping areas marked by high spillover risk of Bolivian Hemorrhagic Fever (BHF) and Argentinian Hemorrhagic Fever (AHF) which are caused by two different NWAs, MACV and JUNV, respectively. Persistence of some of the potential hotspots in endemic regions was in alignment with the finding that in previously recorded endemic areas such as Portuguesa state in Venezuela, Silva-Ramos et al. (2024) have shown increased and persistent hotspot zones for VHF outbreaks 30. Since the higher FOI estimate depended on having a high rodent occurrence as well as a high human population, we assumed a higher frequency of rodent-human contacts based on population density. This means it is possible that the disease risk was overestimated. Historically, Salazar et al.(2002) found that the extent of habitat of rodent reservoirs was much bigger compared to the disease endemic areas that recorded any outbreaks for NWAs 31. On the other hand, it is highly probable that the NWAs could spill over into non-endemic regions due to changes in human movement patterns as well as changes in the rodent habitats that increased proximity to human settlements.

In general, the changes in spillover risk corresponded with the predicted changes in the contact pattern of humans and rodent reservoirs that was also concluded by Tsui et al. (2024), where predicting human movements due to adverse climate change or weather patterns in conjunction with habitat changes in non-endemic areas might be necessary to predict the spillover risks 32. Our outcomes conform with the findings of previous studies which showed that ecological traits of rodent reservoir species in the New World are sensitive to the changes in temperature range and/ or seasonality as well as precipitation patterns and the rainy season 33–35. Secondary effects of climate change such as alterations in anthropogenic land use and subsequent effects on disease dynamics have also been reported previously 36. Due to changing ecological conditions, rodent life cycle disruptions are expected, which may lead to population booms in previously non-habitable zones for the species that maintain viral reservoirs 37.

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Our models predicted increased risk in non-endemic regions that might be ill-equipped in their public health apparatus to deal with large scale outbreaks. As climate continues to change, disease reservoirs will adapt by changing habitat patterns which will in turn increase the reservoir-to-human contacts that can lead to outbreaks. Flexible prediction frameworks such as this can be instrumental in identifying and monitoring high risk hotspot zones for zoonotic outbreaks. Considering that the global climate trajectory is along the lines of the moderate climate change scenario, our predictions are particularly salient for the responsible public health systems in terms of prioritizing surveillance and close monitoring of potential outbreak hotspots thereby making efficient use of scarce health resources. Furthermore, our methodological framework for these diseases can be adapted to other neglected diseases, as well as other climate scenarios that can serve as templates for global health agencies to prioritize at-risk communities and countries facing disproportionately large health burdens due to outbreak risks.

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# Acknowledgements

All figures in this manuscript were compiled from original sub-figures using BioRender.com.

# Funding

This work was supported by the Wellcome Trust grant number 226099/Z/22/Z. P.S.P. is also supported by the National Science Foundation under Award Number DMS-2325267.