Development of a dynamic model for the emergence of Lassa fever in West Africa

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David Simons

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Contents

Declaration . . . 7
Abstract . . . 8
Impact statement . . . 9
List of Acronyms . . . 9
Definitions used . . . 9
Acknowledgements . . . 10
Chapter overview and collaborators . . . 11
Thesis outputs . . . 12

1 Introduction **13**

1.1 Zoonotic infectious diseases . . . 13
1.2 Global climate change and zoonoses . . . 15
1.3 Zoonoses discovery and species afinity: sampling considerations . . . 16
1.4 Focussing in on rodent borne zoonoses . . . 17
1.5 Geographic hotspots for zoonosis risk in the light of varying surveillance activity . . . 21
1.6 Lassa fever: A case study of a rodent borne zoonosis in West Africa . . . 22
1.6.1 *Lassa mammarenavirus* and Lassa fever . . . 24
1.6.2 Lassa fever epidemiology . . . 26
1.6.3 Rodent hosts of *Lassa mammarenavirus* . . . 29

1.7 Thesis aims and structure . . . 34

2 Rodent trapping studies as an overlooked information source for understanding endemic and novel zoonotic spillover. 36

2.1 Preface . . . 36
2.2 Abstract . . . 36
2.3 Introduction . . . 37
2.4 Methods . . . 39
2.4.1 Host and pathogen trapping data . . . 39
2.4.2 Description of included studies . . . 41
2.4.3 What is the extent of spatial bias in the rodent trapping data? . . . 42
2.4.4 What is the difference in rodent host distributions between curated datasets and rodent trapping studies? . . . 44
2.4.5 Are rodent trapping derived host-pathogen associations present in a consolidated zoonoses dataset? . . . 44
2.4.6 What is the spatial extent of pathogen testing within host ranges? . . . 44
2.5 Results . . . 45
2.5.1 What is the extent of spatial bias in the rodent trapping data? . . . 45
2.5.2 What is the difference in rodent host distributions between curated datasets and rodent trapping studies? . . . 47
2.5.3 Are rodent trapping derived host-pathogen associations present in a consolidated zoonoses dataset? . . . 50
2.5.4 What is the spatial extent of pathogen testing within a host's range? . . . 50
2.6 Discussion . . . 53

3 Small mammal species community structures vary importantly by land-use type in a Lassa fever endemic region of Sierra Leone. 57

3.1 Preamble . . . 57
3.2 Abstract . . . 57
3.3 Introduction . . . 57
3.4 Methods . . . 57
3.4.1 Study area . . . 57
3.4.2 Rodent sampling . . . 57
3.4.3 Statistical analysis . . . 57

3.5 Results . . . 57
3.5.1 Rodent occurrence and species assemblage structure . . . 57
3.5.2 Estimating the effect of land use on species occurrence and richness . . . 57
3.5.3 Co-occurrence of rodent species . . . 57
3.6 Discussion . . . 57
3.7 Summary . . . 57

4 Reconstructing rodent contact networks to understand potential routes of *Lassa mammarenavirus* transmission. 58

4.1 Preamble . . . 58
4.2 Introduction . . . 58
4.3 Methods . . . 58
4.3.1 Study area . . . 58
4.3.2 Rodent sampling . . . 58
4.3.3 *Lassa mammarenavirus* serology . . . 58
4.3.4 Statistical analysis . . . 58
4.4 Results . . . 58
4.4.1 *Lassa mammarenavirus* serology . . . 58
4.4.2 Rodent contact networks . . . 58
4.5 Discussion . . . 58
4.6 Summary . . . 58

5 Conclusions and future research directions. 59

5.1 Contribution to understanding biases in currently available data . . . 60
5.2 Integrating species assemblages into the hazard of zoonotic pathogen spillover . . . 60
5.3 Understanding the epidemiology and risk of Lassa Fever . . . 60
5.4 Future directions . . . 60

6 Bibliography 62

7 Appendix 76

List of Figures

1.1 The sampling of the global host-pathogen system is incomplete and sparse. Bars indicate the number of known pathogens within different mammalian orders; the values within the bars indicate the number of species within the order known to host these pathogens. Data obtained from CLOVER (Gibb et al. 2021). 18

1.2 Discovery of pathogens in Rodentia, the order containing the greatest number of zoonotic pathogens, has increased over time. Data obtained from CLOVER (Gibb et al. 2021). 19

1.3 Global Health Security Index country scores for the sub-domains of2.3) Real-time surveillance and reporting (top) and 1.2.2) Zoonotic disease surveillance (bottom). Real-time surveillance and reporting for epidemics of potential international concern is rated highly in several North and South American countries and countries in East and South East Asia and Oceania. Zoonotic disease surveillance in animals is rated highly in European, North and South American countries and Oceania. Generally surveillance for zoonotic infectious disease is limited across much of Africa, with the notable exception of Nigeria for real-time surveillance and reporting. Data obtained from the Global Health Security Index. 23

1.4 Lassa fever is considered endemic in eight West African countries, sporadic outbreaks have been reported from a further two countries within the region. The red border indicates the range of *Mastomys natalensis* in West Africa, its range extends East and South across the continent (not shown here). Data on Lassa fever endemicity is obtained from the WHO, data on *Mastomys natalensis* range is obtained from the International Union for Conservation of Nature Red List. 27

1.5 Confirmed Lassa fever cases from countries in West Africa 2008-2023. Confirmed cases show variability by year with the greatest number of cases reported from Nigeria, Sierra Leone and Liberia. Grey shaded regions represent periods of regional or global epidemics which may have affected Lassa fever reporting (i.e., the Ebola epidemic and SARS-CoV-2 pandemic). The yellow shaded region represents 2023 where an incomplete year is shown. Data compiled from multiple sources. 28

1.6 Prevalence of acute infection with LASV or antibodies to LASV in rodent species sampled in West Africa. The size of a point relates to the number of samples of that species tested and the colour to the country in which the rodent was sampled. Where possible the rodent species is identified, for individuals only identified to genus level the genera from which samples obtained is shown. Six rodent species have been found to be acutely infected with LASV with 10 species having detectable antibodies. The majority of samples have been obtained from rodents trapped in Guinea and Sierra Leone. (Will add in all the references) 32

2.1 **Rodent trapping sites across West Africa.** A) The location of trapping sites in West Africa. No sites were recorded from Togo or The Gambia. Heterogeneity is observed in the coverage of each country by trap night (colour) and location of sites. For example, Senegal, Mali and Sierra Leone have generally good coverage compared to Guinea and Burkina Faso. B) Histogram of trap nights performed at each study site, a median of 248 trap nights (IQR 116-500) was performed at each site. A labelled map of the study region is attached in S5 Fig. Basemap shapefile obtained from GADM 4.0.4 (GADM, 2022) 42

2.2 **Relative trapping effort bias across West Africa.** Modelled relative trapping effort bias adjusted for human population density, proportion urban land cover and area of the administrative region. Brown regions represent areas with a bias towards increased trapping effort (e.g., North West Senegal), Green regions represent areas with a bias towards reduced trapping effort (e.g., Northern Nigeria). Basemap shapefile obtained from GADM 4.0.4 (GADM, 2022) 46

2.3 **Locations of detection and non-detection sites for rodent species in West Africa.** Each row corresponds to a single rodent species. L) Presence recorded in GBIF (black points) overlaid on IUCN species range (red-shaded area). R) Detection (purple) and non-detection (orange) from rodent trapping studies overlaid on IUCN species ranges. *M. musculus* has no IUCN West African range. Basemap shapefile obtained from GADM 4.0.4 (GADM, 2022) 48

2.4 **Host-Pathogen associations detected through acute infection.** Identified species level host-pathogen associations through detection of acute infection (i.e. PCR, culture). Percentages and colour relate to the proportion of all assays that were positive, the number of individuals tested for the pathogen is labelled N. Associations with a black border are present in the CLOVER dataset. 51

2.5 **Host-Pathogen associations detected through evidence of prior infection.** Identified species level host-pathogen associations through serological assays (i.e. ELISA). Percentages and colour relate to the proportion of all assays that were positive, the number of individuals tested for the pathogen is labelled N. Associations with a black border are present in the CLOVER dataset. 52

List of Tables

1 Comparison of IUCN, GBIF and rodent trapping ranges for the 7 rodent species trapped at the most sites. 49

2 Comparison of pathogen sampling ranges for the 5 most widely sampled pathogens and the 5 most sampled rodent host species. 53

A dissertation submitted in partial fulfilment of the requirements for the degree of **Doctor of Philosophy**

Declaration

I certify that:

- The thesis being submitted for examination is my own account of my own research;
- My research has been conducted ethically;
- Where I have drawn on the work, ideas and results of others this has been appropriately cited in the thesis;
- Where any collaboration has taken place with other researchers, I have clearly stated in the thesis my own personal contribution;
- The entirety of the work described in the thesis has been undertaken subsequent to my registration for the higher degree for which I am submitting for examination;
- The thesis submitted is within the required word limit as specified by the RVC.

Abstract

Within West Africa endemic zoonotic infectious diseases cause preventable morbidity and mortality, the burden of which is expected to increase under future environmental, climate and biodiversity change. Rodents are important hosts of both vectors of zoonotic pathogens and of specific rodent borne zoonoses, an understanding of local scale rodent ecology is vital to quantify the risk of rodent borne zoonotic disease spillover into human populations. In this thesis I synthesise the available rodent trapping literature to summarise rodent distributions across West Africa and the extent of sampling biases of rodent hosts, their pathogens and host-pathogen associations. I find that current sampling efforts are spatially and taxonomically biased, limiting generalisability and inference able to be drawn from currently available data. I suggest approaches that are required to counteract some of these identified biases. The data collated has been incorporated into a global biodiversity database to support its re-use and to inform future models of zoonotic spillover risk.

I used this review of rodent trapping studies to design and implement a two-year, systematic, longitudinal study of rodent ecology in a Lassa fever endemic region of Eastern Sierra Leone to investigate the association of landuse type on rodent occurrence. I model the composition of rodent communities at fine spatial scale to infer the changing hazard of Lassa fever spillover across anthropogenic landuse gradients. I find that the known reservoir species of the Lassa fever virus is generally more likely to occur in locations of human landuse disturbance. I identify important biotic interactions between the primary reservoir of Lassa fever and other rodent species that lead to reduced occurrence in urbanised settings, which may abate the risk of pathogen spillover in these settings.

Finally, I reconstruct rodent direct and indirect contact networks to model the transmission networks of Lassa fever virus among rodent hosts across an anthropogenic landuse gradient. I find that hosts of Lassa fever virus have greater rates of contact events in species rich agricultural landuse settings compared to within villages. This suggests that contacts between susceptible and infectious rodents in agricultural settings may be maintaining viral prevalence which can then enter village dwelling rodent communities increasing the risk of pathogen spillover into human communities.

This thesis improves our understanding of the distribution of rodent hosts and endemic zoonotic pathogens across West Africa with a focus on the local rodent ecology maintaining Lassa fever endemism in Sierra Leone. I find that the hazard of zoonotic spillover is governed by biotic and abiotic systems at a local level and identify future directions to translate knowledge about these dynamic rodent communities into contextually relevant public health interventions using a One Health framework.

Impact statement

Placeholder

List of Acronyms

Placeholder

Definitions used

Zoonosis

Host

Pathogen

Microorganism

Land use

Acknowledgements

Placeholder

Chapter overview and collaborators

- **Chapter 1:** Background information is given. This information helps motivate future chapters.
- **Chapter 2:** This chapter presents a study conducted to synthesise rodent trapping data from West Africa. Focussing on a comparison to consolidated data sources on rodent host species ranges, presence-absence data and host-pathogen associations. The spatial biases of rodent trapping data are explored and data is presented in a suitable format for other researchers to incorporate in their analyses to mitigate bias from other data sources.
- **Chapter 3:** This chapter presents data from a two year rodent trapping study implemented as part of this thesis. This chapter focusses on rodent detection in different land use types. A model of occurrence by land use type is produced accounting for imperfect detection in observations of rodents.
- **Chapter 4:** This chapter presents data on rodent antibody prevalence to *Lassa mammarenavirus* from samples obtained as part of the two year rodent trapping study. The prevalence of antibodies to this virus are described at species and land use level. Contact networks between individuals of different species are reconstructed to investigate potential transmission networks.
- **Chapter 5:** Results from all previous Chapters are summarised and discussed as a whole. The strengths and weaknesses of the analysis in this thesis are outlined. Further work is outlined.

Thesis outputs

This thesis has produced: peer reviewed papers; preprints; talks at academic conferences and a dashboard for exploring relevant data. These outputs are detailed in the following section.

Peer reviewed papers

- Simons D., Attfield L., Jones K., Watson-Jones D., Kock R. *Rodent trapping studies as an overlooked information source for understanding endemic and novel zoonotic spillover*, PLOS NTD, 2023, …
- Simons D. *Lassa fever cases suffer from severe under-reporting based on reported fatalities*, International Health, 2023, …

Papers under review

- …

Software

- **Exploring Rodent Trapping Studies in West Africa**: Developed to showcase the data extracted and synthesised in the Chapter 2 and the associated publication "Rodent trapping studies as an overlooked information source for understanding endemic and novel zoonotic spillover article". Link: https://diddrog11.shinyapps.io/scoping_review_app/

Talks

- **Planetary Health Alliance**
- **EEID 2022**
- **Transmissible Vaccines 2023**

1 Introduction

1.1 Zoonotic infectious diseases

Zoonotic infectious diseases - or "zoonoses" - in humans are caused by pathogens transmitted either directly (e.g., bites or scratches) or indirectly (e.g., via vectors, environmental or food contamination) from from animal hosts, including livestock, wildlife, and pets (World Health Organization, Food and Agriculture Organization of the United Nations and World Organisation for Animal Health, 2019). Zoonoses include bacterial, fungal, parasitic and viral microorganisms. Within their animal hosts, zoonotic pathogens do not always cause clinical disease. For example, *Lassa mammarenavirus* (LASV), the causative agent of Lassa fever in humans is not considered to cause significant clinical disease in rodent host species' as measured through organ dysfunction, weight loss or behavioural change (Safronetz *et al.*, 2022). However, in humans LASV infection can lead to severe clinical symptoms and death (Thielebein *et al.*, 2022). In contrast, Highly Pathogenic Avian Influenza, caused by *Influenza A virus* (subtype H5N1), leads to significant morbidity and mortality in infected bird species alongside pathogenicity in humans (Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus, 2008; Haider *et al.*, 2017).

The wider term "zoonotic disease" is often used for a disease that first originated in non-human animals and may continue to be used, even when disease transmission is no longer dependent on an animal reservoir (e.g., HIV, SARS-CoV-2) (Kock and Caceres-Escobar, 2022). Individual transmission events from vertebrate animal populations into human populations - "spillover events" - can, lead to sustained outbreaks that may progress to localised epidemics or global pandemics (Plowright *et al.*, 2017). The patterns of spillover differ across zoonoses. For example, Nipah virus infection (*Nipah henipavirus*) and LASV spillover events from wild animal sources occur at relatively frequent intervals but result in limited, onward human-to-human transmission leading to small-sized, geographically constrained outbreaks of human disease (Luby *et al.*, 2009; Lo Iacono *et al.*, 2015). In contrast, Ebola virus disease (*Sudan ebolavirus* and *Zaire ebolavirus*) and mpox (formerly Monkeypox caused by the *Mpox virus*) exhibit sustained human-to-human transmission following spillover, but due to the transmission dynamics of these pathogens, outbreaks are generally constrained to local epidemics (Fine *et al.*, 1988; Legrand *et al.*, 2007). In addition, some pathogens may be better adapted to transmission among humans due to their specific properties or similarities between human physiology or immunology and those of the primary vertebrate reservoir. Such pathogens are able to rapidly expand beyond the geographic region of the initial spillover event via human transmission chains and may become zoonotic diseases with no further important transmission from wild or domestic animal populations (e.g.,

HIV and SARS-CoV-2) (Marx, Apetrei and Drucker, 2004; Ye *et al.*, 2020). Spillover may not be limited to a single direction of animal to human transmission and "spillback" can potentially play important roles in maintaining pathogen endemicity with subsequent "secondary spillover" into human populations, and alternatively, spillback can lead to morbidity and mortality in animal populations (Fagre *et al.*, 2022).

The different patterns of spillover are observable through phylogenetic analysis of viral sequences from human populations. For example, phylogenetic analysis of the SARS-CoV-2 virus suggests an initial spillover event into human populations in October and November of 2019 with establishment in the local human population ultimately leading to a global pandemic beginning in early 2020 (Pekar *et al.*, 2021). Similarly, the multi-country mpox outbreak in 2022 is proposed to be secondary to human-to-human sustained transmission from a single origin endemic country, either directly linked to a spillover event or cryptic (i.e., unobserved) transmission among local human populations (Isidro *et al.*, 2022). In contrast, phylogenetic analysis of LASV sequences indicate that the most common recent ancestor of viruses currently circulating in Nigeria originated >1000 years prior, while sequences from Guinea and Sierra Leone suggest a more recent introduction 220 and 150 years ago respectively (Andersen *et al.*, 2015). The interpretation of studies on LASV phylogenetics are consistent with repeated spillover events into human populations from pathogens circulating within a single or multiple reservoir species (Andersen *et al.*, 2015; Kafetzopoulou *et al.*, 2019; Villabona-Arenas, Hanage and Tully, 2020). While the 2022 mpox outbreak and ongoing SARS-CoV-2 pandemic are important examples of zoonoses causing epidemics and pandemics beyond their host species' ranges, these remain relatively rare events when compared to recurrent spillover events within endemic regions (Lloyd-Smith *et al.*, 2009; Dudas *et al.*, 2018). The example of LASV highlights the risk of recurrent local spillover into human populations in endemic regions and reinforces the importance of surveillance of known zoonoses.

When considering interventions to reduce the health impact of zoonoses in endemic settings (e.g., through reducing the risk of recurrent local spillover events), an approach that incorporates knowledge of multiple interacting systems are required. Understanding the role of environmental, wildlife and human factors on the risk of spillover events are necessary. This is often termed the "One Health" framework: a "collaborative, multisectoral, and transdisciplinary approach - working at the local, regional, national and global levels - with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment." (*One health | CDC*, 2022). This framework is particularly useful when considering how spillover of zoonoses occur in a context of ongoing climate, land use and biodiversity change.

1.2 Global climate change and zoonoses

Anthropogenic climate change has long been known to modify the risk of spillover of zoonoses into human populations through several mechanisms (Daszak, Cunningham and Hyatt, 2001; Jones *et al.*, 2013). For example, changes in mean temperature and precipitation will alter environmental suitability for both pathogens and hosts leading to expansion or contraction of endemic regions (Mills, Gage and Khan, 2010). In addition, environmentally transmitted zoonoses such as *Leptospira spp.* (causing Leptospirosis), become better able to persist in the environment under changes that increase ambient temperature in the presence of increased precipitation, leading to higher prevalence and incidence of infection (Lau *et al.*, 2010; Llop *et al.*, 2022). Vector borne zoonoses such as West Nile Virus are currently demonstrating range expansion as both mosquito vector abundance and occurrence is increased across a larger geographic range, likely due to a combination of warmer winter periods, increased precipitation and a higher prevalence of potential breeding sites (Hoover and Barker, 2016; Farooq *et al.*, 2022).

Climate change is occurring in step with anthropogenic land use change. Human driven conversion of natural landscapes towards human dominated use occurs at both a local and global scale through direct and indirect human actions (i.e., agricultural development, natural resource extraction, and urbanisation) (Gottdenker *et al.*, 2014). The association of land use change and pathogen transmission is complex, with increasing, decreasing and no change in pathogen transmission reported from observational studies of pathogen systems (Gottdenker *et al.*, 2014). Encroachment of human activity into zoonotic host animal ranges, as can occur under conditions of land use change, has been hypothesised to increase the risk of spillover events into human populations, through increasing the animal-human interface and raising the probability of direct and indirect contact with infected hosts of zoonoses (Murray and Daszak, 2013). Additionally, heightened interactions between wildlife and domesticated animals as a consequence of land use change and progression to intensive livestock production may also increase the risk of subsequent zoonosis spillover into human populations, where wild sylvatic animals are hosts of pathogens that can be amplified in domesticated animals (e.g., Nipah and Hendra virus) (Epstein *et al.*, 2006; Plowright *et al.*, 2015). In tandem, climate and land use change can also modify species' home ranges (Sultaire *et al.*, 2016; Brodie, 2016). As a consequence, an increased frequency of contact events between current and potential future hosts of zoonoses are produced, increasing the potential for cross-species pathogen transmission and the subsequent expansion of a zoonosis' endemic range (Carlson *et al.*, 2022). This has been observed with regards to Hendra virus, where Southern range expansion of the black fruit bat (*Pteropus alecto*) has resulted in domesticated horses in Australia being infected, with subsequent spillover events into human populations (Yuen *et al.*, 2021).

Animal biodiversity (or lack therof) has also been proposed to modulate zoonosis spillover risk, with sev-

eral mechanisms proposed. The "Dilution effect" - initially applied to the Lyme disease system (*Borrelia burgdorferi sensu lato*), which comprises several vectors and animal hosts - hypothesises that in settings of low species diversity (operationalised as species richness), infection rates increase in a host species. The inverse scenario is one in which higher levels of animal biodiversity is protective to human health through reducing the rate of zoonosis spillover into human populations (Ostfeld and Keesing, 2000). This theory has been supported by studies of several pathogen systems across parasites, bacteria, viruses and fungi (Keesing *et al.*, 2010; Civitello *et al.*, 2015). There is ongoing debate as to whether the Dilution effect is a general property of zoonosis systems, with several studies suggesting the inverse. This opposing mechanism, termed the "Amplification effect", occurs when increasing biodiversity, particularly through introduction of a new or more competent host species can increase the rate of infection in hosts and potentially the risk of zoonosis spillover (Johnson and Hoverman, 2012; Halliday *et al.*, 2017). These two effects may exist as a spectrum where dominance of one over the other is dependent on the specific disease context (Gómez-Hernández *et al.*, 2023).

Climate, land use and biodiversity change are interacting components within an ecosystem and attributing an effect of each independently to the risk of zoonosis spillover is challenging (Gibb, Franklinos, *et al.*, 2020). A synthesis of the effect of land use change on biodiversity across multiple spatial scales and zoonosis systems found that species richness of zoonotic pathogen host species, but not non-host species, increased along an anthropogenic land use gradient (Gibb, Redding, *et al.*, 2020). It should also be noted that the observed land use changes are occurring at different rates globally, which may complicate current findings. Climate, land use and biodiversity change occurring in regions associated with a greater diversity of known zoonotic pathogens may potentially have a greater impact on the risk of zoonosis spillover than in settings of low diversity of zoonotic pathogens.

1.3 Zoonoses discovery and species afinity: sampling considerations

The majority of microorganisms are non-pathogenic to humans or animals and provide vital ecosystem services. The small subset of microorganisms (<1%) that are pathogenic are typically able to replicate in multiple hosts (Cleaveland, Laurenson and Taylor, 2001; Woolhouse, Taylor and Haydon, 2001; Editors, 2011). It has been estimated that 60% of emerging human infectious diseases are associated with known zoonoses; therefore, it is not rare for a human infectious disease to be a zoonosis (Jones *et al.*, 2008). The discovery of zoonoses is variable across mammalian taxa, with sampling efforts increased in orders with increased human interaction or of special interest (i.e., primates and livestock species). Zoonoses are known to exist in the majority of terrestrial mammal orders (21/27) with the number of hosts of zoonotic pathogens

strongly positively associated with the species richness of these orders (Han, Kramer and Drake, 2016). A recently compiled dataset (CLOVER) contains an increased number of documented pathogens in Primates, Artiodactyla (ungulates) and Carnivora alongside Rodentia and Chiroptera (Gibb, Gregory F. Albery, *et al.*, 2021a; Gibb, Carlson and Farrell, 2021). 1.1 shows the number of known pathogens in these mammalian orders. Of these, Rodentia contain the greatest number of pathogens known to be zoonotic (Han, Kramer and Drake, 2016).

As can be gleaned from 1.1, two mammalian taxa, Rodentia and Chiroptera are associated with the greatest number of species that are hosts of zoonoses and overall number of zoonoses (Han *et al.*, 2015). It is unclear whether these taxa represent special reservoirs that lead to an increased proportion of zoonotic viruses circulating within these species or make them more likely to transmit pathogens to humans, or whether the increased number of zoonoses associated with these taxa is driven by their increased species richness (Wolfe, Dunavan and Diamond, 2007; Olival *et al.*, 2012; Luis *et al.*, 2013; Mollentze and Streicker, 2020).

These documented pathogens notwithstanding, the discovery of zoonoses is biased both by our ability to detect them and the sampling effort within different animal species and geographic regions (Grange *et al.*, 2021; Gibb, Gregory F. Albery, *et al.*, 2021b). The discovery rate of viral zoonoses, an important subset of all zoonoses, has increased with improvements in the technical means to detect and identify them (Woolhouse *et al.*, 2008). The rate of discovery has exceeded prior expectations of viral biodiversity, but continues to remain taxonomically and geographically biased, thus limiting the inferences that can be made with regardss to, for example, the risk of spillover events drawing on current data sources (Wille, Geoghegan and Holmes, 2021). Similar limitations are likely for other zoonoses taxa including bacteria, fungi and parasites. The general trend of increasing rates of pathogen discovery over time are shown for Rodentia in 1.2.

1.4 Focussing in on rodent borne zoonoses

A growing body of evidence is highlighting the importance of rodents as a key reservoir for known and expected zoonoses. Rodents are a diverse, globally distributed mammalian order that provide important and beneficial ecosystem services including pest regulation and seed dispersal (Fischer *et al.*, 2018). Of the almost 2,600 species, representing 40% of all mammalian species, 282 species (~11%) have been identified to be reservoirs of 95 known zoonoses, a greater number than other mammal orders (Han, Kramer and Drake, 2016; D'Elía, Fabre and Lessa, 2019; Ecke *et al.*, 2022). The majority of these zoonoses are viruses (34) and bacteria (26) with the remaining including helminths, protozoa and fungi. As discussed above the high prevalence in this order may be driven by high species richness, rather than any inherent properties of the order Rodentia (Mollentze and Streicker, 2020).

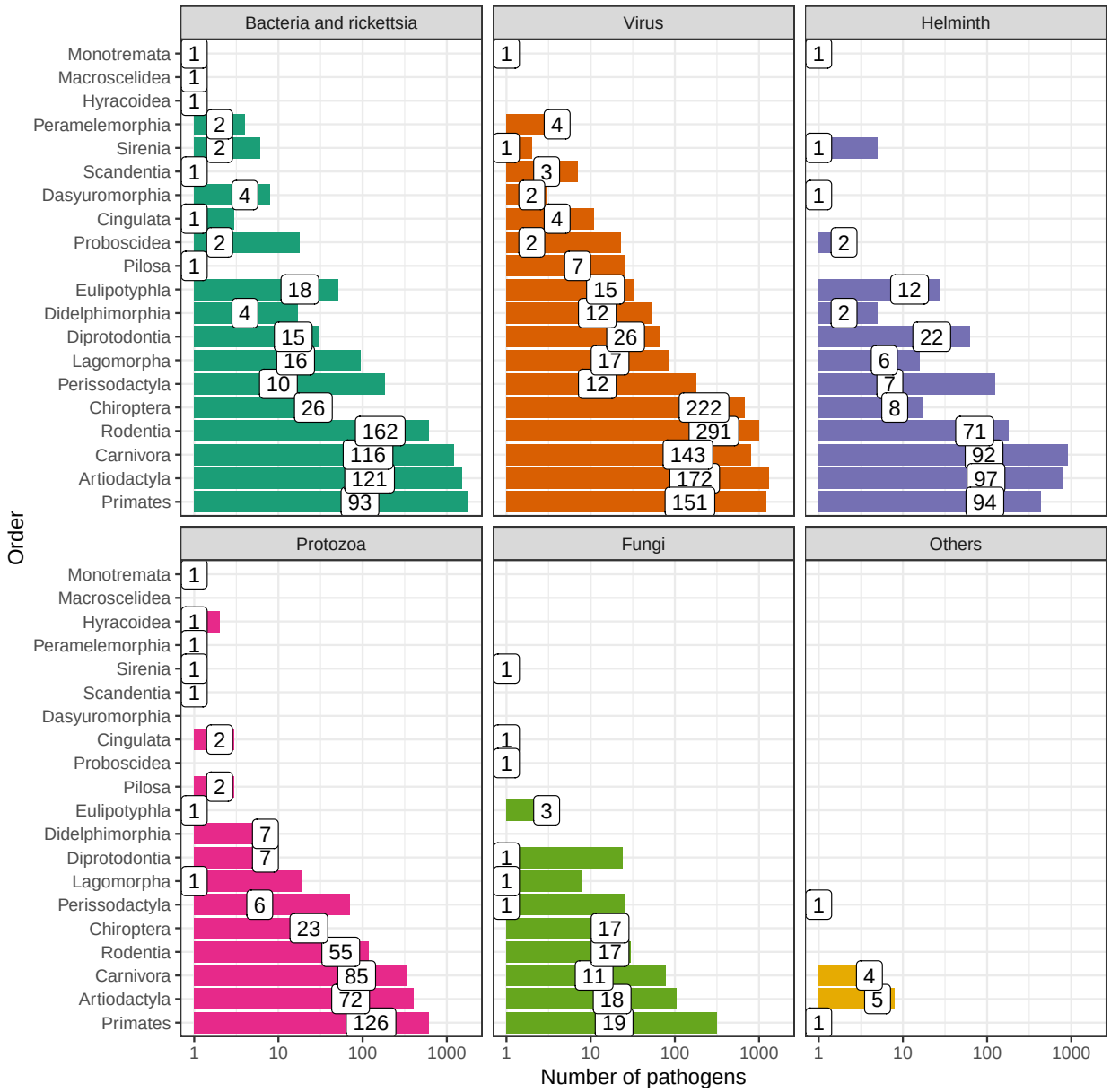

Figure 1.1: The sampling of the global host-pathogen system is incomplete and sparse. Bars indicate the number of known pathogens within different mammalian orders; the values within the bars indicate the number of species within the order known to host these pathogens. Data obtained from CLOVER (Gibb et al. 2021).

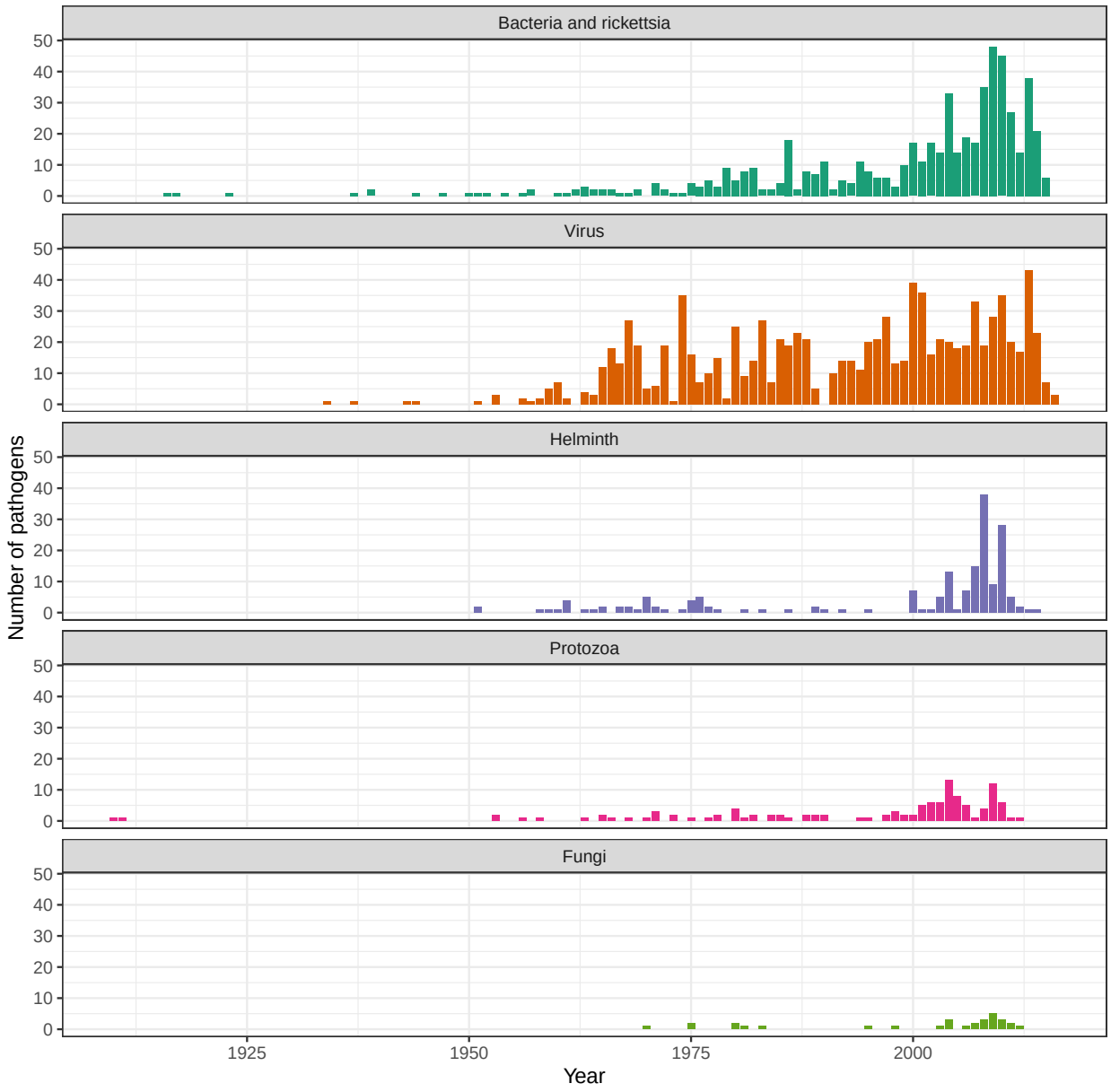

Figure 1.2: Discovery of pathogens in Rodentia, the order containing the greatest number of zoonotic pathogens, has increased over time. Data obtained from CLOVER (Gibb et al. 2021).

Within this order, the prevalence of zoonoses are disproportionally high within species that demonstrate "fast" life history strategies, although the effect of sampling biases and confounding effects such as synanthropy may be producing some of this observed effect (Han *et al.*, 2015; Albery and Becker, 2021). Fast-lived rodent species (i.e., those prioritising reproduction over survival and longevity), are typically small, abundant and are more commonly urban-adapted (Albery and Becker, 2021). These species favour inexpensive, nonspecific immune defenses, which make them more likely to be hosts of zoonoses, although whether these properties are consistent within genera is unclear and whether these findings are replicated in wild, as opposed to laboratory, animals is unknown (Martin, Weil and Nelson, 2007; Viney and Riley, 2017).

Irrespective of the causal drivers of high zoonoses prevalence among rodent species, components of their life histories increase the risk of spillover into human populations. Synanthropy describes an organism that lives near and benefits from humans and their environmental modifications, this property is common among rodent species, more so among rodent species known to be reservoirs of zoonoses (Ecke *et al.*, 2022). Synanthropic species tend to be highly abundant in locations in which they occur, with high population densities and dynamic population fluctuations in response to resource availability, which promotes both fequency- and density-dependent transmission of pathogens among hosts (Ecke *et al.*, 2022). The high abundance of these species in human dominated landscapes increases the rate of contact with humans providing increased opportunities for both direct- and indirect transmission of rodent borne zoonoses (Iacono *et al.*, 2016; Morand *et al.*, 2019).

Rodent species that have wide ranges may display heterogeneity across their range in both their biology and behaviour. For example, studies in *Clethrionomys* voles, hosts of Puumala orthohantavirus, have been observed to display different population dynamics across a latitudinal gradient from Northern Finland to Central Europe, affecting pathogen dynamics within these populations (Turchin and Hanski, 1997; Henttonen and Wallgren, 2001). Similarly, while the primary reservoir species of LASV, *Mastomys natalensis*, has been observed to have dramatic population fluctuations in the Eastern extent of its range (Tanzania), the same amplitude of population fluctuations have not been observed in West African populations (i.e., Guinea) where they host LASV (Leirs *et al.*, 1997; Fichet-Calvet *et al.*, 2008). This may impact the generalisability of studies conducted in specific locations within a rodents range when attempting to understand the broader geographic risk of rodent borne zoonosis spillover.

1.5 Geographic hotspots for zoonosis risk in the light of varying surveillance activity

Geographic hotspots of zoonotic disease risk are predicted to occur where mammalian host species richness is greatest, such as in the tropics (Han, Kramer and Drake, 2016). West Africa is one such location of high mammalian biodiversity (Ceballos and Ehrlich, 2006). This region is also undergoing significant anthropogenic change, driven by increasing human populations, agricultural development, urbanisation and resource extraction alongside effects of anthropogenic climate change such as desertification and changes in precipitation dynamics (Nicholson, Tucker and Ba, 1998; Bongaarts, 2009; Maconachie, 2012; Walther, 2021; Haggblade, Diarra and Traoré, 2022). It has also been the location of several recent zoonosis epidemics and outbreaks, for example, the 2014 Ebola epidemic and ongoing Lassa fever outbreaks.

While the number of zoonotic infectious disease outbreaks and, human morbidity and mortality associated with them, has been observed to rise in West Africa, it is imperative to consider these trends in the local context of anthropogenic change described above, particularly as the number of people at risk of infection is continuing to increase (Makoni, 2020). Alongside these global changes, improved pathogen discovery in addition to improved access to diagnostics and healthcare, and improved reporting of cases may jointly result in an apparent increase in the burden of zoonotic infectious diseases in the region. An example of intensifying pathogen discovery is the PREDICT program, conducted between 2009 and 2020, which tested in excess of 164,000 samples from animals and humans in 14 African countries and 12 Asian countries identifying 949 novel viruses including 217 known zoonoses (*About PREDICT. School of veterinary medicine*, 2019; Amman *et al.*, 2020). Projects such as PREDICT can importantly change our understanding of the prevalence and locations of zoonoses, although these pathogens have likely circulated in the region for many years prior to discovery. Improved diagnostics and reporting of zoonoses are evident in the case of Lassa fever, particularly in Nigeria. Here, the Nigerian Center for Disease Control (NCDC) opted to expand the availability of testing. Prior to 2005, molecular diagnosis of Lassa fever infection was not possible in Nigeria with samples transferred to the Lassa fever unit at Kenema General Hospital, Sierra Leone (Naidoo and Ihekweazu, 2020). Between 2005 and 2012 testing was established in Lagos and Irrua, Nigeria with further laboratory capacity established at the National Reference Laboratory in Abuja and in Ebonyi state in 2018. The expansion of testing capacity has led to in excess of 20,000 individuals being tested for Lassa fever between 2018 and 2021. As such, any increasing trends in the number of reported cases of Lassa fever from Nigeria need to be considered in light of this (Dalhat *et al.*, 2022).

The detection of zoonotic infectious disease outbreaks typically relies upon clinical case detection of infected

humans within healthcare settings (i.e., real-time surveillance and reporting) rather than monitoring transmission among wild or domestic animals (i.e., zoonotic disease surveillance). No public health system has to date implemented active surveillance systems through testing of animal populations in West Africa. Elsewhere (e.g., in Europe), active surveillance in birds and horses is conducted for West Nile Virus to inform risk assessments of human disease outbreaks (Gossner *et al.*, 2017). The Global Health Security Index measured activities conducted by countries to assess their ability to respond to a potential emerging outbreak of a zoonotic infectious disease (Global Health Security Index, 2022). Figure 1.3 shows results from two components of this assessment, highlighting that few African countries have widely implemented real-time human surveillance or zoonotic disease surveillance in animals. Real-time surveillance is generally rated as poor across the African countries, with the notable exception of Nigeria, suggesting that these countries may not be able to rapidly identify outbreaks of endemic zoonotic diseases of epidemic potential (i.e., Ebola, mpox and Lassa fever). Zoonotic disease surveillance among animal host species in West Africa is currently limited to academic or programmatic research which informs local policy and identifies regions at potentially greater risk for spillover events. This information has been used by public health agencies to aid risk stratification of patients that present with symptoms consistent with these diseases, based on when, where, and why they present to local healthcare services (Leski *et al.*, 2015; Happi *et al.*, 2022). Few countries globally, with none in West Africa, have surveillance systems that combine animal and human data (Wendt, Kreienbrock and Campe, 2015).

1.6 Lassa fever: A case study of a rodent borne zoonosis in West Africa

The above sections have introduced zoonotic infectious diseases, the effect of a changing world on potential disease emergence, the role of rodents in zoonotic infectious disease transmission, and the particular risk of emergence and outbreaks in West Africa. The remainder of this introduction will focus on the case study of this thesis, Lassa fever, in West Africa and more specifically Sierra Leone. Despite the discovery of LASV more than 50 years ago and the expected hundreds of thousands of annual human cases research into this disease system adopting a One Health framework is currently limited. Lassa fever also serves as a useful case study of rodent associated zoonoses given the interaction between multiple small mammal species', potential roles of climate change and land use change on disease risk and the relatively high frequency of spillover events.

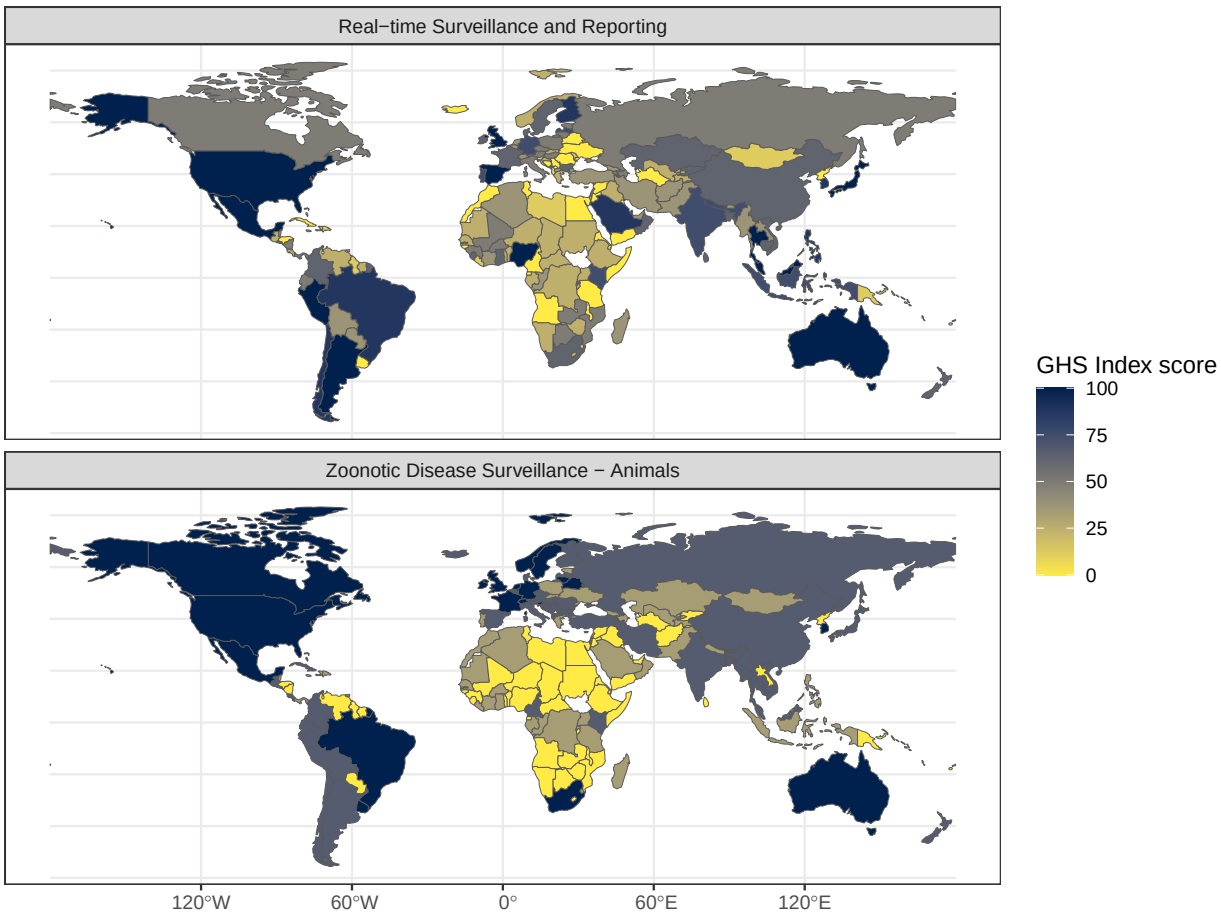

Figure 1.3: Global Health Security Index country scores for the sub-domains of2.3) Real-time surveillance and reporting (top) and 1.2.2) Zoonotic disease surveillance (bottom). Real-time surveillance and reporting for epidemics of potential international concern is rated highly in several North and South American countries and countries in East and South East Asia and Oceania. Zoonotic disease surveillance in animals is rated highly in European, North and South American countries and Oceania. Generally surveillance for zoonotic infectious disease is limited across much of Africa, with the notable exception of Nigeria for real-time surveillance and reporting. Data obtained from the Global Health Security Index.

1.6.1 *Lassa mammarenavirus* and Lassa fever

Lassa mammarenavirus (LASV) an enveloped, bisegmented, single stranded RNA virus of the Arenaviridae family. It is a zoonotic pathogen and is the causative agent of Lassa fever in humans. Lassa fever is a potentially lethal viral haemorrhagic fever, first identified from a case series of infected patients seeking healthcare in Jos, Nigeria in 1969, (Frame *et al.*, 1970). Human LASV infection is caused by spillover of the virus from infected rodents and their excreta, with a limited role of human-to-human secondary transmission (McCormick *et al.*, 1987; Lo Iacono *et al.*, 2015). The primary host of LASV has been identified as the multimammate rat (*M. natalensis*) following an outbreak in Sierra Leone between 1970-2 (Monath *et al.*, 1974). This synanthropic rodent species is found across much of sub-Saharan Africa, however, outside of West Africa, no individuals of this species have been found to be infected with LASV (Colangelo *et al.*, 2013; Bellocq *et al.*, 2020; Grobbelaar *et al.*, 2021).

Lassa mammarenavirus has four confirmed lineages (I-IV) and three additional lineages (V-VII) based on geographic and phylogenetic analysis (Li, 2023). Lineages I, II, III and VI are located within Nigeria; lineage IV contains all isolates from the Mano River region of Guinea, Liberia and Sierra Leone; lineage V contains samples from Mali and the Ivory Coast; and lineage VII contains recently sampled sequences from Togo (Andersen *et al.*, 2015; Manning, Forrester and Paessler, 2015; Whitmer *et al.*, 2018; Ehichioya *et al.*, 2019). Lineage I is believed to be the most ancient, originating around 1,000 years ago in the North East of Nigeria, with subsequent radiation and establishment of lineages II and III in the Southern and Central areas of the country, respectively (Andersen *et al.*, 2015; Ehichioya *et al.*, 2019). Lineage IV represents a Westward expansion of the virus into the Mano River region, dated around 350 years ago (Andersen *et al.*, 2015).

Host cell entry of the virus is mediated by a trimeric glycoprotein complex that interacts with host cell receptors and leads to fusion of the viral and host membranes, *in vivo* this protein undergoes substantial host-derived glycosylation, effectively reducing available antibody binding domains (Hastie and Saphire, 2018). Once within the host cell, the viral nucleoprotein associates with viral RNAs forming ribonucleoprotein complexes facilitating transcription and replication of viral RNA within the host cell cytoplasm (Hass *et al.*, 2004). The process of viral entry into host cells is expected to lead to the observed tissue tropism in experimental infection models in guinea pigs and *M. natalensis* (Torriani, Galan-Navarro and Kunz, 2017). Within infected guinea pigs and *M. natalensis*, LASV load was highest transiently in the lymph nodes with sustained high titres in the lungs and spleen (Jahrling *et al.*, 1982; Safronetz *et al.*, 2022). Minimal pathological changes were observed in guinea pigs or *M. natalensis*, with no evidence of clinical disease in these animals.

Among infected humans with clinical symptoms, the viral incubation period is between 7 and 18 days (McCormick *et al.*, 1987). Initial symptoms are non-specific with fever, weakness, malaise, cough, sore throat and a typically frontal headache (Knobloch *et al.*, 1980). The majority of symptomatic patients will go on to develop joint and lumbar pain, a non-productive cough with many developing severe retrosternal chest pain, nausea with vomiting and diarrhoea and abdominal pain (McCormick and Fisher-Hoch, 2002). Up to a third of hospitalised patients will significantly decline 6-8 days post onset of fever with a minority developing haemorrhagic syndrome with bleeding from the mucosal surfaces. Severe pulmonary oedema and soft tissue oedematous changes in the head and neck are common in fatal cases (Knobloch *et al.*, 1980). The vast majority of infections, commonly reported as 80%, are asymptomatic although in the absence of long term prospective studies, the proportion of asymptomatic infections is difficult to estimate (McCormick *et al.*, 1987). There is some limited evidence that disease severity may vary by infecting lineage (Garry, 2023).

Treatment options for acute cases of Lassa fever are limited. Ribavirin is the standard of care for treating acute cases although the effectiveness of this treatment is questionable (Salam *et al.*, 2022). Supportive care therefore remains the mainstay of treatment for hospitalised individuals. There are no currently available vaccinations for Lassa fever, although three candidate vaccines have begun clinical trials (Salami *et al.*, 2019; Inovio Pharmaceuticals, 2020, 2022; Themis Bioscience GmbH, 2022; International AIDS Vaccine Initiative, 2023).

The case-fatality rate of Lassa fever has been reported to be as high as 29.7% although this varies by country and year (Kenmoe *et al.*, 2020). This estimate is based on a systematic review of the published scientific literature and does not include data from epidemiological reports or WHO bulletins. A recent review and integration of both epidemiological reports and the published literature to derive the case-fatality rate among confirmed cases in order to estimate the scale of underreporting in Lassa fever produced an estimated case-fatality rate of 16.5% (+/- 5%) among confirmed cases (Simons, 2022b). Importantly, this estimate is sensitive to biases in reporting and is likely a grossly inflated rate of mortality. Severe cases are more likely to come into contact with healthcare services and be tested for Lassa fever, and these cases are also more likely to result in disease associated mortality skewing confirmed cases to those with severe disease. Therefore, this case-fatality rate should be considered a severe disease case-fatality rate, with the majority of mildly symptomatic cases likely to have a dramatically reduced probability of mortality, which will lower the total case-fatality rate and increase the number of underreported cases.

Survivors of symptomatic Lassa fever may have lasting effects of the disease. Sensorineural hearing loss is reported to occur in up to a third of Lassa fever survivors and potentially causes significant social and public health burden in the region that have not been well studied (Mateer *et al.*, 2018). Additional neurological

sequealae reported in Lassa fever survivors include cerebellar ataxia and visual impairment, although few patients have been assessed for these complications and progression over time is unclear (Ezeomah *et al.*, 2019; Li *et al.*, 2020). Most hospitalised patients, following recovery, rapidly clear viral RNA. Most patient sera are negative for viral RNA at hospital discharge, however, up to 50% of male survivors have detectable viral loads in seminal fluid at 3 months post-hospitalisation raising concerns that human-to-human sexual transmission may be possible (Thielebein *et al.*, 2022).

1.6.2 Lassa fever epidemiology

Annual Lassa fever incidence is unknown, with estimates ranging between 150,000 to 4,300,000 cases per year annually (McCormick *et al.*, 1987; Basinski *et al.*, 2021). The wide uncertainty surrounding these estimates is due to a combination of few serological studies, limited disease surveillance and an overlap between the symptomatology of Lassa fever with other infectious diseases in these endemic regions (e.g., malaria). Lassa fever is currently considered endemic in 8 West African countries: Benin, Ghana, Guinea, Liberia, Mali, Nigeria, Sierra Leone and Togo by the World Health Organisation (WHO), with sporadic cases reported from Burkina Faso and the Ivory Coast (1.4) (World Health Organisation, 2022). The endemic region is entirely contained within the range of the primary reservoir species *M. natalensis*. Imported cases have been reported from non-West African countries such as the United Kingdom, Germany and the United States of America with few observed events of secondary human-to-human transmission outside of the endemic region (Tuite *et al.*, 2019; Wolf *et al.*, 2020).

Nigeria and Sierra Leone have historically reported the greatest number of Lassa fever cases (1.5). This is likely driven by increased availability of testing for acute cases in these countries. Human seroepidemiological surveys in Guinea, Mali and the Ivory Coast - countries that have generally reported few acute cases - report seroprevalence in excess of 20%, which suggests undetected localised transmission of LASV (Bausch *et al.*, 2001; Akoua-Koffi *et al.*, 2006; Kerneis *et al.*, 2009; Sogoba *et al.*, 2016; Safronetz *et al.*, 2017). The number of reported cases across the region declined during the Ebola and SARS-CoV-2 epidemic where changes in healthcare seeking behaviour and availability of Lassa fever testing may have reduced. The number of cases reported in Nigeria has generally increased since data became routinely available in 2012. In contrast, there has been a dramatic fall in cases reported from Sierra Leone since 2012. Whether these trends represent actual changes in the underlying spillover risk remains unclear.

The number of reported confirmed cases of Lassa fever in endemic countries is likely to be significantly underreported. Cases tend to occur in rural and remote locations where healthcare access is generally low, and financial and societal costs of accessing healthcare relatively high while testing facilities are concentrated

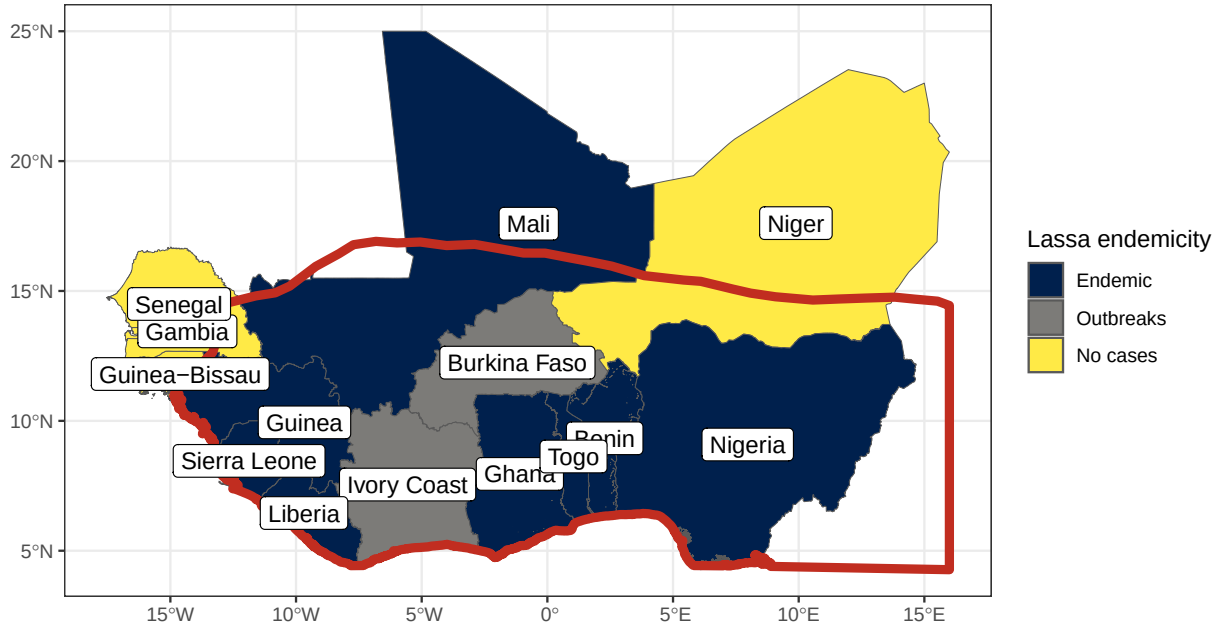

Figure 1.4: Lassa fever is considered endemic in eight West African countries, sporadic outbreaks have been reported from a further two countries within the region. The red border indicates the range of *Mastomys natalensis* in West Africa, its range extends East and South across the continent (not shown here). Data on Lassa fever endemicity is obtained from the WHO, data on *Mastomys natalensis* range is obtained from the International Union for Conservation of Nature Red List.

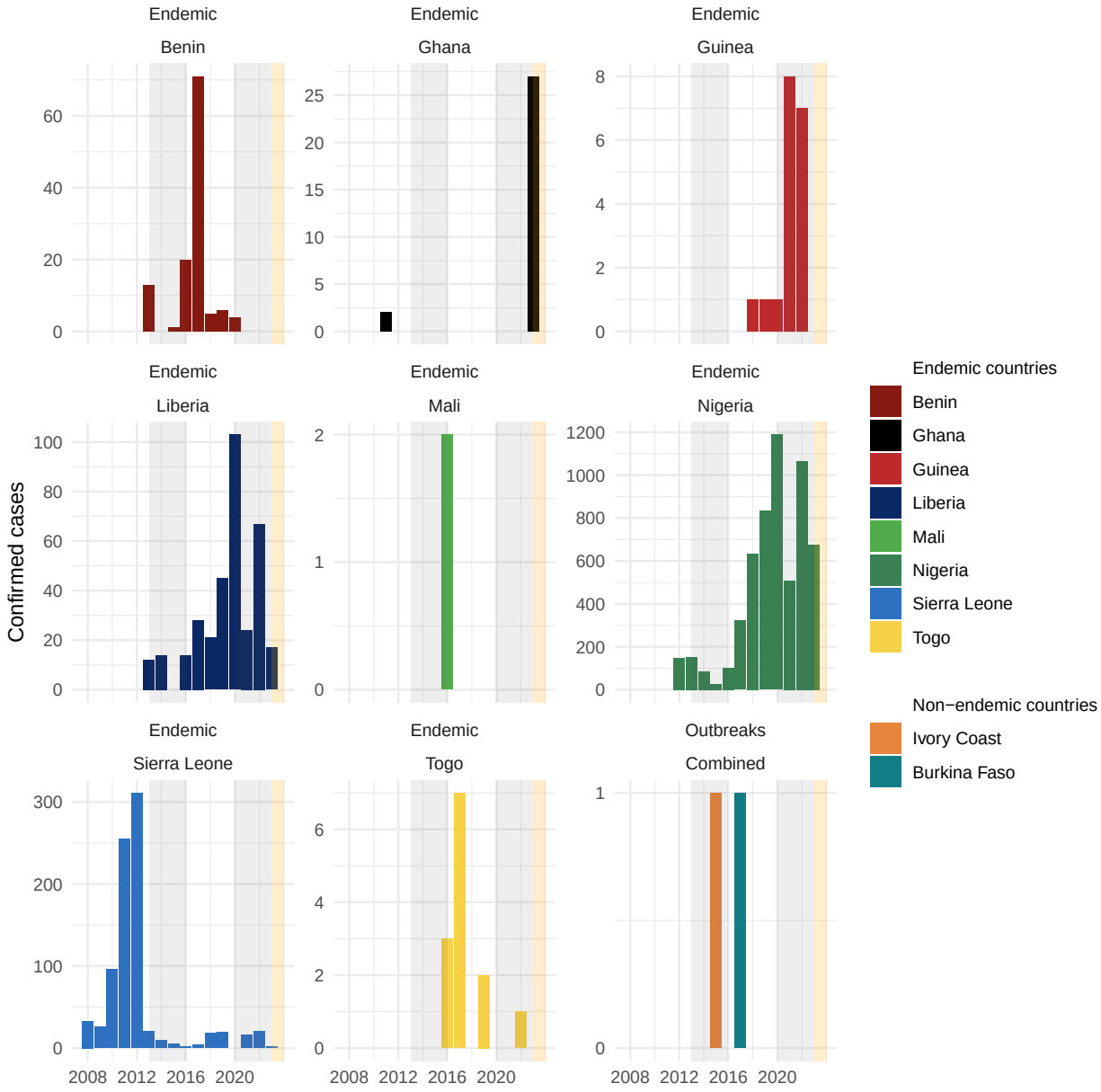

Figure 1.5: Confirmed Lassa fever cases from countries in West Africa 2008-2023. Confirmed cases show variability by year with the greatest number of cases reported from Nigeria, Sierra Leone and Liberia. Grey shaded regions represent periods of regional or global epidemics which may have affected Lassa fever reporting (i.e., the Ebola epidemic and SARS-CoV-2 pandemic). The yellow shaded region represents 2023 where an incomplete year is shown. Data compiled from multiple sources.

in large urban settings (Bhadelia, 2019; Nnaji *et al.*, 2021). Additionally while clinicians in endemic settings have good awareness of symptoms that may indicate acute Lassa fever infection, access to testing and timely reporting were identified as factors that could lead to diagnostic delay, poor patient outcomes and delayed public health responses to outbreaks (Olowookere *et al.*, 2014; Rohan, 2022). An estimate of the degree of underreporting was conducted using reported Lassa fever disease associated mortality, assuming a consistent 16.5% case-fatality rate across the region. Using this approach Nigeria was found to report the highest proportion of all expected cases (63%) while countries with generally fewer observed outbreaks reported significantly fewer than expected cases (e.g., Ghana - 17%, Guinea - 25%) (Simons, 2022b).

Human seroepidemiological studies conducted in several regions of Sierra Leone suggest that despite the observed fall in human cases of disease infection remains prevalent (Grant *et al.*, 2023).This study in Sierra Leone also suggests that widespread transmission of LASV is occurring outside the traditionally considered endemic region of Eastern Sierra Leone. A large-scale serological study conducted by the Coalition for Epidemic Preparedness Innovations across Benin, Guinea, Liberia, Nigeria and Sierra Leone to understand the prevalence to antibodies against LASV has been implemented and results are awaiting (Penfold *et al.*, 2023).

1.6.3 Rodent hosts of *Lassa mammarenavirus*

While *M. natalensis* is considered the primary reservoir of LASV 11 other rodent species have been found to be acutely infected or have antibodies to the virus (Monath *et al.*, 1974; Demby *et al.*, 2001; Fichet-Calvet *et al.*, 2014; Olayemi *et al.*, 2016). The role of the wider rodent species community in viral transmission in endemic areas is not currently well understood. Further, evidence exists for prior exposure to LASV in non-rodent species, including domestic dogs, non-human primates and shrews. The role of these species in the ecology of LASV is even less clear (Kenmoe *et al.*, 2020).

Mastomys natalensis is a synanthropic rodent species, native to Africa. This species is considered a pest species across much of its range, as it lives within and around human communities consuming grain within the fields and in stores (Swanepoel *et al.*, 2017). The species demonstrates archetypal fast life history traits with rapid sexual maturity (4 months), short life span (<1 year) and large litter sizes (mean of 9 live offspring) (Coetzee, 1975; Albery and Becker, 2021; Safronetz *et al.*, 2021). The proportion of reproductively active individuals is observed to increase in the late wet season and early dry season with a nadir in the late dry season, leading to a population boom in the late wet season (Mlyashimbi *et al.*, 2018; Mayamba *et al.*, 2021). Importantly, the majority of population dynamic studies in this species have been conducted in Tanzania, where abundance has been observed to be closely linked to food availability. However, the drivers of these

population dynamics may not be as extreme in West Africa where the population dynamics are less closely linked to rainfall patterns (Fichet-Calvet *et al.*, 2008; Olayemi *et al.*, 2018; Bangura *et al.*, 2021).

As a synanthropic species *M. natalensis* typically occurs within areas of human habitation and agriculture and is found to be an early invader of land converted to agricultural use (Makundi, Massawe and Mulungu, 2007). This land use preference is consistent across the entirety of its range with few individuals trapped in forested landscapes (Coetzee, 1975; Leirs, Verheyen and Verhagen, 1996; Fichet-Calvet *et al.*, 2008; Olayemi *et al.*, 2018; Bangura *et al.*, 2021). This would suggest that abundance of this species is heterogeneous across its proposed range with expected absence in the forested regions of sub-Saharan Africa. This species is non-territorial, co-existing with conspecifics and other rodent species and with a limited home range of ~30m, although dispersal across greater distances has been observed (Leirs, Verheyen and Verhagen, 1996). Contact with other rodent species is therefore assumed to be common and this is reflected by the high rodent species richness in locations where *M. natalensis* is detected (Fichet-Calvet *et al.*, 2008; Bangura *et al.*, 2021). The high frequency of contacts may be potentially important for the transmission of LASV among rodent hosts as it potentially facilitates transmission of the virus across the heterogeneous land use types of the endemic region.

While this species is distributed across sub-Saharan Africa genomic studies suggest that six phylogroups (A-I to A-III and B-IV to B-VI) have formed which correspond to different geographic regions of Africa. The West African clade, A-I is genetically distinct and is found in the endemic region of LASV (Colangelo *et al.*, 2013). Individuals of the other clades have not been found to be infected with LASV but have tested positive for other Arenaviridae, including Mayo Ranewo (A-II), Dhati Welel (A-III), Gairo (B-IV), Morogoro (B-V), and Mopeia viruses (B-VI) (Bellocq *et al.*, 2020). The presence of clade specific Arenaviridae may explain why the Lassa fever endemic region is constrained to the Western radiation of *M. natalensis* despite it being found throughout sub-Saharan Africa and may limit any future geographic expansion of the virus.

While LASV is considered to primarily infect *M. natalensis* the prevalence of LASV in rodent communities varies importantly across the region and over time. Figure 1.6 shows the prevalence of acute infection or antibodies to LASV among sampled *M. natalensis* communities. When detected LASV prevalence varies both within and between countries. In Guinea, LASV was detected in 10 to 55% of trapped individual rodents. In a single study conducted in Mali, acute infection was detected in 25% of individuals, while in, Sierra Leone, sampled rodents showed a wide range of prevalence from 5% to 100%. However, most of the sampling events in these settings did not detect any acute infection (not shown in 1.6). The number of individuals tested for acute infection is typically lower than those tested for antibodies due to availability of reagents, cost and laboratory requirements. There are also selection biases in which rodents are tested for

acute infection which may increase the proportion of positive samples. For example, testing may only be performed in antibody positive rodents or rodents trapped in the location of a confirmed human case.

Figure 1.6 also highlights the detection of LASV in non-*M. natalensis* species. *Mastomys erythroleucus* a morphologically indistinguishable, closely related species to *M. natalensis* has been found to co-occur with *M. natalensis* in several regions of Guinea, Sierra Leone and Nigeria (Brouat *et al.*, 2009). The proportion of *M. erythroleucus* individuals found to be infected with LASV was not too dissimilar from *M. natalensis* and may indicate that this species can also be involved in viral transmission in locations where these species co-exist. Three other native rodent species *Mus minutoides*, *Mus baoulei* and *Hylomyscus pamfi* have been found to be acutely infected with LASV although the number of individuals of these tested is small. *Mus minutoides* and *Mus baoulei* are African pygmy mice - i.e., a complex of 17-19 morphologically similar rodents that may contain a number of undescribed subspecies (Britton-Davidian, Robinson and Veyrunes, 2012). They occupy a wide range of land use types and are not considered synanthropic, with a habitat preference for forest and shrubland habitats, although they are often detected in cultivated landscapes (Long *et al.*, 2013). Finally, the non-native, invasive rodent species, *Rattus rattus* has been found to be acutely infected with LASV. This synanthropic rodent species has been found to co-occur with *M. natalensis* in locations which it has invaded and may represent a relatively recent host of LASV within the endemic region (Olayemi *et al.*, 2018; Bangura *et al.*, 2021).

More rodent species have been found to have antibodies to LASV than those found to have acute infection. Whether these species are competent hosts of the virus and are able to produce subsequent rodent-to-rodent or rodent-to-human transmission is not known. Additionally, some of these detections may be due to the presence of cross-reactive antibodies to other Arenaviridae; however, a validated, commercial, ELISA assay used for many of these surveys shows a sensitivity of 97.1% and specificity of 100% to LASV (Soubrier *et al.*, 2022). The proportion of all samples that tested positive for LASV antibodies across all species is typically lower, consistent with the greater number of samples assayed and less targeted sampling. Additional species found to have antibodies to LASV include the native rodents *Praomys daltoni*, *Praomys rostratus*, *Lemniscomys striatus*, *Lophuromys sikapusi*, *Mus musculus* and *Gerbilliscus kempii*. Of these species, only *P. daltoni* and the invasive *M. musculus*, are considered synanthropic, typically found in villages and nearby agricultural areas in West Africa (Nicolas *et al.*, 2008; Diagne *et al.*, 2017; Lippens *et al.*, 2017; Mikula *et al.*, 2020). *P. rostratus* and *L. sikapusi* are more commonly found in forested or fragmented forest, shrubland and agricultural habitats (Iyawe, 1988; Félix Houphouët-Boigny University, Côte d'Ivoire *et al.*, 2018). *L. striatus* and *G. kempii* are considered savannah rodents, rarely detected within villages but often detected in forested habitats, shrubland and agriculture (Davis, 1949; Lourie *et al.*, 1975; Hoffmann and Klingel, 2001).

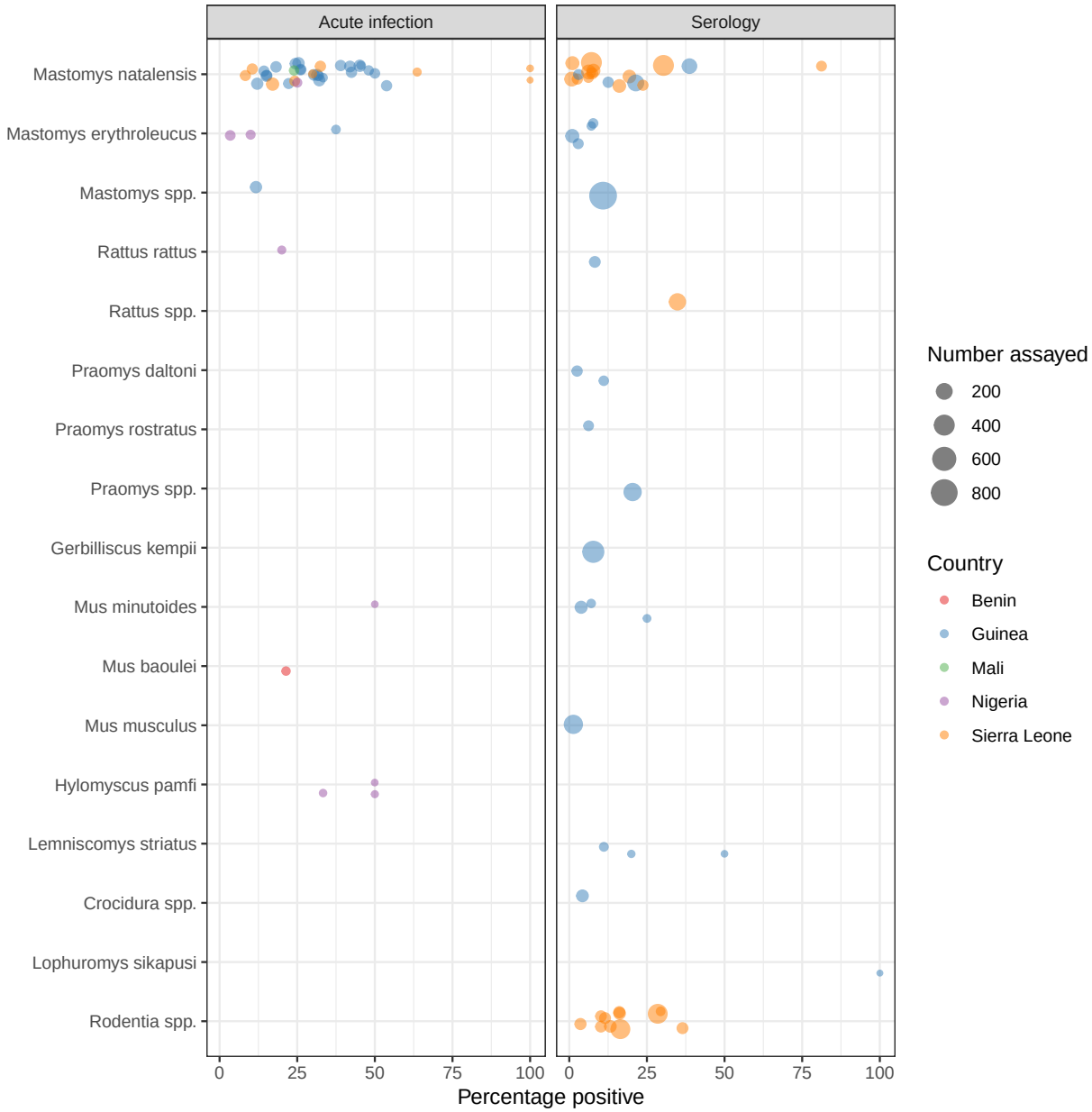

Figure 1.6: Prevalence of acute infection with LASV or antibodies to LASV in rodent species sampled in West Africa. The size of a point relates to the number of samples of that species tested and the colour to the country in which the rodent was sampled. Where possible the rodent species is identified, for individuals only identified to genus level the genera from which samples obtained is shown. Six rodent species have been found to be acutely infected with LASV with 10 species having detectable antibodies. The majority of samples have been obtained from rodents trapped in Guinea and Sierra Leone. (Will add in all the references)

Finally, non-rodent, small mammal species found to have antibodies to LASV include individuals of the species rich insectivorous shrew order (*Crocidura spp.*). As morphological identification to species level is typically not performed, the grouping is at the order level.

Two invasive rodent species, *Mus musculus* and *R. rattus* are increasingly common in West Africa. These species have been introduced through human activity, typically in coastal regions, beginning in the 15th century with subsequent expansion into the interior of countries along human transport networks (Dalecky *et al.*, 2015; Lippens *et al.*, 2017). Populations of these species have been found to establish communities in areas of human habitation demonstrating their synanthropic properties (Hima *et al.*, 2019; Puckett, Orton and Munshi-South, 2020). These species appear to have potentially different effects on local rodent species richness following establishment, with *M. musculus* but not *R. rattus* leading to reduced rodent species richness in locations in which it is detected (Dalecky *et al.*, 2015). This may have important implications for the prevalence of LASV in the endemic region: if displacement of the primary reservoir by these invasive species that are potentially less competent hosts of viral transmission the risk of Lassa fever outbreaks may subsequently decrease.

Sampling of rodent species and locations of confirmed human cases have been used to produce risk maps of Lassa fever outbreaks. Risk maps may be based on human cases, *M. natalensis* occurrence or a combination of both. These risk maps consistently identify the Mano River region and Nigeria as hotspots of risk (Fichet-Calvet and Rogers, 2009; Mylne *et al.*, 2015; Gibb *et al.*, 2017; Basinski *et al.*, 2021). The studies are conducted at the regional scale and are not able to incorporate the heterogeneity of rodent species occurrence or abundance that has been observed in rodent sampling studies. The potential contribution of wider rodent communities to viral transmission or maintenance is not incorporated in these models as they all consider *M. natalensis* as the sole reservoir of LASV.

Importantly, sampling of rodents and LASV in West Africa is biased taxonomically and geographically with increased sampling effort in locations reporting historical outbreaks of Lassa fever (Beck *et al.*, 2014; Klitting *et al.*, 2022). Limiting sampling to these locations may be artificially biasing risk towards these regions, with a study accounting for some of these biases suggesting that risk is more evenly distributed across West Africa than what has historically been reported (Peterson, Moses and Bausch, 2014). A better understanding of sampling biases in both small mammal communities and pathogen sampling will assist in identifying regions in which additional sampling is required. Further, prediting future change in risk that could ensue from ongoing global change will be limited by data suffering from these biases (Boria *et al.*, 2014; Wille, Geoghegan and Holmes, 2021).

1.7 Thesis aims and structure

To better understand the current and future risk of Lassa fever spillover in West Africa, biases in available data need to be characterised and systematic sampling of the entire rodent community is required. This thesis aimed to address some of the critical gaps in understanding of LASV transmission among rodent communities in endemic settings and the effect of anthropogenic change on the structure of rodent communities and how this may modulate Lassa fever spillover risk.

The first part of this thesis (Chapter 2) attempts to understand a key problem in the sampling of both rodents and their pathogens across West Africa. The research question Chapter 2 seeks to address is whether the sampling bias of rodents and associated pathogens can be quantified and mitigated against. To achieve this, a review of rodent trapping studies in West Africa was conducted. Data from included studies were synthesised and assessed for spatial biases, identifying regions that have been relatively under-sampled and therefore locations in which inference my be limited based on available datasets. This dataset was subsequently compared with a commonly used resource, the Global Biodiversity Information Facility (GBIF), to explore the benefit of incorporating primary rodent trapping data within this larger, consolidated dataset. The results presented in this chapter and the planned incorporation of this data into GBIF will aid researchers attempting to model risks of rodent associated zoonoses in West Africa and the effect of future anthropogenic change on rodent distributions across the region.

The second part of this thesis (Chapter 3 and 4) present the results of a systematic study of rodent ecology and LASV prevalence in an endemic region of Eastern Sierra Leone. Following primary data collection in the form of a 2 and half year longitudinal rodent trapping study, comprising in excess of 35,000 trap nights, chapter 3 describes the composition of rodent communities in Eastern Sierra Leone and aims to address the question as to whether rodent species richness and diversity vary along an anthropogenic land use gradient. This study explores the biotic interactions between rodent species to infer the risk of LASV transmission among rodent communities along a land use gradient using species occupancy models which account for incomplete detection. Chapter 4 expands on this work to explicitly model potential contact networks among individual rodents in different land use types to investigate the interactions within these rodent communities. The key research question addressed is whether the primary reservoir is more likely to interact with members of the same species and what consequences this may have for viral transmission. I use Exponential Random Graph Models fitted to produced networks of rodent contacts based on rodent trapping data to assess the probability of inter- and intra-specific contact rates to understand viral transmission within rodent communities. This chapter describes the prevalence of antibodies to LASV to gauge the risk of Lassa fever spillover in these settings.

The thesis concludes with a discussion of how insights from this body of work enhance our understanding of the risk of rodent borne zoonoses in West Africa in general, and Lassa fever emergence in Sierra Leone in particular. Future directions of study required to better quantify this dynamic risk are discussed, alongside how dynamic risk estimates can guide timely public health interventions to reduce disease associated morbidity and mortality.

2 Rodent trapping studies as an overlooked information source for understanding endemic and novel zoonotic spillover.

2.1 Preface

As detailed in the previous chapter, rodent-associated zoonoses produce significant global public health burdens, particularly in regions with resource constrained healthcare systems such as West Africa. Assessment of the risk of rodent-associated zoonoses outbreaks is typically limited to country-level risk maps (i.e., the WHO Lassa fever endemic region map), however, increasing research and public health effort is directed at producing higher spatial resolution risk maps for important disease such as Lassa fever, … []. A better understanding of the spatial distribution of risk can aid the targetting of public health interventions. Current datasources used to generate these spatial risk models are taxanomically biased for both rodents and their pathogens and geographically biased []. The work wihtin this chapter was performed to quantify this bias across the region and to supplement currently available datasets. This research has been published in *PLOS Neglected Tropical Diseases* (Appendix A.1) [] and an associated data paper has been submitted to the journal X to facilitate incorporation into GBIF. Currently the associated data is available online in a Zenodo repository and a web based application () has been developed to support exploration and visualisation of this dataset [].

2.2 Abstract

Rodents, a diverse, globally distributed and ecologically important order of mammals are nevertheless important reservoirs of known and novel zoonotic pathogens. Ongoing anthropogenic land use change is altering these species' abundance and distribution, which among zoonotic host species may increase the risk of zoonoses spillover events. A better understanding of the current distribution of rodent species is required to guide attempts to mitigate against potentially increased zoonotic disease hazard and risk. However, available species distribution and host-pathogen association datasets (e.g. IUCN, GBIF, CLOVER) are often taxonomically and spatially biased. Here, we synthesise data from West Africa from 127 rodent trapping studies, published between 1964-2022, as an additional source of information to characterise the range and presence of rodent species and identify the subgroup of species that are potential or known pathogen hosts. We identify that these rodent trapping studies, although biased towards human dominated landscapes across West Africa, can usefully complement current rodent species distribution datasets and we calculate the discrepancies between these datasets. For five regionally important zoonotic pathogens (Arenaviridae spp., Borrelia spp., *Lassa mammarenavirus*, Leptospira spp. and *Toxoplasma gondii*), we identify host-pathogen

associations that have not been previously reported in host-association datasets. Finally, for these five pathogen groups, we find that the proportion of a rodent hosts range that have been sampled remains small with geographic clustering. A priority should be to sample rodent hosts across a greater geographic range to better characterise current and future risk of zoonotic spillover events. In the interim, studies of spatial pathogen risk informed by rodent distributions must incorporate a measure of the current sampling biases. The current synthesis of contextually rich rodent trapping data enriches available information from IUCN, GBIF and CLOVER which can support a more complete understanding of the hazard of zoonotic spillover events.

2.3 Introduction

There is increasing awareness of the global health and economic impacts of novel zoonotic pathogen spillover, driven by the ongoing SARS-CoV-2 pandemic and previous HIV/AIDs and Spanish Influenza pandemics (Bernstein *et al.*, 2022). The number of zoonotic disease spillover events and the frequency of the emergence of novel zoonotic pathogens from rodents are predicted to increase under intensifying anthropogenic pressure driven by increased human populations, urbanisation, intensification of agriculture and climate change leading to altered rodent species assemblages (Allen *et al.*, 2017; Hassell *et al.*, 2017; McMahon, Morand and Gray, 2018; García-Peña *et al.*, 2021). The impact of endemic zoonoses meanwhile remains underestimated (Maudlin, Eisler and Welburn, 2009). Endemic zoonoses disproportionally affect those in the poorest sections of society, those living in close contact with their animals and those with limited access to healthcare (Molyneux *et al.*, 2011; Halliday *et al.*, 2015; Judson and Rabinowitz, 2021).

Rodents along with bats contribute the greatest number of predicted novel zoonotic pathogens and known endemic zoonoses (Han *et al.*, 2015; Gibb, Gregory F. Albery, *et al.*, 2021b). Of 2,220 extant rodent species, 244 (10.7%) are described as reservoirs of 85 zoonotic pathogens (Han *et al.*, 2015). Most rodent species do not provide a direct risk to human health and all species provide important and beneficial ecosystem services including pest regulation and seed dispersal (Fischer *et al.*, 2018). Increasing risks of zoonotic spillover events are driven by human actions rather than by rodents, for example, invasive rodent species being introduced to novel ranges through human transport routes. Rodents typically demonstrate "fast" life histories which allow them to exploit opportunities provided by anthropogenic disturbance (Dobson and Oli, 2007). Within rodents, species level traits such as early maturation and short gestation times are associated with increased probabilities of being zoonotic reservoirs (Han *et al.*, 2015; Albery and Becker, 2021). Rodent species with these traits are able to thrive in human dominated landscapes, displacing species less likely to be reservoirs of zoonotic pathogens (Gibb, Redding, *et al.*, 2020). The widespread occurrence of reservoir species and

their proximity to human activity make the description of rodent species assemblages and host-pathogen associations vitally important to understanding the hazard of zoonotic disease spillover and novel zoonotic pathogen emergence (Han, Kramer and Drake, 2016).

Despite the importance of understanding these complex systems, current evidence on host-pathogen associations is considerably affected by taxonomic and geographical sampling biases (Gibb, Franklinos, *et al.*, 2020; Gibb, Gregory F. Albery, *et al.*, 2021b). Curated biodiversity datasets such as the Global Biodiversity Information Facility (GBIF) and resources produced by the International Union for Conservation of Nature (IUCN) suffer from well described spatial and temporal sampling biases (Boakes *et al.*, 2010; Bowler *et al.*, 2022). These data are typically obtained from museum specimen collections and non-governmental organisation surveys. These sampling biases can importantly distort produced species distribution models that are used to infer risk of zoonotic disease spillover (Beck *et al.*, 2014). Datasets on host-pathogen associations (i.e., CLOVER) also can suffer from biases introduced from literature selection criteria and taxonomic discrepancies resulting in differential likelihood of accurate host-pathogen attribution by host species. These biases are important because identification of potential geographic hotspots of zoonotic disease spillover and novel pathogen emergence are often produced from these types of host species distributions and host-pathogen associations (Plowright *et al.*, 2019; Carlson *et al.*, 2021). For example, systematically increased sampling, over-representation of certain habitats and clustering around areas of high human population could lead to an apparent association between locations and hazard that is driven by these factors rather than underlying host-pathogen associations (Redding *et al.*, 2017; Gibb, Gregory F. Albery, *et al.*, 2021b; Wille, Geoghegan and Holmes, 2021). Predictions of zoonotic disease spillover and novel zoonotic pathogen emergence must account for these biases to understand the future hazard of zoonotic diseases (Carlson *et al.*, 2021).

West Africa has been identified as a region at increased risk for rodent-borne zoonotic disease spillover events, the probability of these events are predicted to increase under different projected future land-use change scenarios (Grace *et al.*, 2012; García-Peña *et al.*, 2021). Currently within West Africa, some rodent species are known to be involved in the transmission of multiple endemic zoonoses with large burdens on human health, these pathogens include Lassa fever, Schistosomiasis, Leptospirosis and Toxoplasmosis (Meerburg, Singleton and Kijlstra, 2009; Galeh *et al.*, 2020). The presence of other species within shared habitats may mitigate the spread of these pathogens through the "dilution effect", where ongoing loss of biodiversity may further increase the risk to human populations (McMahon, Morand and Gray, 2018). Understanding of the distribution of these zoonoses are limited by biases in consolidated datasets. Rodent trapping studies provide contextually rich information on when, where and under what conditions rodents were trapped, potentially enriching consolidated datasets (Bovendorp, MCCleery and Galetti, 2017). Studies have been conducted

in West Africa to investigate the distribution of rodent species, their species assemblages, the prevalence of endemic zoonoses within rodent hosts (e.g., Lassa fever, Schistosomiasis) and to identify emerging and novel zoonotic pathogens (Fichet-Calvet *et al.*, 2010; Catalano *et al.*, 2019; USAID, 2021). However, individual level data from these studies have not previously been synthesised for inclusion in assessments of zoonotic disease spillover and novel zoonotic pathogen emergence.

Here, we synthesise rodent trapping studies conducted across West Africa published between 1964-2022. First, we use this dataset to investigate the geographic sampling biases in relation to human population density and land use classification. Second, we compare this to curated host datasets (IUCN and GBIF) to understand differences in reported host geographic distributions. Third, we compare identified host-pathogen associations with a consolidated dataset (CLOVER) to explore discrepancies in rodent host-pathogen associations and report the proportion of positive assays for pathogens of interest. Finally, within our dataset we investigate the spatial extent of current host-pathogen sampling to identify areas of sparse sampling of pathogens within their host ranges. We expect that rodent trapping studies provide an important additional source of high-resolution data that can be used to enrich available consolidated datasets to better understand the hazard of zoonotic disease spillover and novel zoonotic pathogen emergence across West Africa.

2.4 Methods

2.4.1 Host and pathogen trapping data

To identify relevant literature, we conducted a search in Ovid MEDLINE, Web of Science (Core collection and Zoological Record), JSTOR, BioOne, African Journals Online, Global Health and the pre-print servers, BioRxiv and EcoEvoRxiv for the following terms as exploded keywords: (1) Rodent OR Rodent trap* AND (2) West Africa, no date limits were set. We also searched other resources including the UN Official Documents System, Open Grey, AGRIS FAO and Google Scholar using combinations of the above terms. Searches were run on 2022-05-01, and returned studies conducted between 1964-2021.

We included studies for further analysis if they met all of the following inclusion criteria; i) reported findings from trapping studies where the target was a small mammal, ii) described the type of trap used or the length of trapping activity or the location of the trapping activity, iii) included trapping activity from at least one West African country, iv) recorded the genus or species of trapped individuals, and v) were published in a peer-reviewed journal or as a pre-print on a digital platform or as a report by a credible organisation. We excluded studies if they met any of the following exclusion criteria: i) reported data that were duplicated from a previously included study, ii) no full text available, iii) not available in English. One author screened

titles, abstracts and full texts against the inclusion and exclusion criteria. At each stage; title screening, abstract screening and full text review, a random subset (10%) was reviewed by a second author.

We extracted data from eligible studies using a standardised tool that was piloted on 5 studies (**S1 Table**). Data was abstracted into a Google Sheets document, which was archived on completion of data extraction (Simons, 2022a). We identified the aims of included studies, for example, whether it was conducted as a survey of small mammal species or specifically to assess the risk of zoonotic disease spillover. we extracted data on study methodology, such as, the number of trap nights, the type of traps used and whether the study attempted to estimate abundance. For studies not reporting number of trap nights we used imputation based on the number of trapped individuals, stratified by the habitat type from which they were obtained. This was performed by multiplying the total number of trapped individuals within that study site by the median trap success for study sites with the same reported habitat type. Stratification was used as trap success varied importantly between traps placed in or around buildings (13%, IQR 6-24%) compared with other habitats (3%, IQR 1-9%).

We also recorded how species were identified within a study and species identification was assumed to be accurate. The number of individuals of these species or genera was extracted with taxonomic names mapped to GBIF taxonomy (GBIF: The Global Biodiversity Information Facility, 2021b). We expanded species detection and non-detection records by explicitly specifying non-detection at a trap site if a species was recorded as detected at other trapping locations within the same study.

Geographic locations of trapping studies were extracted using GPS locations for the most precise location presented. Missing locations were found using the National Geospatial-Intelligence Agency GEOnet Names Server (National Geospatial-Intelligence Agency, 2023) based on place names and maps presented in the study. All locations were converted to decimal degrees. The year of rodent trapping was extracted alongside the length of the trapping activity to understand seasonal representativeness of trapping activity. The habitats of trapping sites were mapped to the IUCN Habitat Classification Scheme (Version 3.1). For studies reporting multiple habitat types for a single trap, trap-line or trapping grid, a higher order classification of habitat type was recorded.

For included studies with available data we extracted information on all microorganisms and known zoonotic pathogens tested and the method used (e.g., molecular or serological diagnosis). Where assays were able to identify the microorganism to species level this was recorded, for non-specific assays higher order attribution was used (e.g., to family level). A broad definition of known zoonotic pathogen was used, a species of microorganism carried by an animal that may transmit to humans and cause illness. We do not include

evolved pathogens acquired originally through zoonotic pathways in our definition (i.e., HIV). The term microorganism is used where either the microorganism is not identified to species level, in which case it remains unclear whether it is a zoonotic pathogen (i.e., Arenaviridae), or the species is not known to be a zoonotic pathogen (i.e., *Candidatus Ehrlichia senegalensis*). We recorded the species of rodent host tested, the number of individuals tested and the number of positive and negative results. For studies reporting summary results all testing data were extracted, this may introduce double counting of individual rodents, for example, if a single rodent was tested using both molecular and serological assays. Where studies reported indeterminate results, these were also recorded.

2.4.2 Description of included studies

Out of 4,692 relevant citations, we identified 127 rodent trapping studies (**S2 Table**). Of these, 55 (43%) were conducted to investigate rodent-borne zoonoses, with the remaining 77 (57%) conducted for ecological purposes (i.e., population dynamics, distribution) in rodents, including those known to be hosts of zoonotic pathogens. The earliest trapping studies were conducted in 1964, with a trend of increasing numbers of studies being performed annually since 2000. The median year of first trapping activity was 2007, with the median length of trapping activity being 1 year (IQR 0-2 years) (**S1 Fig.**). Studies were conducted in 14 West African countries, with no studies reported from The Gambia or Togo, at 1,611 trap sites (Figure 2.1 A.).

Included studies explicitly reported on 601,184 trap nights, a further 341,445 trap nights were imputed from studies with no recording of trapping effort based on trap success, leading to an estimate of 942,629 trap nights (Figure 2.1 B.). A minority of studies trapped at a single study site (30, 24%), with 46 (36%) trapping at between two and five sites, the remaining 51 studies (40%) trapped at between six and 93 study sites.

In total 76,275 small mammals were trapped with 65,628 (90%) identified to species level and 7,439 (10%) identified to genus, with the remaining classified to higher taxonomic level. The majority of the 132 identified species were Rodentia (102, 78%), of which Muridae (73, 72%) were the most common family. Soricomorpha were the second most identified order of small mammals (28, 21%). 57 studies tested for 32 microorganisms, defined to species or genus level that are known or potential pathogens. Most studies tested for a single microorganism (48, 84%). The most frequently assayed microorganisms were *Lassa mammarenavirus* or Arenaviridae (21, 37%), *Borrelia sp.* (9, 16%), *Bartonella sp.* (4, 7%) and *Toxoplasma gondii* (4, 7%). Most studies used Polymerase Chain Reaction (PCR) to detect microorganisms (37, 65%), with fewer studies using serology-based tests (11, 19%) or histological or direct visualisation assays (11, 21%). From 32,920 individual rodent samples we produced 351 host-pathogen pairs. With *Rattus rattus*, *Mus musculus*, *Mastomys*

erythroleucus, *Mastomys natalensis* and *Arvicanthis niloticus* being assayed for at least 18 microorganisms.

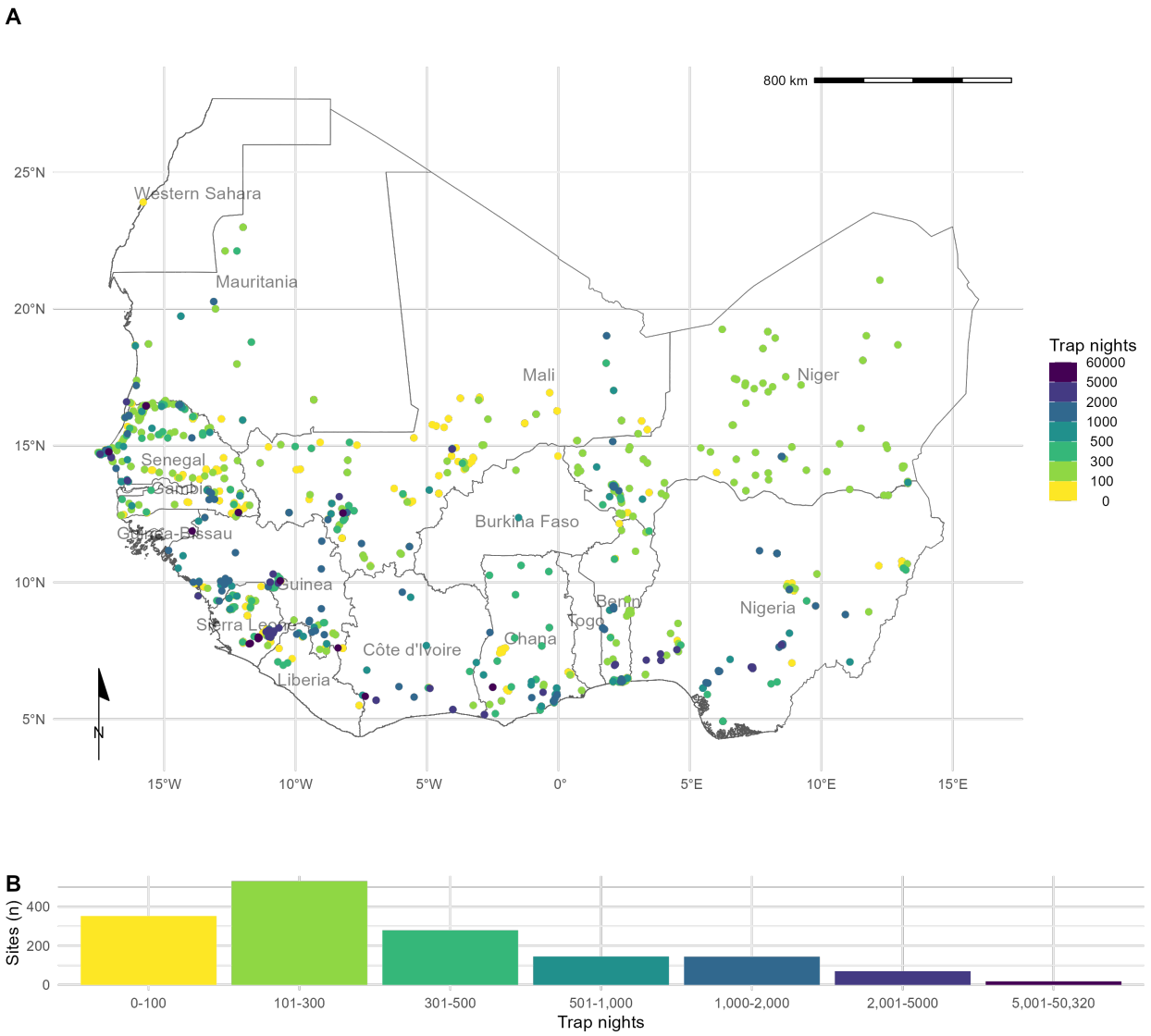

Figure 2.1: **Rodent trapping sites across West Africa.** A) The location of trapping sites in West Africa. No sites were recorded from Togo or The Gambia. Heterogeneity is observed in the coverage of each country by trap night (colour) and location of sites. For example, Senegal, Mali and Sierra Leone have generally good coverage compared to Guinea and Burkina Faso. B) Histogram of trap nights performed at each study site, a median of 248 trap nights (IQR 116-500) was performed at each site. A labelled map of the study region is attached in S5 Fig. Basemap shapefile obtained from GADM 4.0.4 (GADM, 2022)

2.4.3 What is the extent of spatial bias in the rodent trapping data?

To investigate the extent of spatial bias in the rodent trapping data, we calculated trap-night (TN) density within each West African level-2 administrative region. The `sf` package in the R statistical language (R version 4.1.2) was used to manipulate geographic data, administrative boundaries were obtained from GADM

4.0.4 (Pebesma, 2018; R Core Team, 2020; Database of Global Administrative Areas, 2022). Trap-night density ($TN_{density}$) was calculated by dividing the number of trap nights by the area of a level-2 administrative area (R_{area}). For studies not reporting trap nights imputation was used as previously described. Human population density was obtained for the closest year (2005) to the median year of trapping (2007) from Socioeconomic Data and Applications Center (SEDAC) gridded population of the world v4 at ~ 1km resolution ($P_{density}$) (Socioeconomic Data and Applications Center, 2021). Median population density was then calculated for each level-2 administrative region. Land cover classification was obtained from the Copernicus climate change service at ~300m resolution (European Space Agency Climate Change Initiative, 2022). The proportion of cropland, shrubland, tree cover (ψ_{tree}) and urban land cover (ψ_{urban}) within a level-2 administrative region in 2005 was calculated.

We investigated the association between relative trapping effort, measured as TN density, and the proportion of urban, cropland, tree cover and human population density using Generalised Additive Models (GAM) incorporating a spatial interaction term (longitude and latitude, X and Y) (Pedersen *et al.*, 2019). Spatial aggregation of relative trapping effort was modelled using an exponential dispersion distribution (Tweedie) (Kendal, 2002). The models were constructed in the `mgcv` package (Wood, 2017). Selection of the most parsimonious model was based on Deviance explained and the Akaike Information Criterion (AIC) for each model (Equations 1-5 below). Relative trapping effort was then predicted across West Africa using these covariates. We performed two sensitivity analyses, first, by removing sites with imputed trapping effort, second, by associating trap locations to ~1km pixels rather than level-2 administrative areas.

$$TN_{density} \sim \text{Tweedie}(X * Y) \tag{1}$$

$$TN_{density} \sim \text{Tweedie}(P_{density} + (X * Y)) \tag{2}$$

$$TN_{density} \sim \text{Tweedie}(P_{density} + R_{area} + (X * Y)) \tag{3}$$

$$TN_{density} \sim \text{Tweedie}(P_{density} + \psi_{tree} + \psi_{urban} + (X * Y)) \tag{4}$$

$$TN_{density} \sim \text{Tweedie}(P_{density} + R_{area} + \psi_{urban} + (X * Y)) \tag{5}$$

2.4.4 What is the difference in rodent host distributions between curated datasets and rodent trapping studies?

We assessed the concordance of curated rodent host distributions from IUCN and GBIF with observed rodent presence and absence from rodent trapping studies for seven species with the most trap locations (*M. natalensis*, *R. rattus*, *M. erythroleucus*, *M. musculus*, *A. niloticus*, *Praomys daltoni* and *Cricetomys gambianus*). We obtained rodent species distribution maps as shapefiles from the IUCN red list and translated these to a ~20km resolution raster (IUCN, 2021). Distributions were cropped to the study region for globally distributed rodent species. We obtained rodent presence locations from GBIF as point data limited to the study region (GBIF: The Global Biodiversity Information Facility, 2021a). Presence locations were associated to cells of raster with a ~20km resolution produced for the study region.

For each of the seven species, we first calculated the area of the IUCN expected range, and then the percentage of this range covered by presence detections in GBIF, and from detections in the rodent trapping data. We then calculated the area of both GBIF and rodent trapping detections outside of the IUCN expected range. For rodent trapping data, we additionally calculated the area of non-detections within the IUCN expected area. Finally, we calculated the combined area of detection from both GBIF and rodent trapping data.

2.4.5 Are rodent trapping derived host-pathogen associations present in a consolidated zoonoses dataset?

To examine the usefulness of rodent trapping studies as an additional source of data we compared identified host-pathogen associations from trapping studies investigating zoonoses with a consolidated zoonoses dataset (CLOVER) (Gibb, Gregory F. Albery, *et al.*, 2021b; Gibb, Carlson and Farrell, 2021). CLOVER is a synthesis of four host-pathogen datasets (GMPD2, EID2, HP3 and (Shaw *et al.*, 2020)) and was released in 2021, it contains more than 25,000 host-pathogen associations for Bacteria, Viruses, Helminth, Protozoa and Fungi. We compared the host-pathogen networks across the two datasets, where the CLOVER data was subset for host species present in the rodent trapping data.

For host-pathogen pairs with assay results consistent with acute or prior infection, we calculated the proportion positive and identify those absent from CLOVER. We expand the analysis to host-pathogen pairs with pathogens identified to genus level in **S4 Fig**.

2.4.6 What is the spatial extent of pathogen testing within host ranges?

We use the sampled area of three pathogen groups and two pathogens (Arenaviridae, Borreliaceae, Leptospiraceae, *Lassa mammarenavirus* and *Toxoplasma gondii*) to quantify the bias of sampling within their

hosts ranges. For each pathogen, we first describe the number of host species assayed, for the five most commonly tested species we associate the locations of sampled individuals to ~20km pixels and calculate the proportion of the IUCN range of the host in which sampling has occurred. We compare this figure to the total area in which the host has been detected to produce a measure of relative completeness of sampling within the included rodent trapping studies.

Data and code to reproduce all analyses are available in an archived Zenodo repository (Simons, 2022a).

2.5 Results

2.5.1 What is the extent of spatial bias in the rodent trapping data?

We found non-random, spatial clustering of rodent trapping locations across the study region, suggestive of underlying bias in the sampling or rodents across West Africa. Trap sites were situated in 256 of 1,450 (17.6%) level-2 administrative regions in 14 West African nations. The regions with the highest TN density included the capitals and large cities of Niger (Niamey), Nigeria (Ibadan), Ghana (Accra), Senegal (Dakar), Ghana (Accra) and Benin (Cotonou). Outside of these cities, regions in, Northern Senegal, Southern Guinea, Edo and Ogun States in Nigeria and Eastern Sierra Leone had the greatest TN density (Figure 2.1 A)).

The most parsimonious GAM model (adjusted R2 = 0.3, Deviance explained = 48.7%) reported significant non-linear associations between relative trapping effort bias and human population densities (Effective Degrees of Freedom (EDF) = 7.13, $p < 0.001$), proportion of urban landscape (EDF = 1.92, $p < 0.002$) and region area (EDF = 3.63, $p < 0.001$), alongside significant spatial associations (EDF = 27.3, $p < 0.001$) (Supplementary table 3.1). Greatest trapping effort bias peaked at population densities between 5,000-7,500 individuals/km^2, proportion of urban landscape >10% and region areas < 1,000km2. Increased trapping effort was found in North West Senegal, North and East Sierra Leone, Central Guinea and coastal regions of Nigeria, Benin and Ghana; in contrast South East Nigeria, Northern Nigeria and Burkina Faso had an observed bias towards a reduced trapping effort (Figure 2.2). In sensitivity analysis, excluding sites with imputed trap nights, Mauritania, Northern Senegal and Sierra Leone remained as regions trapped at higher rates, with Nigeria being trapped at lower than expected rates (**S3A Fig**). In pixel-based sensitivity analysis spatial coverage was reduced with similar patterns of bias observed to the primary analysis (**S3B Fig**).

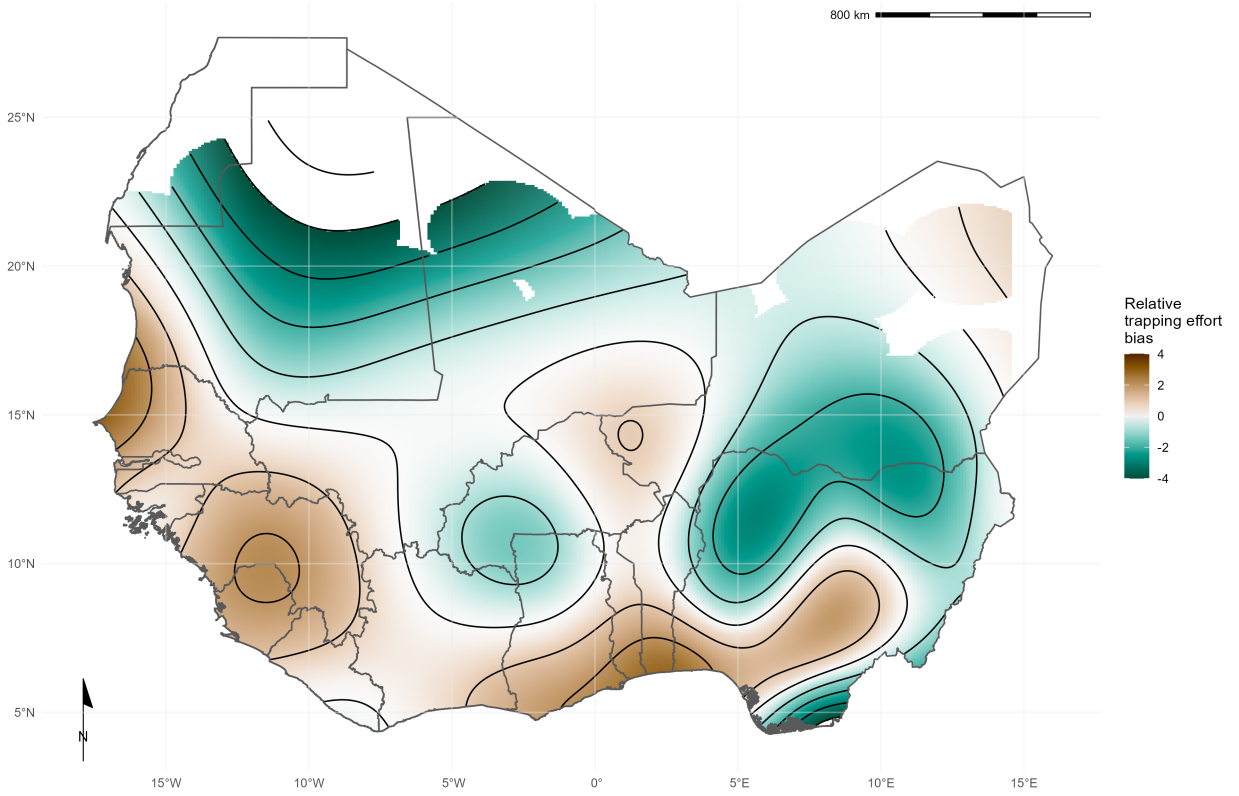

Figure 2.2: **Relative trapping effort bias across West Africa.** Modelled relative trapping effort bias adjusted for human population density, proportion urban land cover and area of the administrative region. Brown regions represent areas with a bias towards increased trapping effort (e.g., North West Senegal), Green regions represent areas with a bias towards reduced trapping effort (e.g., Northern Nigeria). Basemap shapefile obtained from GADM 4.0.4 (GADM, 2022)

2.5.2 What is the difference in rodent host distributions between curated datasets and rodent trapping studies?

We found that for six of the seven most frequently detected rodent species (*M. natalensis*, *R. rattus*, *M. erythroleucus*, *M. musculus*, *A. niloticus* and *P. daltoni*), trapping studies provided more distinct locations of detection and non-detection than were available from GBIF. For the endemic rodent species (*M. natalensis*, *M. erythroleucus*, *A. niloticus*, *P. daltoni* and *C. gambianus*) IUCN ranges had good concordance to both trapping studies and GBIF, however, individuals of *A. niloticus* and *P. daltoni* were detected outside of IUCN ranges. In contrast, the non-native species *R. rattus* and *M. musculus* were detected across much greater ranges than were expected from IUCN distributions. Comparisons for *M. natalensis*, *R. rattus* and *M. musculus* are shown in Figure 2.3, the remaining species are shown in **S4 Fig**.

Comparison of the proportion of a species IUCN range in which detections and non-detections occurred showed that sampling locations of these seven species within GBIF covered between 0.09-0.26% of expected ranges (Table 1), compared to 0.03-0.24% for rodent trapping data. Detections occurred outside IUCN ranges for all species in both the GBIF and rodent trapping data, most noticeably for *A. niloticus* and *R. rattus*.Combining GBIF and rodent trapping data increased the sampled area by a mean of 1.6 times compared to the GBIF area alone, demonstrating limited overlap between the locations providing information to either dataset. Non-detection of a species occurred across species ranges (mean = 0.11%, SD = 0.03%), suggestive of spatial heterogeneity of presence within IUCN ranges.

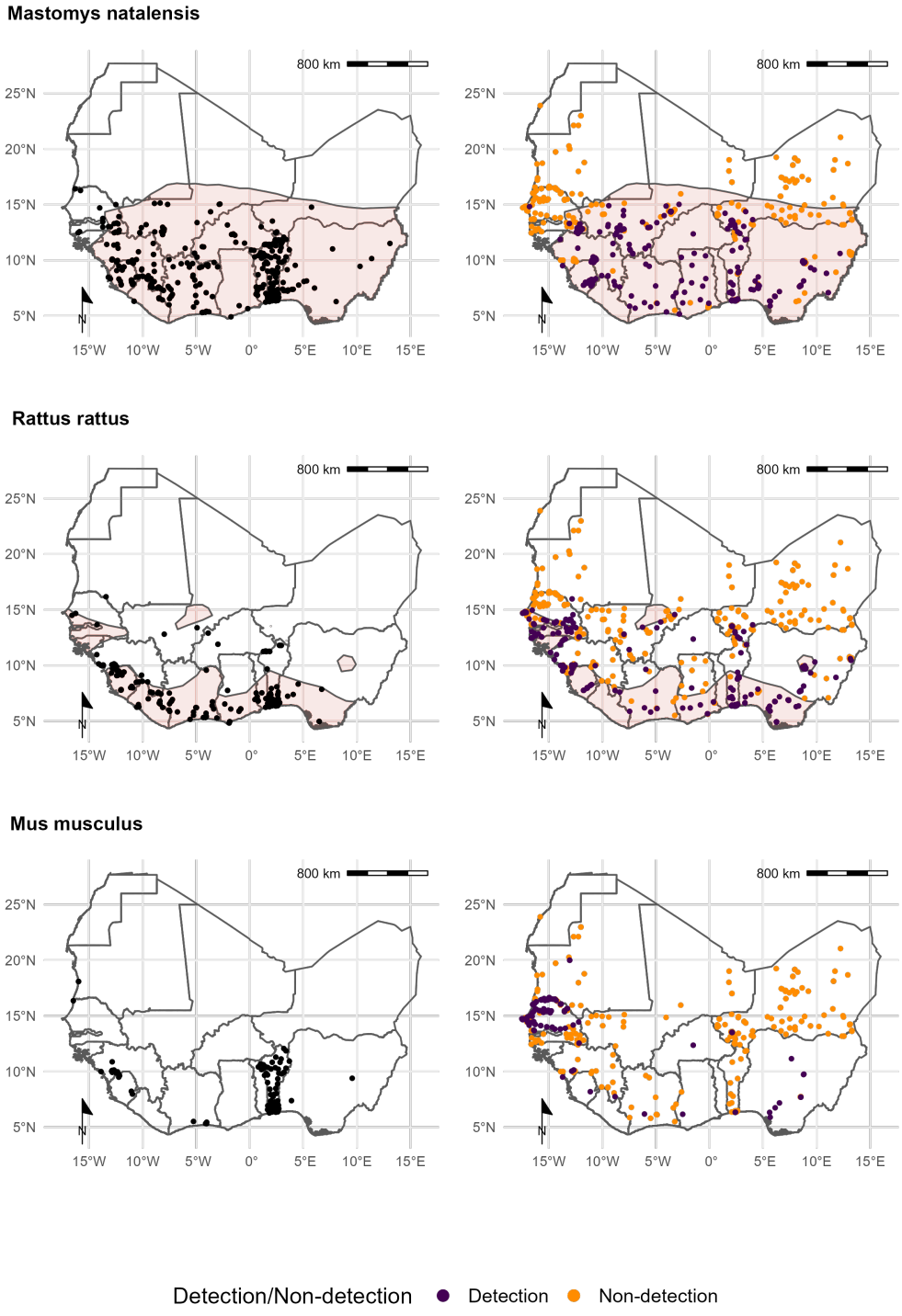

Figure 2.3: **Locations of detection and non-detection sites for rodent species in West Africa.** Each row corresponds to a single rodent species. L) Presence recorded in GBIF (black points) overlaid on IUCN species range (red-shaded area). R) Detection (purple) and non-detection (orange) from rodent trapping studies overlaid on IUCN species ranges. *M. musculus* has no IUCN West African range. Basemap shapefile obtained from GADM 4.0.4 (GADM, 2022)

Table 1: Comparison of IUCN, GBIF and rodent trapping ranges for the 7 rodent species trapped at the most sites.

	IUCN	GBIF		Trapping studies			Combined
Species	Range*	Area inside range* (% of IUCN)	Area outside range*	Detection area inside range*	Area outside range* (% of IUCN)	Non-detection area inside range* (% of IUCN)	Detection area inside range* (% of IUCN)
Mastomys natalensis	3,257	6.83 (0.21%)	0.19	4.4 (0.14%)	0.17	3.12 (0.1%)	12.73 (0.33%)
Rattus rattus	1,019	2.61 (0.26%)	0.52	2.42 (0.24%)	1.21	1.3 (0.13%)	5.72 (0.48%)
Mastomys erythroleucus	3,735	4.48 (0.12%)	0.04	3.24 (0.09%)	0.12	4.35 (0.12%)	11 (0.2%)
Mus musculus	NA	NA	2.15	NA	1.85	NA	3.94
Arvicanthis niloticus	1,829	1.69 (0.09%)	2.41	1.98 (0.11%)	0.34	3.09 (0.17%)	5.96 (0.2%)
Praomys daltoni	2,658	4.03 (0.15%)	0.29	2.03 (0.08%)	0.15	2.78 (0.1%)	8.21 (0.22%)
Cricetomys gambianus	2,476	5 (0.2%)	0.17	0.75 (0.03%)	0.06	2.99 (0.12%)	8.37 (0.23%)

[a] Mus musculus does not have an IUCN range in West Africa

[b] * Area is reported in 1,000

2.5.3 Are rodent trapping derived host-pathogen associations present in a consolidated zoonoses dataset?

We found potentially important differences between the host-pathogen networks produced from included rodent trapping studies and the consolidated CLOVER dataset. When limited to taxonomic classification of both pathogen and host to species level we identified 25 host-pathogen pairs among 14 rodent and 6 pathogen species (Figure 2.4 and Fig 2.5). We identified negative associations (non-detection through specific assays) for 45 host-pathogen pairs among 35 rodent and 7 pathogen species. CLOVER contained 10 (40%) of our identified host-pathogen associations, the remaining 15 (60%) were not found to be present in CLOVER, additionally CLOVER recorded positive associations for 4 (9%) of the negative associations produced from the rodent trapping data.

CLOVER included an additional 492 host-pathogen associations we do not observe in rodent trapping studies. The majority of these 392 (80%) pairs are from species with global distributions (*M. musculus*, *R. rattus* and *R. norvegicus*), or from those with wide ranging distributions in sub-Saharan Africa (38, 8%) (i.e., *A. niloticus*, *M. natalensis* and *Atelerix albiventris*).

For pathogens not identified to species level (i.e. family or higher taxa only), we identified 148 host-pathogen pairs among 32 rodent species and 25 pathogen families (Supplementary Fig 4.), with CLOVER containing 66 (45%) of these associations.

Rodent trapping studies identified additional rodent host species for six pathogens; *Lassa mammarenavirus* (5), *Toxoplasma gondii* (4), Usutu virus (2), *Coxiella burnetii* (2), *Escherichia coli* and *Klebsiella pneumoniae* (both 1), that were not present in this consolidated host-pathogen association dataset.

2.5.4 What is the spatial extent of pathogen testing within a host's range?

The five most widely sampled pathogen species/families in included studies were Arenaviridae, Borreliaceae, *Lassa mammarenavirus*, Leptospiraceae and *Toxoplasma gondii* (Table 2). Assays to identify Arenaviridae infection were performed in 44 rodent species with evidence of viral infection in 15 species. *Lassa mammarenavirus* was specifically tested for in 43 species with 10 showing evidence of viral infection. The most commonly infected species for both Arenaviridae, generally, and *Lassa mammarenavirus* specifically, were *M. natalensis* and *M. erythroleucus*. These species were assayed across between 10-20% of their trapped area, equating to ~0.02% of their IUCN range (Table 2).

Infection with species of Borreliaceae was assessed in 42 species, with evidence of infection in 17 rodent species. The greatest rates of infection were among *A. niloticus* (16%), *Mastomys huberti* (11%) and *M. erythroleucus*

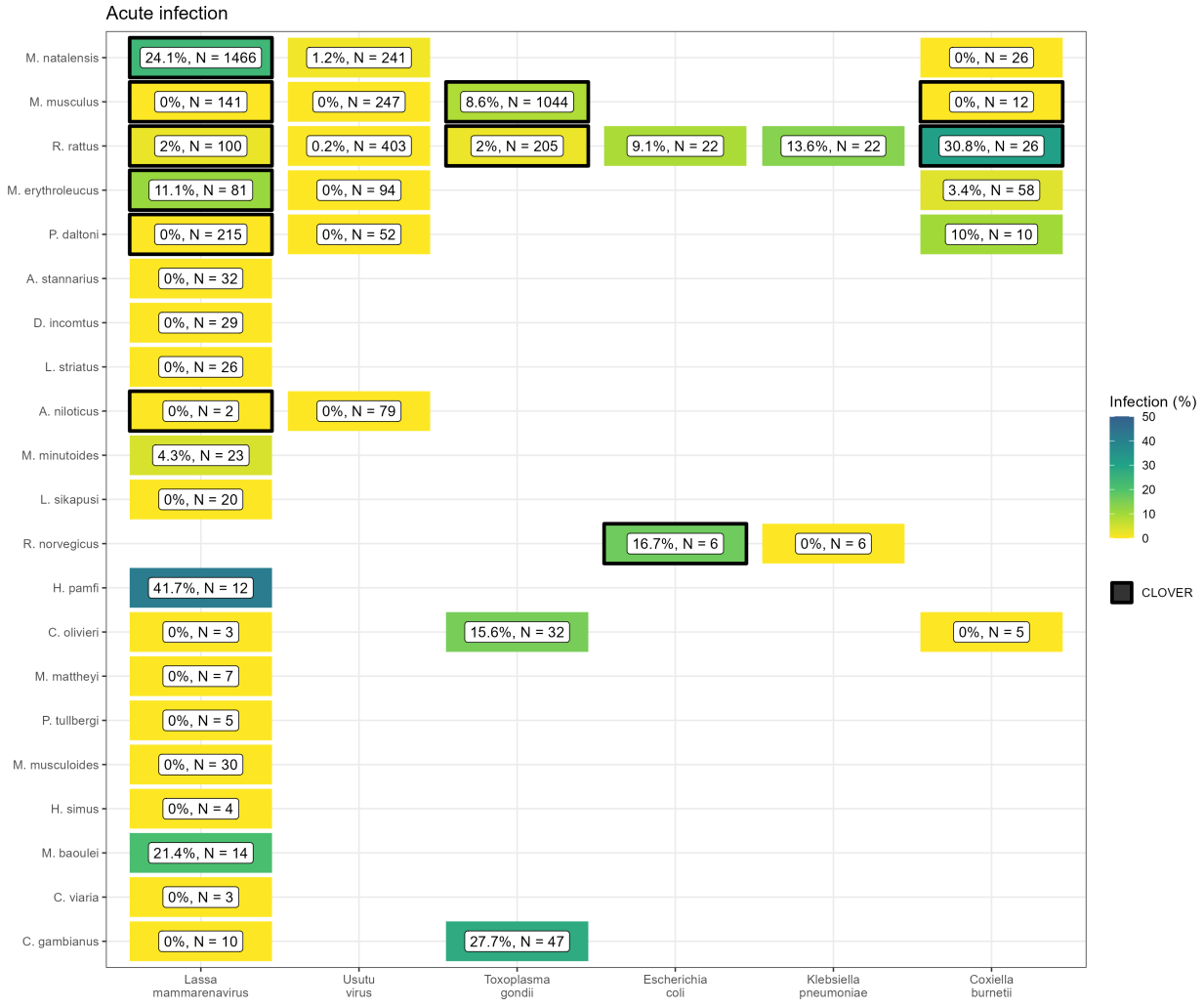

Figure 2.4: **Host-Pathogen associations detected through acute infection.** Identified species level host-pathogen associations through detection of acute infection (i.e. PCR, culture). Percentages and colour relate to the proportion of all assays that were positive, the number of individuals tested for the pathogen is labelled N. Associations with a black border are present in the CLOVER dataset.

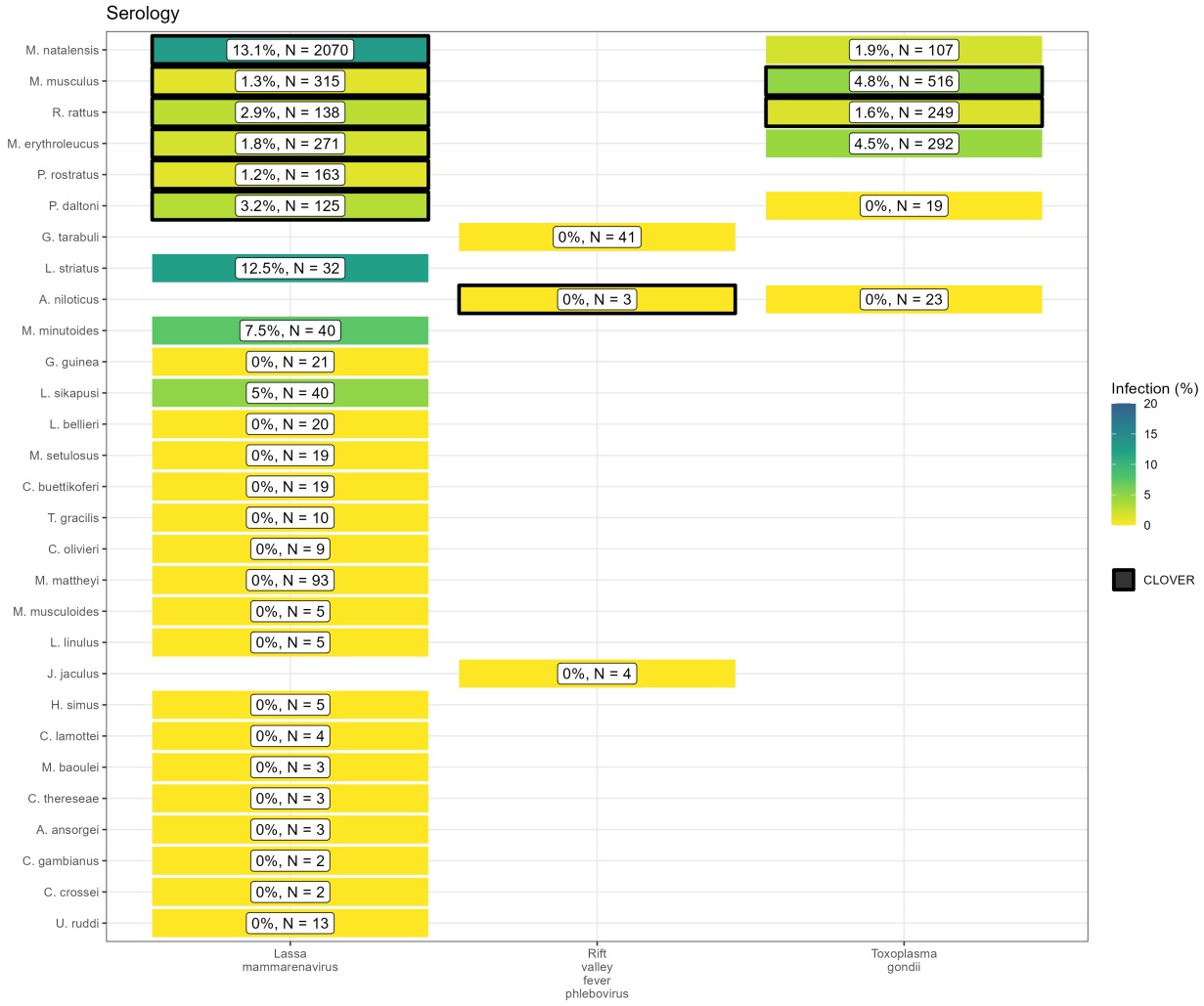

Figure 2.5: **Host-Pathogen associations detected through evidence of prior infection.** Identified species level host-pathogen associations through serological assays (i.e. ELISA). Percentages and colour relate to the proportion of all assays that were positive, the number of individuals tested for the pathogen is labelled N. Associations with a black border are present in the CLOVER dataset.

Table 2: Comparison of pathogen sampling ranges for the 5 most widely sampled pathogens and the 5 most sampled rodent host species.

Pathogen	Species	Tested	Positive	Pathogen testing area*	Pathogen testing area within trapped area (%)	Pathogen testing area within IUCN range (%)
Arenaviridae sp.						
	Mastomys natalensis	2,841	104	0.614	13.4	0.02
	Praomys daltoni	854	6	0.423	19.4	0.02
	Mastomys erythroleucus	398	20	0.403	12.0	0.01
	Rattus rattus	396	4	0.382	10.5	0.04
	Praomys rostratus	310	5	0.127	12.5	0.02
Borrelia sp.						
	Mastomys erythroleucus	1,586	140	1.142	33.9	0.03
	Arvicanthis niloticus	1,551	253	0.660	28.5	0.03
	Mastomys natalensis	733	54	0.688	15.1	0.02
	Mastomys huberti	731	83	0.228	29.8	0.04
	Mus musculus	686	26	0.453	24.5	NA
Lassa mammarenavirus						
	Mastomys natalensis	3,199	580	1.034	22.6	0.03
	Mastomys erythroleucus	352	14	0.357	10.6	0.01
	Rattus rattus	177	2	0.337	9.3	0.03
	Praomys rostratus	163	2	0.274	27.0	0.04
	Mus musculus	147	0	0.042	2.3	NA
Leptospira sp.						
	Rattus rattus	646	65	0.404	11.1	0.04
	Arvicanthis niloticus	221	10	0.021	0.9	0.00
	Crocidura olivieri	141	14	0.340	25.2	NA
	Mastomys natalensis	136	26	0.361	7.9	0.01
	Rattus norvegicus	79	19	0.212	40.1	NA
Toxoplasma gondii						
	Mus musculus	1,548	115	0.621	33.6	NA
	Rattus rattus	428	8	0.355	9.8	0.03
	Mastomys erythroleucus	292	13	0.372	11.1	0.01
	Mastomys natalensis	107	2	0.083	1.8	0.00
	Cricetomys gambianus	47	13	0.062	7.6	0.00

[a] Mus musculus does not have an IUCN range in West Africa
[b] * Area is reported in 1,000

(9%). Testing was more widespread than for Arenviruses with coverage between 15-34% of their trapped area, however, this remains a small area in relation to their IUCN ranges (<0.05%). Leptospiraceae and *Toxoplasma gondii* was assessed in 8 species, with evidence of infection in 5 and 6 rodent species respectively. The spatial coverage of testing for these pathogens was more limited within IUCN host species ranges (~0.01%).

2.6 Discussion

Endemic rodent zoonoses and novel pathogen emergence from rodent hosts are predicted to have an increasing burden in West Africa and globally (Han *et al.*, 2015). Here we have synthesised data from 126 rodent trapping studies containing information on more than 72,000 rodents, from at least 132 species of small mammals (Rodentia = 102, Soricidae = 28, Erinaceidae = 2), across 1,611 trap sites producing an estimated 942,669 trap nights from 14 West African countries. Locations studied are complementary to curated datasets (e.g., IUCN, GBIF), incorporation of our synthesised dataset when assessing zoonosis risk based on host distributions could counteract some of the biases inherent to these curated datasets (Boakes *et al.*, 2010). Most assayed rodents were not found to be hosts of known zoonotic pathogens. We identified 25 host-pathogen pairs reported from included studies, 15 of these were not included in a consolidated host-pathogen dataset. Generally, the number of different species tested for a microorganism and the spatial extent of these

sampling locations were limited. These findings highlight a number of sampling bias, supporting calls for further microorganism sampling across diverse species in zoonotic hotspots (Harvey and Holmes, 2022).

We found that rodent trapping data, like biodiversity data, showed important spatial biases (Beck *et al.*, 2014). Relative trapping effort bias was greater in Benin, Guinea, Senegal and Sierra Leone driven by long-standing research collaborations investigating the invasion of non-native rodent species (*M. musculus* and *R. rattus*) and the hazard of endemic zoonosis outbreaks (e.g., *Lassa mammarenavirus*). In addition to identifying point locations of prior rodent and pathogen sampling (Figure 2.1), additional information on the trapping effort (density of trap-nights), human population density and land use type have been incorporated to produce a value of relative effort that will assist researchers in identifying specific locations where predictions based on these underlying data sources may suffer from effects of sampling bias. This approach improves the ease of identifying under sampled locations, for example, Figure 2.1 may suggest that South East Senegal, Southern Mali and Southern Niger are well sampled based on locations of trapping sites. When the number of trap nights, human population density and land use of these regions are taken into account (Figure 2.2) and compared with better sampled locations (i.e., Western Senegal, Eastern Sierra Leone) these areas are found to be relatively under sampled and would benefit from further sampling effort. This contrasts to North West Nigeria where no trapping has occurred (Figure 2.1), our modelling approach has perhaps highlighted this region as an immediate priority for sampling of rodents and their pathogens given high human population densities and a human dominated landscape.

Much of West Africa remains relatively under sampled, particularly Burkina Faso, Côte d'Ivoire, Ghana and Nigeria, despite these countries facing many of the same challenges. For example, annual outbreaks of Lassa fever are reported in Nigeria and there are potentially 60,000 unrecognised cases of Lassa fever every year in Côte d'Ivoire and Ghana (Basinski *et al.*, 2021). Our estimates of the proportion of a rodent species range that have been sampled, along with pathogen testing within their sampled range, are sensitive to our choice of raster cell size. Smaller area cells will reduce the reported coverage while larger cells will have the opposite effect. Despite this, the observed patterns are unlikely to importantly change, with the finding of sparse sampling of both rodents and their pathogens remaining present across cell scales. Rodent sampling should be targeted towards currently under sampled regions to reduce the potential impact of current biases and improve our understanding of both the distribution of rodent hosts and the prevalence of pathogens within their populations. This will allow for better estimation of risk from endemic and novel zoonoses.

Rodent trapping studies provide geographic and temporally contextualised data on both species detection and non-detection which are not available from curated datasets. Non-detection data can improve models of species distributions, unfortunately, high levels of missing data on trapping effort will continue to confound

the allocations of non-detections as true absences (Václavík and Meentemeyer, 2009). Models of host species occurrence and abundance, improved by incorporating species absence, are important to assess the effect of land use and climate change on endemic zoonosis spillover to human populations and direct limited public health resources towards regions at greatest risk (Zeimes *et al.*, 2012; Judson *et al.*, 2018).

Currently available consolidated datasets on host-pathogen associations (e.g., CLOVER, EID2 and GMPD2) do not include spatial or temporal components (Gibb, Gregory F. Albery, *et al.*, 2021a). The current synthesis of rodent trapping studies has highlighted that pathogens have been sparsely sampled within a host's range. Current zoonosis risk models dependent on these sources of data are therefore not able to incorporate spatial heterogeneity in pathogen prevalence across the host range. Additional uncertainty in current models of zoonotic disease risk arises from host-pathogen associations that have not been reported in these consolidated datasets. For example, *Hylomyscus pamfi* infected with *Lassa mammarenavirus* and *R. rattus* infected with *Coxiella burnetii*, will not be included when solely based on consolidated host-pathogen datasets. Further, detection of zoonotic pathogens in multiple, co-occurring, host species supports the adoption of multi-species approach to better understand the potential range of endemic zoonoses (Wilkinson *et al.*, 2019).

Few studies stratified detection and non-detection of hosts or pathogen prevalence by time, therefore limiting inference of temporal changes in host and pathogen dynamics. This limitation prevents calculation of incidence of infection and the abundance of infectious rodents which potentially varies by both time and space (Fichet-Calvet *et al.*, 2016). Understanding temporal changes in viral burden and shedding for endemic zoonoses is required to accurately predict current and future risk of pathogen spillover.

Finally, due to data sparsity, we were unable to account for temporal change over the six decades of rodent trapping studies. Land use change and population density have changed dramatically over this period in West Africa (Herrmann *et al.*, 2020). We attempted to mitigate against this by using the median year of trapping to understand the spatial and land use biases in trapping activity. It is possible that land use and population density at trapping sites varied importantly between when rodent trapping was conducted and the conditions in 2005. Despite this limitation, the finding that trapping is biased towards high density, human dominated landscapes is unlikely to substantially change.

We have shown that synthesis of rodent trapping studies to supplement curated rodent distributions can counteract some of the inherent biases in these data and that they can add further contextual data to host-pathogen association data. Together this supports their inclusion in efforts to model endemic zoonotic risk and novel pathogen emergence. Contribution of rodent trapping studies as data sources can be improved by

adopting reporting standards and practices consistent with Open Science, namely sharing of disaggregated datasets alongside publication (Foster and Deardorff, 2017).

Future rodent trapping studies should be targeted towards regions that are currently under-studied. Further information on rodent presence and abundance across West Africa will aid the modelling of changing endemic zoonosis risk and the potential for novel pathogen emergence. Sharing of disaggregated data alongside research publications should be promoted with adoption of data standards to support ongoing data synthesis. Specifically, inclusion of exact locations of trapping sites, trapping effort and the dates at which trapping occurred would support more detailed inference of the spatio-temporal dynamics of host populations and the risk of endemic zoonosis spillover events. Despite these challenges we propose that rodent trapping studies can provide an important source of data to supplement curated datasets on rodent distributions to quantify the risk of endemic zoonosis spillover events and the hazard of novel pathogen emergence.

3 Small mammal species community structures vary importantly by land-use type in a Lassa fever endemic region of Sierra Leone.

3.1 Preamble

3.2 Abstract

3.3 Introduction

3.4 Methods

3.4.1 Study area

3.4.2 Rodent sampling

3.4.3 Statistical analysis

3.4.3.1 Rodent occurrence and species assemblage structure

3.4.3.2 Co-occurrence of rodent species

3.5 Results

3.5.1 Rodent occurrence and species assemblage structure

3.5.2 Estimating the effect of land use on species occurrence and richness

3.5.3 Co-occurrence of rodent species

3.6 Discussion

3.7 Summary

4 Reconstructing rodent contact networks to understand potential routes of *Lassa mammarenavirus* transmission.

4.1 Preamble

4.2 Introduction

4.3 Methods

4.3.1 Study area

4.3.2 Rodent sampling

4.3.3 *Lassa mammarenavirus* serology

4.3.4 Statistical analysis

4.3.4.1 How does landuse-, species- and individual-level heterogeneity influence contact networks?

4.4 Results

4.4.1 *Lassa mammarenavirus* serology

4.4.2 Rodent contact networks

4.5 Discussion

4.6 Summary

5 Conclusions and future research directions.

The work presented in this thesis provides important new insights on the role of rodent ecology on zoonotic infectious disease spillover risk and the association of anthropogenic land use change with rodent community structure. This final chapter summarises the key findings of this work, placing them in the broader context and includes suggestions for future research.

In Chapter 2, I synthesised data from rodent trappping studies to investigate current spatial sampling biases of rodent populations. This consolidated dataset was compared to two commonly used data sources for understanding the occurrence of rodents in West Africa. I found that rodent trapping studies can provide a useful additional source of information, counteracting some of the biases present in alternative sources and substantially increasing the sampled area of common rodent species important to zoonotic disease emergence. This study quantified rodent and zoonosis sampling bias in West Africa, identifying host and pathogen taxa and geographic regions that would benefit from further investigation to improve inference for zoonotic infectious disease spillover risk in the region.

In Chapter 3, I designed and implemented a three year standardised rodent sampling study in a Lassa fever endemic region of Sierra Leone to characterise rodent communities and investigate the response of this community structure to an anthropogenic land use gradient. This study confirmed that synanthropic rodent species were associated with increasing anthropogenic land use change, with higher probability of occurrence within these settings. This study shed light on the biotic interactions between species in these settings sand how this shaped rodent communities. This effect of species interactions highlighted the need to adopt community scale measurement within species distribution modelling as applied to disease ecology where host species may have variable impact on pathogen transmission and spillover risk.

In Chapter 4, I used the rodent trapping dataset to infer contact dynamics within rodent communities. I found that contacts among rodents followed a long tailed distribution with most individuals having few contacts while few individuals have many direct and indirect contacts. These network properties will direct pathogen transmission among these networks and suggest that assumptions of well mixed populations may not hold for rodent associated zoonoses. Failing to account for this contact rate heterogeneity by species, rodent abundance and land use type will limit the accuracy of pathogen transmission dynamic models within rodent communities. I observed low LASV pathogen prevalence, measured through seropositivity, in the studied system. This limited the ability to directly model the effect of these contact networks on pathogen transmission. There is therefore a need to conduct these studies over longer time periods to better understand the temporal and spatial variation in transmission of LASV within the endemic region of Sierra

Leone.

5.1 Contribution to understanding biases in currently available data

It is recognised that biases exist within currently available data on species distributions and that these biases are not homogenous []. Data are more readily available with less geographic and temporal biases for animal species of economic, cultural, or scientific value []. This has led to rodents and other small mammals being systematically under-reported within available records, which can lead to a greater effect of geographic and temporal biases []. These biases limit inference from these datasets when investigating the distribution of rodent hosts of rodent-associated zoonoses. The study presented in Chapter 2 is the first attempt to quantify the effect of these rodent sampling biases in the context of zoonoses in West Africa.

Recognition of the existence of biases in data is but a first step to counteracting their role in limiting inference.

Relatively small regions of important rodent zoonotic hosts have been sampled, this suggests that inference of risk may be associated with low confidence in these estimates.

Within these host distributions an even smaller area has been sampled for the pathogens of interest. Further work is requried across greater geographic scales to understand how pathogens are distributed within host species.

The lack of sufficient data and poor reporting of timing of studies makes it challenging to understand how risk may change based on changing host distributions under pressures including land use and climate change. Improved reporting standards and data sharing are required.

I intend to expand this work to other regions including South East Asia and South America to improve availability of rodent and rodent-associated zoonosis data to the scientific community.

5.2 Integrating species assemblages into the hazard of zoonotic pathogen spillover

5.3 Understanding the epidemiology and risk of Lassa Fever

5.4 Future directions

Antigenic escape in dynamic populations can lead to selection for increased virulence (https://pubmed.ncbi.nlm.nih.gov/34949816/)

Challenges to reconstruct direct transmission based on genomic work when viral populations vary dramati-

cally day-to-day. i.e., the variants being observed from the host may not be seen in the infectee three days post infection due to dynamics within the infectee, because of this we will not see links when we are multiple days out from infection (https://journals.asm.org/doi/full/10.1128/JVI.00171-17)

Future landuse change and the effect on rodent communities. Networks of rodent communities moderating viral persistence and transmission within endemic settings. Immunology - differences between same species across landscapes. Does the same species have the same response to acute infection? Does this modulate the risk of transmission between rodents and into human populations? What would we need to do to further understand this? Population dynamics - challenges estimating abundance from removal trapping. Do the dynamics match those observed in Tanzania. Estimated abundance across these studies do not suggest the same spikes and crashes occur. How does Lassa persist in areas of apparently high transmission and low transmission. Contrasting locations of very high seroprevalence among rodents with those of low seroprevalence. Antigenic drift within LASV depending on spatial mixing of rodents within an endemic setting. Does this drive selection towards more virulent strains potentially explaining geographic variation in CFR of Lassa fever. How can we understand virulence in Lassa fever, in the context of epidemiological data paucity and biases. Expansion of invasive rodent species, affecting rodent communities in the endemic region and implications for expansion or reduction of the Lassa fever endemic region. Describe and quantify data requirements to better understand the system and allow prediction/real-time forecasting of Lassa outbreaks. Rodent population dynamics in endemic settings - abundance, fecundity, population cycles Viral transmission dynamics among rodents across scales Spillover rates into human populations, age-stratified contact rates how does infection actually occur? Immunity and disease severity among humans, who gets sick, why?

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7 Appendix

This will be Appendix A.