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

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# Abstract

The long-term impacts of climate change on the risk of zoonotic disease outbreaks such as New World arenaviral hemorrhagic fevers are poorly understood and understudied. Endemic areas and their surrounding regions are expected to undergo significant changes in both climate patterns and anthropogenic activities. Through this study we aimed to advance insight into the impact of climate change on the spillover risks of neglected high-impact zoonotic diseases such as New World Arenaviruses (NWAs) in South America. A robust predictive modeling framework that integrated force-of-infection models with comprehensive species distribution algorithms was developed for understanding the effects of climate change on zoonotic disease risk.

We predicted a substantial increase in the risk of NWA spillover from known rodent reservoirs to humans in the next two decades. Risk was predicted to increase with climate change and related anthropogenic factors regardless of the severity of the projected climate change scenario modeled. For all NWAs studied, reservoir habitats were predicted to spread out in the future, increasing the chance of human-rodent interactions and consequently the spillover of NWA infections. Depending on the reservoir species, habitat changes were found to be sensitive to the long-term changes in varying climate and land-use features.

## Keywords

Mammarenavirus, rodent reservoirs, species distribution, spillover, machine learning

# 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. Multiple climate models have predicted shifts in the habitats of vectors, including changes in rainfall and temperature patterns 2, leading to an increased transmission and potential outbreak risk of arthropod-borne diseases like Yellow fever, Dengue, and Lyme disease in non-endemic regions 2. Indeed, localized endemic neglected tropical diseases are being increasingly reported in neighboring, previously unaffected, areas 3. Similar to arthropod-borne diseases, rodent-borne diseases are also expected to be affected by climate change 2,3,5.

Climate change affects disease risk via three key mechanisms: (i) the expansion of suitable habitats, (ii) warmer zones changing vector behavior , and, in turn, (iii) longer disease outbreak seasons6. Carlson et al. (2022), estimated that, globally, more than 3000 mammalian species, including rodents, are expected to change habitats by 2070 7. 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 8. 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), will be affected given the expected changes in climate and the environment in the coming two to five decades 9. Due to their potential impact, Lassa fever virus and Junin virus (JUNV) have been selected as prototype viruses for pandemic preparedness10–12. Specifically, the risk of Lassa fever (reservoir *Mastomys natalensis*) in Western African countries is projected to increase significantly as the regional climate changes over the coming two decades13.

Arenavirus spillover into humans is strongly affected by human-rodent contact and the distribution of rodent reservoirs. 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. 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 and biting from reservoir hosts 15,16. Increasing reports of emerging zoonotic arenaviruses may also be attributed to improvement of detection capacities alongside likely increased rodent host range and species interactions influenced by changing environmental variables 17,18. 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 2,19

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% 20. 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 21–23. 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) and the US State Department, the disease dynamics and reservoir distributions of GTOV, MACV, and JUNV have not been modeled, to our knowledge 11. 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 (SSP, CMIP6) 24. Moreover, precipitation followed by prolonged droughts may increase wildfire risk and become prominent 25. 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 26. 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 27. Similarly, temperature, rainfall, and land-use changes are all presumed to influence rodent populations in South America￼￼. 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 New World Arenaviruses 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. The NWAs under study, namely, GTOV, MACV and JUNV have caused historically confirmed outbreaks of Venezuelan, Bolivian, and Argentine Hemorrhagic fevers, respectively. FOI estimates were mechanistically modeled based on the species distribution patterns and estimated population density of six known rodent reservoir species for NWAs (hereafter genus name is abbreviated to its first letter followed by a period): *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 29￼ , namely, (ii) SSP 2-4.5 (Moderate Climate Change Scenario) and (iii) SSP 5-8.5 (Extreme Climate Change Scenario) of years 2041-2060. We also present insights into the association between projected changes in bioclimatic and environmental data and projected changes in the FOI.

# Results and Discussion

## 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 where the hotspots (highest 10% of FOI estimates) for all three modeled NWAs were concentrated in coastal and metropolitan areas(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 results. When compared with the current climate scenario, the differences with SSP 2-4.5 were more prominent than with SSP 5-8.5 (Figure 1 and Figure 2). We also projected that various eco-regions in countries historically affected by NWAs will have higher FOIs in both climate change scenarios when compared to the current scenario.

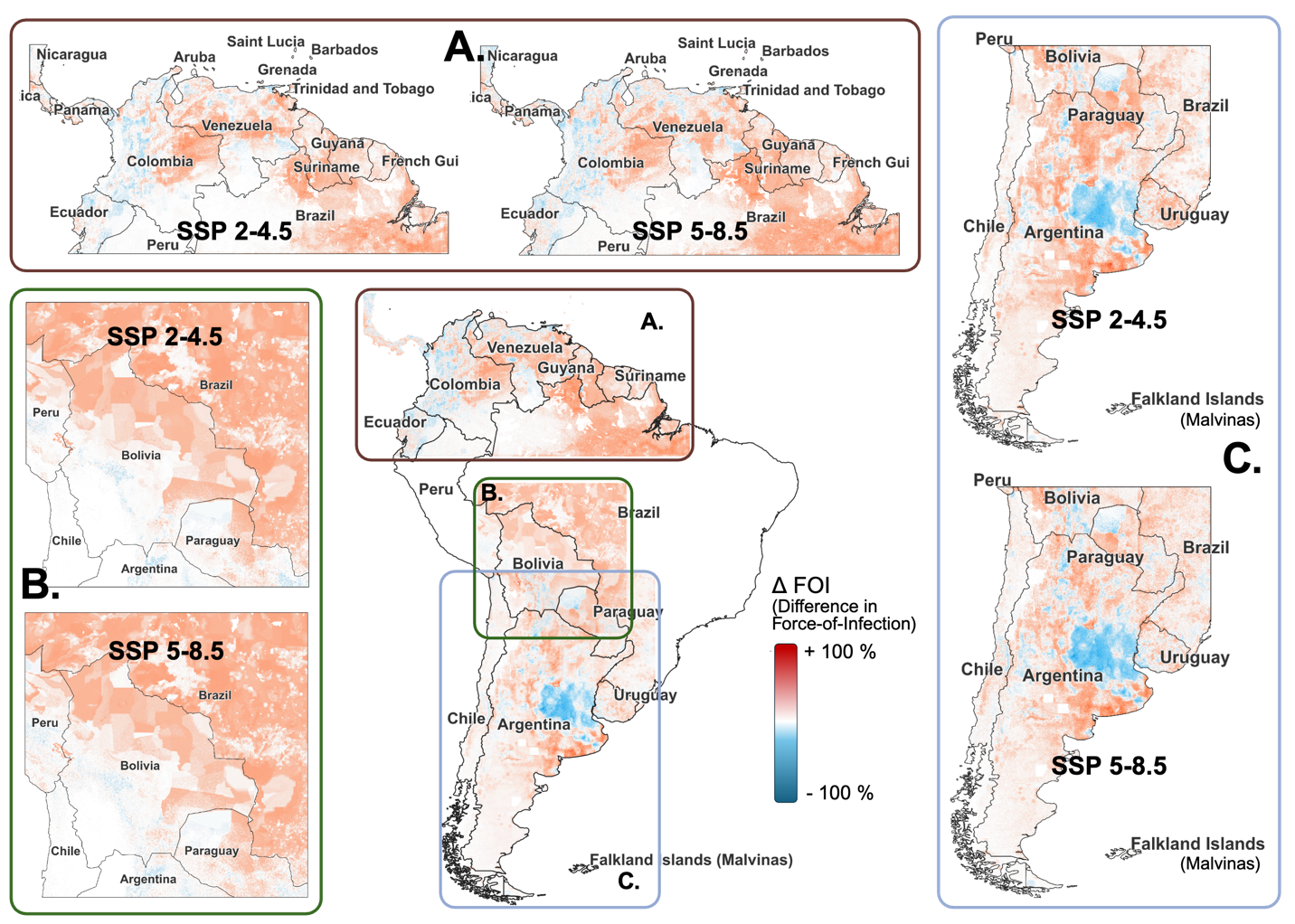


Figure 1. Changes in zoonotic risk of New World Arenaviruses (NWAs) represented by the difference in Force-Of-Infection (FOI) estimates between the current climate and two projected climate change scenarios: SSP 2-4.5 (Moderate Climate Change Scenario) and SSP 5-8.5 (Extreme Climate Change Scenario). A: Map of the difference between FOI estimates in future scenarios and the current climate for Guanarito Virus (GTOV), which causes Venezuelan Hemorrhagic Fever (VHF); each subpanel shows the range of difference: blue = lower FOI and red = higher FOI). B: Map of the difference in FOI estimates for Machupo Virus (MACV), which causes Bolivian Hemorrhagic Fever (BHF). C: Map of the difference in FOI estimates for Junin Virus (JUNV), which causes Argentine Hemorrhagic Fever (AHF).

In both climate change scenarios, the risk of GTOV transmission was estimated to be more widespread, showing up outside of the endemic zones of historical outbreaks. This signals a shift in the disease risk. Non-endemic areas, especially in the eastern countries of Guyana, Suriname and northern Brazil, showed a positive change in risk compared to the currently endemic zones across the extent of the habitat of the reservoir species (Figure 1A). Our models also predicted higher disease risk for the non-endemic northern part of Colombia in the current climate scenario, which has not reported a prior outbreak of Venezuelan Hemorrhagic Fever (VHF). In contrast, the endemic regions along the northern seashore of Venezuela showed a negative change in estimated FOI for both climate change scenarios. This predicted risk for endemic areas was also lower for the two future scenarios. The FOI remained unchanged in the interior region, distant from the coastal areas beyond the endemic regions but 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 overall risk in terms of FOI was higher for both future climate change scenarios compared to the current estimates. The endemic zones along the eastern foothills of the Bolivian Andes mountains had a negative change in FOI, whereas the non-endemic zones of interior grasslands in Bolivia and Paraguay showed a positive change 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).

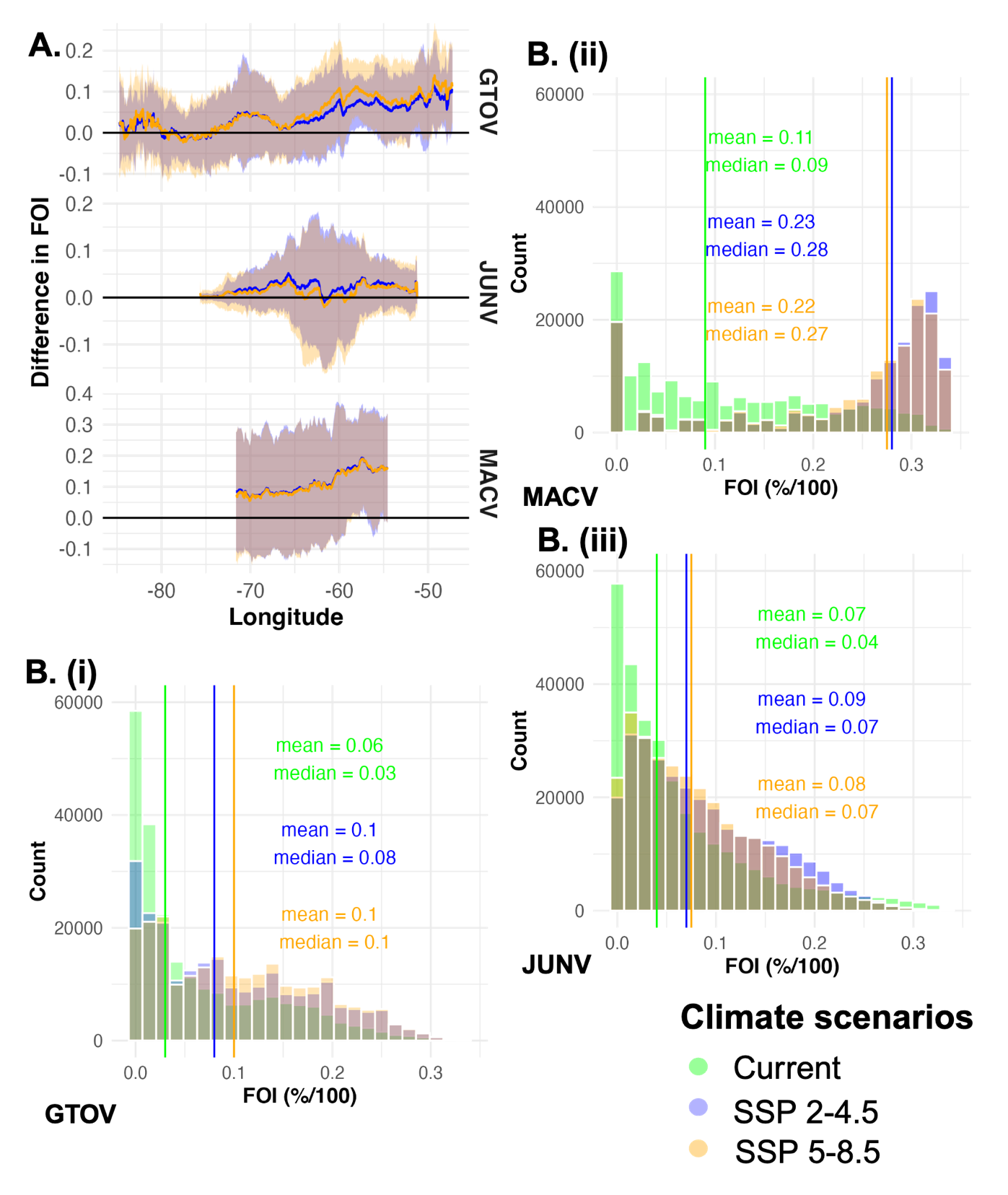


Figure 2. Descriptive statistics of the FOI estimates and their differences for all three climate scenarios (1 current; 2 Shared Socio-economic Pathways - SSPs). A. Difference in FOI estimates across geographical longitude (west to east; x-axis) between current and SSP scenarios (y-axis) with confidence intervals (1.96\*SD) for the three NWAs. B. Histograms of the FOI estimates for current and the two SSP scenarios for (i). GTOV, (ii). MACV and (iii). JUNV (the vertical lines represent the median FOI estimates. Y-axis represents the count of pixels on the raster with resolution = 0.042 degrees).

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). This pattern of higher risk in the east versus the west was not evident for JUNV (possibly because of the shape of Argentina and the Pampas habitat mostly being in the center of the country). For GTOV, the increase in predicted spillover risk in non-endemic regions of Guyana, Suriname, French Guinea and Brazil and a lower risk in endemic zones of northern Venezuela were evident. 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 a substantial portion of potential hotspots for NWA spillover in the current scenario (marked by high FOI predictions) remained persistent in both moderate and extreme climate change scenarios (see supplementary Figure S1.3).

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. Here, by integrating the human population and estimated rodent population data, we added an epidemiological context to the link between the habitat patterns of the NWA rodent reservoirs and the possibility of spillover into humans through direct contact with the rodent reservoir. We defined an FOI metric that calculated the probability of successful transmission of infection from infectious rodents to a susceptible human upon contact between them. With this novel methodology, we improved on our prior study in which we identified the potential hotspots for outbreaks per geographical unit (0.042 degrees) that had high human populations as well as high probabilities of presence for the rodent reservoirs of NWAs 19. Holding the magnitude of human movement constant, previous studies suggest that disease spillover risk might be proportional to rodent reservoir presence 30. Human population movements into areas where contact with reservoirs is likely, could cause emergent spillover into new areas. For example, outbreaks of VHF may emerge in Colombia and northern Brazil related to mass movement of humans along the border due to ongoing geopolitical unrest in Venezuela 16,31. However, there is a significant lack of epidemiological studies in the prior two decades related to NWA spread and spillover risk for comparison with the risk predicted by our models 16,32.

Besides emergence in non-endemic regions, we predicted overlapping potential hotspots 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. Theories exist for mixing and sharing of rodent reservoirs by different NWAs. For example, mixed reservoirs may spread both MACV and Chapare virus in Bolivia, and *Sigmodon alstoni* is a common reservoir for both Guanarito and Pirital viruses in Venezuela 33. Considering this, our predicted hotspots that overlap between two NWAs might be grounds for multi-etiological outbreaks of hemorrhagic fever in the future. Phylogenetic studies have shown that depending on the relatedness of reservoir species, NWAs can indeed switch or exchange reservoirs which have overlapping geographical habitats 34. Further research backed by serological evidence is necessary for confirming competency of rodent species to be implicated as reservoir species for multiple NWAs. 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 33.

Even though an extreme scenario of climate change might exacerbate the risk of human spillover due to changes in rodent-human contact patterns and frequency 35, the opposite might also be true. Zoonotic hazard for rodent-borne viral diseases might not decrease under more optimistic (sustainable) climate change scenarios due to long-term land use changes and other environmental alterations, such as SSP 1-1.9 or SSP 1-2.6 36,37. Moreover, since the higher FOI 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 38. On the other hand, it is highly probable that the NWAs could spillover 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.

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

Projected changes in the NWAs’ FOIs for the two climate change scenarios compared to the current scenario indicated that the FOIs were driven largely by the expected changes in human population in semi-urban and rural areas combined with the predicted changes in the habitat of the rodent reservoir species. 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). While temperature-based features showed an almost monotonic relationship with the changes in FOI, the partial dependences for changes in precipitation and land-use variables were more complex (Figure 3B).

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Figure 3. A. Importance of the different environmental features used for predicting the change in spillover risk represented by the estimated Force-Of-Infection (FOI) B. Partial dependence plots for the top three most important features of the three New World Arenaviruses (NWAs), GTOV, JUNV, MACV, for the moderate climate change (SSP2-4.5) and the extreme climate change (SSP5-8.5) scenarios compared to the current climate.

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 39. In contrast, the estimated change in FOI decreased sharply 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 40.

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. The decrease in FOI corresponded to a flatter trend with a change in precipitation of the driest month (Figure 3B). 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 41,42. Additionally, the human population is predicted to migrate towards the savannahs and non-forested areas in both SSP 2-4.5 and SSP 5-8.5, away from current urban clusters 43.

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, asymptotically positive for increase in urban land and asymptotically negative for precipitation in the warmest quarter (Figure 3B). For the SSP 5-8.5, changes in FOI and changes in all three top features corresponded to flatter curves. 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 19,44.

In general, the changes in spillover risk corresponded with the predicted changes in the contact pattern of humans and rodent reservoirs. This is in line with the conclusions of 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 45. 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 46–48. Secondary effects of climate change such as alterations in anthropogenic land use and subsequent effects on disease dynamics have also been reported previously 49. 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 50. We theorize that this, in addition to shifting patterns of human movement, will increase contact between reservoir species and susceptible human populations.

## Differing Species Distribution Patterns of NWA Rodent Reservoirs predicted in response to climate change

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.

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Figure 4. Change in the species distribution probabilities for six NWA rodent reservoir species between current climate and the projected moderate climate change (SSP 2-4.5) and the extreme climate change (SSP 5-8.5) scenarios. A. Change in species distribution probabilities for Zygodontomys brevicauda and Sigmodon alstoni, the reservoir species for Guanarito virus (GTOV) which causes Venezuelan Hemorrhagic fever (VHF). B. Change in SDM probabilities for Calomys callosus, the reservoir species of Machupo virus (MACV) which causes Bolivian Hemorrhagic Fever (BHF). C. Change in SDM probabilities for Calomys musculinus, Calomys laucha and Oligoryzomys flavescens, the reservoir species of Junin virus (JUNV) which causes Argentine Hemorrhagic Fever (AHF).

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 and metropolitan areas toward more rural and 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. Between the two climate change scenarios of SSP 2-4.5 and 5.85, we predicted very minor differences in the changing patterns of species distribution. Most changes were associated with the actual magnitude of probabilities of presence of a particular rodent species whereas the geographical spread was consistent.

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. Moreover, the feature importance of each algorithm was also different. In general, the most important features for *Z.brevicauda* were crop land and temperature seasonality. For *S.alstoni* the most important features were precipitation seasonality and temperature seasonality. For *C.callosus*, the annual temperature range and the diurnal temperature range were found to be most important. For *C.musculinus*, the most important features were presence of urban land, and 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.

We theorize that the changing temperature and precipitation conditions along with more days with extreme climate might explain the drastic changes predicted in the habitats of the rodent reservoirs in both climate change scenarios. The adverse climate conditions also lead to changes in food and shelter availability with changes in vegetation that indirectly affect the habitats of wild rodents to a large degree 51. Considering that all six of the NWA reservoirs are highly adaptable, habitat changes are expected without significant loss in population size 40. Our predicted widespread habitat distribution for all six rodent species also signals a possible fragmentation of rodent habitats in the future. Particularly for MACV and JUNV, habitat fragmentation is expected in the future in all climate change scenarios for Andean foothill biomes as well as grasslands in northern Argentina, Bolivia and neighboring Paraguay and Chile. 52.

## Modeling framework for changing risk of rodent-borne zoonotic diseases: Performance and Metrics

We applied ensemble Machine Learning (ML) algorithms based on decision tree methods to develop Species Distribution Models (SDMs) for predicting the habitat suitability for six rodent reservoirs of NWAs under two future climate change scenarios (SSP2-4.5 and SSP5-8.5) in the next 20–40 years.

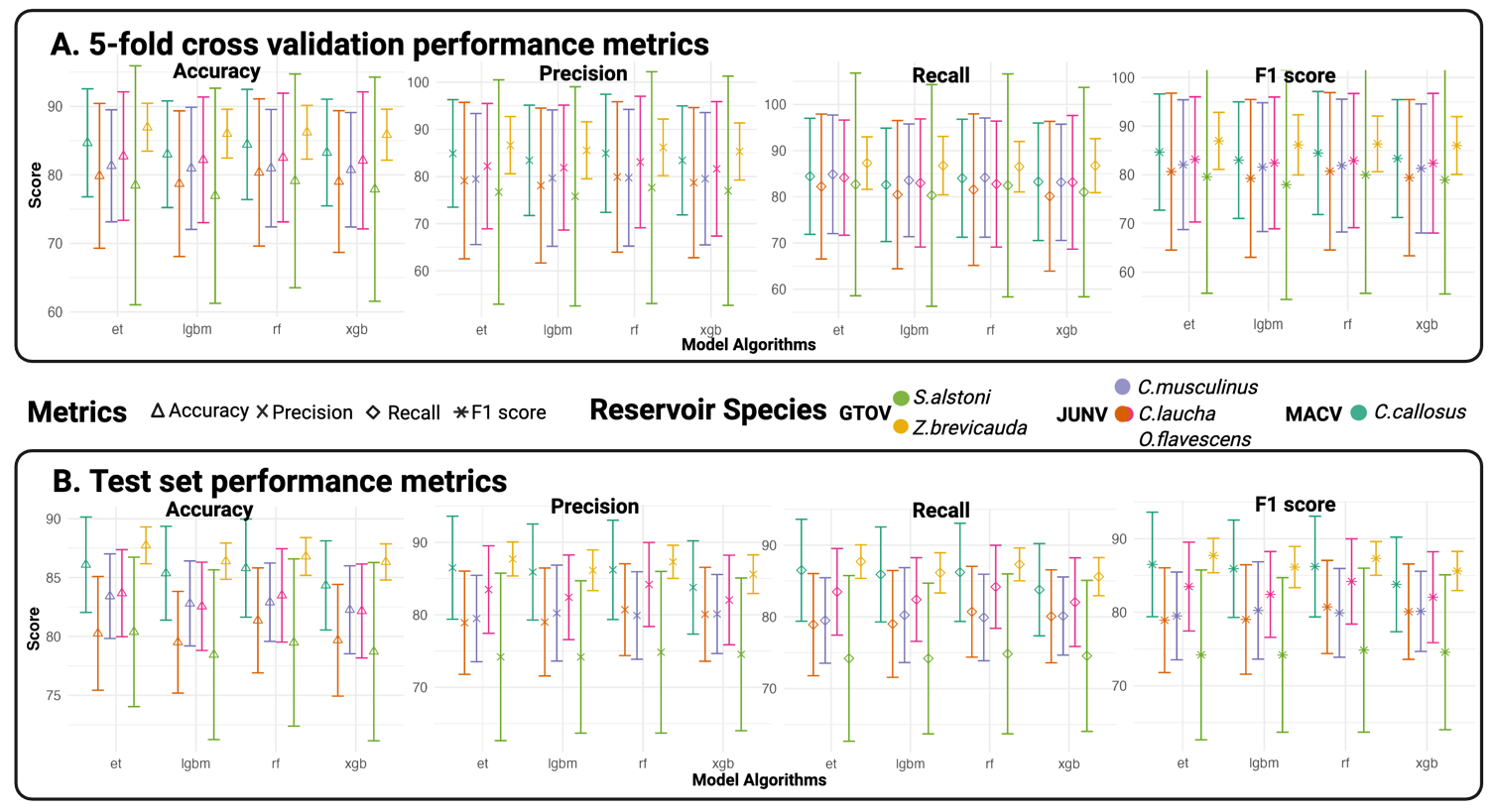


Figure 5. Prediction Performance metrics for the four model algorithms (rf: random forest, et: extra trees, xgb: extreme gradient boost , lgbm: light gradient boosting machine) used to develop Species Distribution Models (SDMs) for the six rodent reservoir species of the three New World Arenaviruses (NWAs), namely, Guanarito virus (GTOV), Machupo virus (MACV) and Junin virus (JUNV). A. 5-fold cross-validation metrics. B. Test-set prediction metrics. All scores have % units.

Overall, our models had a Cross-Validation (CV) accuracy between 77% to 87%. The recall score for species presence (recall for positives) ranged between 80% to 87% and the F1 scores were between 77% and 88% with a 12% to 20% false positive responses (Figure 5A). The metrics based on the test set (25% of the overall data) were not dissimilar to the metrics on the CV set (Figure 5B). In terms of predicting true presences, there were no clear differences in the confusion matrices (misclassification matrices; see Supplementary Figure S2.3).

The performance metrics magnitude was proportional to the number of historical occurrences for the rodent species in both validation and test datasets. This is in line with some of the prior studies which reported that the SDMs were sensitive to the number of positive signals in the sample data 53–56. Further, the geospatial variation within the extent of each species’ habitat also influenced the performance of the model in projecting species presence in future scenarios. This was conforming to prior literature in ensemble modeling in ecological studies 54,56–58. The similarity between the predictive performance on both validation and test datasets suggested that the models were not biased or overfit to the training data.

## General Discussion

This study aimed to establish the long-term impacts of climate change and associated anthropogenic features on the risk of NWA zoonotic spillover in South America. We predicted an expansion in the spillover risk for NWAs beyond the historically reported endemic zones in South America. These historically endemic areas are expected to undergo significant land use changes driven by changes in temperature, precipitation and seasonality patterns, such as the conversion of forests to arable lands and (semi-)urban regions . Further, we predicted that certain regions in South America, especially those around international borders, would see a rise in outbreaks due to the overlapping of species distributions of NWA rodent reservoirs. We established that the predicted risk of arenavirus zoonotic transmission and NWA rodent reservoirs are sensitive to different bioclimatic and land-based features. Through this study we made advances in obtaining insights on understudied but highly impactful zoonotic diseases such as NWAs and the impact of climate change on their zoonotic risks. Our models used an epidemiological perspective to link the habitat patterns of NWA rodent reservoirs to the possibility of a spillover outbreak in humans. This involved integration of human population and estimated rodent population distributions to inform the force-of-infection metric. Therefore, 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 59.

In our study, we restricted the focus to three NWAs--GTOV, MACV and JUNV--which have all been associated with outbreaks of substantial magnitude 39. This restriction excludes nine other potential NWAs out of 19 isolated and distinctly identified mammarenaviruses 49. Several of these NWAs have been shown to be emergent, such as Sabia virus in Brazil, Chapare virus in Bolivia, Pirital virus and Tacaribe virus in Venezuela and Guyana. But not many cases of these lesser-known NWAs have been reported with a confirmed diagnosis or with acute deaths investigated 39. This might be due to inconsistent case reporting caused by geopolitical or other socio-economic concerns, lack of detection capabilities, etc. Examples may include Venezuela, which stopped reporting hemorrhagic fever cases in 2008 due to social and political upheaval, or Bolivia which has not reported cases consistently since the 2017 BHF outbreak 39. Should we propose a solution or a reason why reporting should be encouraged?

We modeled known rodent reservoirs for NWAs, such as *Z. brevicauda* and *S. alstoni* for GTOV, *C.callosus* for MACV and *C. musculinus, C. laucha* and *O. flavescens* for JUNV. However, rodent species that are reservoirs for one virus might also be reservoirs for other similarly transmitted viruses and are thus non-specific reservoirs. For example, reservoirs of VHF caused by Guanarito have also been implicated in carrying viruses from the Bunyaviridae family as well as other Hantaviruses 60. The issue of putative rodent reservoirs is further complicated by the contentious classification of rodent species in the New World. Lendino et al. reported that the identification and classification of rodent reservoirs, especially those belonging to Sigmodontinae sub-family (New World rats and mice) 39. The continuously expanding species diversity and evolving classification of these species (especially around the Andes foothills 61), combined with different nomenclature and local names, makes it difficult to study as well as target reservoirs species of NWAs. To circumvent this issue, we applied a species distribution model for rodent reservoirs that was not limited to the extent of historically endemic zones of NWAs but rather by the geographical extent of reported suitable? habitat zones of the rodents. A macro-ecological outlook that is reservoir-centric rather than disease outbreak-centric could be more helpful given the lack of clarity on reservoir species diversity and their classification 62. Whether multiple reservoirs exist for the same virus, or the same reservoir for multiple viruses or multiple reservoirs carrying multiple viruses, the risk of zoonotic spillover of NWAs heavily depends on the presence, density and habitat patterns of reservoir hosts 62,63. In further studies, these risks may be predicted with increasing accuracy by combining granular data on human and reservoir populations and their interaction along with climate data.

# Conclusion

In this study we developed a novel framework combining species distribution modeling of known disease reservoirs with a mathematical interpretation of force of infection calculation to assess the impact of climate change on zoonotic spillover risk for NWAs in South America. Our predicted outcomes show that regardless of the severity of the climate change scenario, the zoonotic spillover risk and the risk of possible outbreaks of NWAs will increase and become more widespread in the next two decades. 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. Our study showcases the importance of predicting disease risks under the influence of a changing climate and its secondary environmental and anthropogenic effects. Considering that the global climate trajectory is along the lines of the moderate climate change scenario, our predictions are particularly salient for the rapid challenges faced by public health systems. Our methodological framework for these diseases can be adapted to other neglected diseases, as well as other climate scenarios.

# Methodology

## Rodent reservoirs for the New World Arenaviruses (NWA)

A systematic literature search revealed potential host species of arenaviruses that act as reservoirs for spillover of NWA in humans 38,41,47,64–68. Since involvement of certain rodent species as reservoirs for rare NWA are ambiguous or underreported in literature 38, we selected six well-established rodent species that act as reservoirs for NWA and their zoonotic spillover (Table 1). These six species, namely, *Zygodontomys brevicauda* and *Sigmodon alstoni* for GTOV, *Calomys callosus* for MACV, *Calomys musculinus, Calomys laucha* and *Oligoryzomys flavescens* for JUNV, have been established to be associated with outbreaks of their respective NWA in human populations (Table 1). The distribution of these rodent reservoirs over the geographical boundaries of the reported outbreaks of NWA in the past was modeled using species distribution models (SDMs).

Table 1. New World Arenaviruses (NWA) that were reported to cause zoonotic outbreaks in humans with their reported rodent reservoirs

|  |  |  |  |
| --- | --- | --- | --- |
| **Common name of virus** | **Common name of the disease** | **Reported rodent reservoir** | **Outbreaks reported** |
| **Junin virus (JUNV)** | Argentine Hemorrhagic fever | *Calomys musculinus*  *(*Dryland Vesper mouse*)* | 1950s, 1990-2018 |
|  |  | *Calomys laucha*  *(*Small Vesper mouse*)* |  |
|  |  | *Oligoryzomys flavescens*  *(Yellow pygmy rice rat)* |  |
| **Machupo virus**  **(MACV)** | Bolivian Hemorrhagic fever | *Calomys callosus*  *(Large Vesper mouse)* | 1960s |
| **Guanarito virus**  **(GTOV)** | Venezuelan Hemorrhagic fever | *Zygodontomys brevicauda*  *(Short-tailed Cane mouse)* | 1989-2010 |
|  |  | *Sigmodon alstoni*  *(Alston's Cotton rat)* |  |

## Species Distribution Model (SDM)

Modeling frameworks such as Species Distribution Models (SDMs), which can incorporate bioclimatic and environmental factors to estimate the habitats of the rodent reservoirs could be effectively employed in predicting transmission risk for associated diseases 54. Since the modeled association between climate change and species distribution were not expected to be monotonic 69 but rather complex and subtle, modifying the SDM framework to employ ensemble tree-based techniques such as random forest (rf), extra trees (et), extreme gradient boost (xgb) and light gradient boosting machine (lgbm) is warranted 70. We followed a similar protocol to the one we used previously for modeling the species distribution of *Calomys musculinus* in Argentina 19. The protocol was adapted to each of the rodent species selected for this study (Table 1). Here is a summary of the SDM protocol (Figure 6) used to model the rodent reservoirs of NWA following the guidelines established for reporting Ecological Niche Models (ENMs) or SDMs to maximize reproducibility as closely as possible pertaining to our study 71.

### Data

Occurrence data on all six rodent species were sourced from Global Biodiversity Information Facility (GBIF) database (presence-only) 72 using R-package dismo 73 (Derived datasets 74). This data was cleaned to remove duplicates and restricted to years 1990 to the last reported record of occurrence in the GBIF database. All occurrences in the South American continent were retained regardless of the country. Presence-only data was preprocessed to be converted to 1:1 presence-absence data using habitat suitability analysis with R-package *USE::paSampling()* utilizing a uniform approach75. This was done to avoid sample location bias that commonly occurs with random sampling of a geographical extent without considering the environmental conditions as discussed by Da Re et al. (see Supplementary Section C3.4 for details) 76. Environmental and ecological data was sourced from open-source datasets, such as 19 Bioclimatic variables from World Clim (*Bioclim*), Normalized Differential Vegetation Index (*NDVI)* and Digital Elevation Model (*DEM*) from *Moderate-Resolution Imaging Spectroradiometer (MODIS) satellite database and 5 Land Use datasets from Land-Cover and Land-Use Change* (LCLUC) program maintained jointly by NASA and University of Maryland 77–81. These datasets were resampled to the highest common resolution and clipped to the extent of species occurrence data mentioned above for each individual rodent reservoir. In total, three sets of 24 to 26 rasters and six occurrence datasets were used for the SDMs (Supplementary Table S2.1).

Similarly, for predicting the species distribution in the future, analogous raster data for Bioclimactic variables 82, NDVI (data from 2020 for NDVI 78), DEM 79 and land use 83 were downloaded for Shared Socioeconomic Pathways 6 (SSP) scenarios of Moderate (SSP 2-4.5) and Extreme (SSP 5-8.5) predictions for climate change in the future as established by Coupled Model Intercomparison Project v6 (CMIP6) for years 2041 to 2060 29. These datasets were also preprocessed and resampled to the highest common resolution and averaged over the 20-year time period.

### Modeling algorithms

A diagram of different species distribution

AI-generated content may be incorrect.

Figure 6. Schematic illustration of the framework for deriving the impact of climate change on the spillover risk for the three New World Arenaviruses (NWAs) in South America. (Abbrev: ML: Machine Learning, CMIP6: Coupled Model Intercomparison Project phase 6, FOI: Force-of-Infection, H: Human Population/ unit area, R: Rodent Population/ unit area, β: transmission rate parameter)

SDMs were developed by fitting four ensemble tree-based classifier algorithms, namely, random forest (rf), extra trees (et), extreme gradient boost (xgb) and light gradient boosting machine (lgbm). Data was split into train-test ratio of 4:1 (80% train; 20% test) and missing values were imputed using *SimpleImputer()* from *scikit-learn* python library 84. Each algorithm was trained with 5-fold cross validation and the predictions for training and the test set were generated to extract cross-validation accuracy, precision, recall and the F1 score based on (i) 5-fold Cross Validation and (ii) test set confusion matrices. This process was iterated 100 times to add to the robustness of the models using 100 different presence-absence resamples from the occurrence data.

### Hypertuning and Feature selection

Since hyper tuning did not yield significant improvements to any of the four classifier algorithms (results not shown), the default hyper parameters were used. We expected a high level of collinearity between the rasters based on spatial correlation analysis (results not shown), given the nature of geospatial data. To counter this, a recursive feature selection (RFE) was performed in each iteration to improve the accuracy of the model without having potential issues with multicollinearity. In each iteration, 10 features were selected per classifier algorithm based on stratified cross validation of RFE performed before the iterative model training using *RFECV()* from scikit-learn84. Final fitted models were taken as average of all the iterations and of the four classifier algorithms.

### Model fitting, interpolation and projection

Based on the fitted models, the current distribution probabilities of each rodent species were imputed to the geographical extent of their occurrence data using *pyimpute* library in python 85. Similarly, the future distributions of the rodents in response to SSP 2-4.5 and SSP 5-8.5 scenarios of CMIP6 climate change were imputed based on the fitted models. Changes in the distribution probabilities were mapped on the raster for each of the scenarios by subtracting current probabilities from the future probabilities of species distribution. The process is illustrated in Figure 5.

## Zoonotic risk for spillover and force of infection

Based on the distribution probabilities of the SDM for each rodent reservoir, a risk profile for human outbreak, i.e. zoonotic spillover of NWA, was modeled using infection dynamics simulation. The current and CMIP6 scenario-based projections of human population density were overlaid on the SDM probabilities to generate a risk profile based on the force of infection for NWA spillover. Force-of-infection (FOI) was calculated based on the contact rate between humans and the rodent reservoirs and the possibility of the rodent testing positive as reservoir for the NWA.

The mechanistic model used for estimating FOI was a density dependent contact rate model with binomial sampling as detailed in Eq 1.

Eq (1)

Where, is the force of infection defined as the contact rate between susceptible humans and infectious rodents resulting in the successful transmission of infection, is the transmission rate parameter derived from review of analogous viral transmission dynamics studies (see Appendix: Force of Infection), is the population of susceptible humans set at 0.95 times that of total human population in the same geospatial coordinates of SDMs (author’s expertise and from study performed on Lassa Fever in Nigeria 86) and is the infectious proportion of the rodent population based on the binomial sampling between 1 and 15 rodents per grid cell, adjusted with the probability of presence of rodents in the given geospatial coordinates based of the SDMs. The denominator represents the total density of the interacting populations of human hosts and rodent reservoirs. Eq (1) was adapted from a generalized formula used in similar transmission studies of vector and rodent borne infections with and without the effect of climate change 87–89.

A similar methodology was followed using the projected SDM probabilities and the projected human population under the SSP 2-4.5 and SSP 5-8.5 scenarios of CMIP6 43. For generating these maps, the FOI of each reservoir species of the same virus were combined where was the rodent reservoir and .

The FOI of GTOV was formulated as .

The FOI of JUNV was similarly formulated as . The FOI for MACV was .

A similar process was repeated for and .

The differences ( between the future climate change scenarios (SSP 2-4.5 and SSP 5-8.5) and the current scenario of FOI ( and ) were calculated and scaled to be from -100% to +100%.

The map depicting FOI for each of the three viruses under study was further reclassified in 10% quantiles and the geospatial zones which had FOI values in the top 10th percentile (>= 90% of the FOI estimated range across the geographical bounds of the raster) were depicted as potential hotspot zones for outbreak of zoonotic arenaviruses.

## Association of changing risk with climate change

We modeled the associations between the changes in FOI and the changes in 24 bioclimatic and land-use features that were used to predict the species distribution patterns of three NWAs. *NDVI* and *DEM* features were dropped from these analyses due to a high number of missing values in the established resolution (0.042 degrees). The features were converted from raster data to tabular data for current and SSP scenarios. The difference between values was taken for each cell representing the features and the differences were scaled and centered to the mean. A similar process was repeated for the FOI rasters and a dataset representing the changes in the features and FOI was generated. The difference ( between future climate change scenarios (SSP 2-4.5 and SSP 5-8.5) and the current scenario of FOI ( and ) estimates and the features ( were used as inputs in a random forest regressor model for each of the three viruses. A random forest regressor model was fitted to the resulting datasets with and serving as outcomes of the model and and serving as the features.

For each random forest model, the feature importances based on mean impurity reduction were plotted and the top three most important features were extracted for partial dependence plots (*PDPlots*). The random forest models were initially developed using the ranger() package from R 4.1.1 90 and finally fit in *sci-kit learn* python library 84 by using *RandomForestRegressor()* function. *PDPlots* of the top three features for each of the six models (three NWAs X two SSP scenarios) were developed from average grid values and predicted outcomes using functions from scikit-learn, matplotlib and seaborn packages in python 84,91,92.

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