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

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David Simons

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A dissertation submitted in partial fulfillment 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

Understanding rodent host ecology can inform predictions of zoonotic infectious disease spillover events and outbreaks of infections in humans. To do this we need to understand the biases in currently available data and utilise robust survey designs to characterise rodent species assemblages in heterogeneous landscapes. I will show that the composition of rodent species communities varies across a land use gradient and that this may have implications for spillover from rodent host species. Contacts between individuals of zoonotic host and non-host species form dynamic transmission networks for these pathogens that will modulate the risk of pathogen spillover into human populations. Finally, incorporating both host occurrence and co-occurrence with other rodent species can provide additional information that can guide public health interventions to reduce the impact of zoonotic infectious disease outbreaks.

Endemic zoonotic infectious diseases represent a large proportion of preventable morbidity and mortality across much of the world. The potential for endemic zoonotic infectious diseases to undergo range expansion, increasing the number of individuals at risk of infection is of significant concern.

Spillover events of zoonoses into human populations typically occur at a local scale. Sustained human-to-human transmission following spillover can result in epidemics and pandemics of diseases originating from animal reservoirs.

Understanding the locations at greatest risk of spillover events is of particular interest to strengthen local public health responses in endemic regions to outbreaks. Additionally, identifying potential locations of spillover of zoonoses is imperative for efforts to prevent pandemics of pathogens of zoonotic origin.

Studies assessing locations at greatest risk typically rely upon large consolidated databases of host presence and absence data alongside datasets on host-pathogen associations. Here, I have shown that these datasets suffer from spatial and temporal sampling biases. I produce a synthesised dataset of rodent trapping studies to mitigate some of these biases by providing high-resolution rodent detection and non-detection data alongside spatio-temporal host-pathogen associations.

Understanding the interplay between different rodent species in a host-pathogen system is important to understand the hazard of zoonotic spillover events. Here, I have reported on a rodent sampling study in a Lassa Fever endemic region to describe the association of species detection and land use type accounting for imperfect detection.

Within these different land use types species contact each other at different rates. This has implications for

the transmission of pathogens within these settings. Here, I have described the contact patterns between individuals of different species and the prevalence of antibodies to our target pathogen to model potential transmission networks.

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 output

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*, PLOSNTD, 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 are infections caused by pathogens that can cause clinical disease in humans and are transmitted from animal hosts. Specifically, a "zoonosis" is any disease or infection that is naturally transmissible from vertebrate animals or an animal reservoir to humans, either through direct or indirect pathways [reference WHO https://www.who.int/news-room/fact-sheets/detail/zoonoses]. Examples of direct transmission include, bites and scratches (i.e., *Rabies lyssavirus* and *Bartonella hanselae*) while indirect transmission can occur via arthropod vectors (i.e., *Orentia tsustsugamushi*, Scrub typhus), environmental contamination (i.e., Leptospirosis) and through food (i.e., Salmonellosis). The wider term "zoonotic disease" is often used for a disease that first originated in non-human animals, even when disease transmission is currently entirely within the human population in the absence of animals or an animal reservoir (e.g., HIV) (**kock_2022?**). Individual transmission events from vertebrate animal populations into human populations - spillover events - can, under certain circumstances, lead to sustained outbreaks that may progress to localised epidemics or global pandemics (**plowright_2017?**). These zoonotic pathogens may - or may not - cause clinical disease in their animal hosts. For example, *Lassa mammarenavirus* (LASV), the causative agent of Lassa fever in humans does not cause clinical disease in rodent host species' as measured through organ dysfunction, weight loss or behavioural change. LASV infection in humans can lead to severe clinical symptoms and death (Safronetz *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).

Zoonoses display a range of patterns of spillover from wild or domestic animals and transmission in human populations. Nipah virus infection (*Nipah henipavirus*) and Lassa fever (LASV) spillover into human populations 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). Ebola virus disease (*Sudan ebolavirus* and *Zaire ebolavirus*) and mpox (formerly Monkeypox, *Monkeypox virus*) exhibit sustained human-to-human transmission following spillover from wild or domestic animals, but due to the transmission dynamics of these pathogens, outbreaks are generally constrained to local epidemics (Fine *et al.*, 1988; Legrand *et al.*, 2007). Finally, some pathogens may be better adapted to transmission among humans due to their transmission dynamics or similarities between human physiology and their original vertebrate host, these 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 transmission from wild or domestic animal populations (i.e., HIV and SARS-CoV-2) [ref].

These patterns of spillover are evidenced through phylogenetic analysis of viral sequences from human populations. For example, phylogenetic analysis of currently circulating mpox and SARS-CoV-2 indicate a most common recent ancestor **X** years prior [ref]. A similar analysis of LASV human infections indicates a most common recent ancestor **Y** year prior, consistent with repeated spillover events into human populations of genetically distant pathogens [ref]. These findings are suggestive of a limited number of spillover events establishing the epidemics of mpox and SARS-CoV-2 with LASV introduced into human populations at multiple discrete time points. 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 [ref]. The situation of LASV highlights the ongoing hazard of local spillover into human populations in endemic regions and reinforces the importance of surveillance of known zoonoses.

When considering interventions to reduce the impact of zoonoses in endemic settings an approach that incorporates knowledge of multiple interacting systems are required. Understanding the role of environmental, wildlife and human factors on the hazard and risk of spillover events are necessary. This is often termed the "One Health" approach, 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." (**CDC_2023?**). This framework is particularly useful when considering how spillover of zoonoses occur in a setting of ongoing climate, landuse and biodiversity change.

1.2 Global change and zoonoses

Anthropogenic climate change is hypothesised to modify the risk of zoonoses to human populations through several mechanisms [ref]. Changes in mean temperature and precipitation will increase environmental suitability for some pathogens and hosts leading to range expansion of endemic regions. Environmentally transmitted zoonoses such as Leptospira will become viable, with therfore increasing prevalence, in environments where low temperatures or low precipitation previously limited transmission. Vector borne zoonoses such as West Nile Virus are currently demonstrating range expansion as mosquito vector population numbers are increased across a larger geographic range [ref]. Climate change is occurring alongside anthropogenic landuse change with natural habitats converted into human dominated landscapes (i.e., farming and urban landuse) [ref].

Encroachment of human activity into zoonotic host animal ranges has been hypothesised to further increase the risk of spillover events into human populations, through increasing the animal-human interface raising the probability of direct and indirect contact with infected hosts of zoonoses (**murray__2013?**). Additionally, increased interactions between wildlife and domesticated animals can also increase the risk of subsequent zoonosis spillover into human populations where wild sylvatic animals are hosts of pathogens that may be amplified in domesticated animals following transmission (i.e. Nipah virus) [ref]. Together climate and landuse change can also modify species' home ranges. This can drive contact events between current hosts of zoonoses and potential hosts, increasing the potential for cross-species pathogen transmission and the subsequent expansion of a zoonoses' endemic range (**carlson__2022?**). This phenomenon has been observed in Hendra virus where a Southern range expansion of the black fruit bat host (*Pteropus alecto*) has resulted in domesticated horses in Australia being infected, with subsequent spillover events into human populations (**yuen__2021?**).

An additional mechanism through which zoonosis spillover risk is modulated is animal biodiversity. Several mechanisms for the association of animal biodiversity and zoonosis risk have been proposed. The "Dilution effect", initially developed using the Lyme disease (*Borrelia burgdorferi*) zoonosis system which comprises several vectors and animal hosts, proposes that in settings of low species diversity (measured as species richness) that infection rates increase in a specified host species, the inverse being that a greater amount of animal biodiversity reduces the rate of zoonosis spillover into human populations (**ostfeld__2000?**). This theory has been supported by investigations of a large number of zoonoses including parasites, bacteria, viruses and fungi (**keesing__2010?**; **civitello__2015?**). There is ongoing debate as to whether this is a general property of zoonosis systems as several studies have suggested the inverse, an "Amplification effect", where increasing biodiversity, particularly through introduction of a new host, or more competent host species can increase the rate of infection in hosts and potentially the risk of zoonosis spillover (**johnson__2012?**; **halliday__2017?**).

Climate, landuse 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__2020?**). A synthesis of the effect of landuse change on biodiversity across multiple scales and zoonosis systems found that species richness of host species of zoonosis increased but not non-host species across a landuse gradient of anthropogenic disturbance from undisturbed to urban landuse (**gibb__2020?**). These changes are also occurring at different rates globally. Climate, landuse and biodiversity change occurring in regions associated with a greater diversity of known zoonotic pathogens is likely to have a greater impact on the risk of zoonosis spillover than in settings of low diversity of zoonotic pathogens. Because of this, focussing studies in the tropics where

zoonotic pathogen diversity is predicted to be greatest may be beneficial for future research [ref].

1.3 Locations of zoonoses

The overwhelming majority of microorganisms are non-pathogenic and provide important ecosystem services. Pathogenic organisms are typically adapted to a single host species with a small subset of these being zoonoses. Zoonoses are globally distributed, found on all continents. Zoonoses comprise, bacteria, fungi, parasites and viruses. The global virome is estimated at X species with Y expected to be zoonoses. The distribution of known zoonoses is biased by global sampling effort. Expected diversity of zoonoses is greatest in the tropics i.e., South America, Africa and South East Asia.

West Africa is a nexus of for global change in addition to increasing human population. The impact of known and novel zoonoses in this region requires further understanding. + Rate of discovery
+ Surveillance bias
+ Reporting bias

Viruses are important zoonoses.
+ Mutation and diversity
+ Treatment options
+ Transmission potential
+ Health burden

1.4 Hosts of zoonoses

Zoonoses are observed in most animal orders. The orders with the highest number of known zoonoses are Chiroptera and Rodentia. Zoonoses from rodents are expected in West Africa.

Properties of these species support them being hosts of zoonoses. + Trait associations
+ Immunology
+ Host ranges
+ Biodiversity and dilution
+ Human-host interactions

Synanthropy among hosts of zoonoses leads to increased hazard of spillover. + Commensalism
+ Abundance
+ Known zoonoses

1.5 Lassa fever

1.5.1 *Lassa mammarenavirus* and Lassa fever

+ Describe virology and ecology
+ Strains
+ Epidemiology
+ Ecology
+ Viral lifecycle
+ Risk factors of human infection
+ Lassa fever pathology
+ Sequaelae of human infection

1.5.2 Lassa fever in Sierra Leone

+ Current risk
+ Prior research

1.5.3 Rodent hosts of *Lassa mammarenavirus*

+ Known reservoirs
+ Potential reservoirs

1.5.4 Heterogeneity of rodent occurrence and abundance

+ Effect of landuse on occurrence

1.5.5 Surveillance of endemic zoonotic infectious diseases

Currently detection of outbreaks of zoonotic infectious diseases relies primarily upon clinical case detection of infected humans rather than evidence of circulating transmission among wild or domestic animals. Few health systems utilise active surveillance systems with testing of animal populations, a notable exception is *West Nile virus* surveillance in birds and horses in Europe (Gossner *et al.*, 2017). Here, surveillance in an animal-human-vector approach informs public health agencies to increased risk of human infection from this vector borne disease. While in West Africa, detection of outbreaks of endemic zoonotic infectious diseases such as, Ebola, Lassa fever, Monkeypox and Leptospirosis occurs following identification of human cases (Figure 1.1). Surveillance among host species is limited to academic or programmatic research which has been used to identify regions at potentially greater risk for spillover events, this information is then used to

aid risk stratification of patients that present with symptoms consistent with these diseases, based on when in the year they present, the location from which they present and suspected risk behaviours (Leski *et al.*, 2015; Happi *et al.*, 2022). Fewer countries, with none in West Africa have surveillance systems that combine animal and human data (Wendt, Kreienbrock and Campe, 2015).

Human cases presenting to healthcare are classified as suspected, possible, probable or confirmed cases of the disease of interest. This classification occurs based on clinical symptoms, disease progression and known risk factors. Individuals presenting to healthcare may become suspected cases in the context of a known outbreak or failure of treatment for more common infections, such as malaria and bacterial infections [reference needed]. Once suspicion is raised for a potential zoonotic infectious disease as a cause of presentation, individuals may be tested for known pathogens according to local guidance, the availability of this testing varies by location. In Nigeria, the Nigerian Centre for Disease Control have rapidly expanded testing capacity for **Viral Haemorrhagic Fevers** including Lassa fever and Ebola, assays for these pathogens are less available in other regions within the endemic region with samples being transferred to national, regional or international reference laboratories (World Health Organisation, 2022 ; Yadouleton *et al.*, 2020).

Conversely the majority of pathogens of animal species do not cause clinical disease in humans. Surveillance of pathogens in animal populations occurs for multiple reasons including animal health and welfare, conservation and agriculture. The information gathered by sampling efforts in animals can inform

1.5.6 Predicting zoonotic spillover risk in a changing world

One purpose of surveillance in animal species is to inform risk prediction tools of outbreaks of known zoonotic infectious diseases and novel pathogen emergence. These tools aim to guide local public health responses through early warning systems or to effectively direct international investment towards pandemic prevention (Morse *et al.*, 2012; Carlson *et al.*, 2021). Descriptions of previously reported zoonotic spillover events adjusting for reporting biases and combined with known host-pathogen distributions can highlight regions at increased risk (Jones *et al.*, 2008; Han, Kramer and Drake, 2016). These models can also be used to identify host and pathogen species that require further investigations to understand pathogen prevalence. Bats (Chiroptera) and Rodents (Rodentia) are two taxa that contribute the greatest hazard of zoonotic spillover. These characteristics are driven by their widespread occurrence, encroachment of human activity within their natural habitats and species level traits that lead to high zoonotic pathogen burdens [references]. Pathogens that are predicted to spillover into human populations have more diverse pathogen characteristics and come from a wide range of viral, bacterial and fungal taxa. For this reason much of the prediction effort is focussed on the distribution of host species with pathogen prevalence assumed constant among much of a

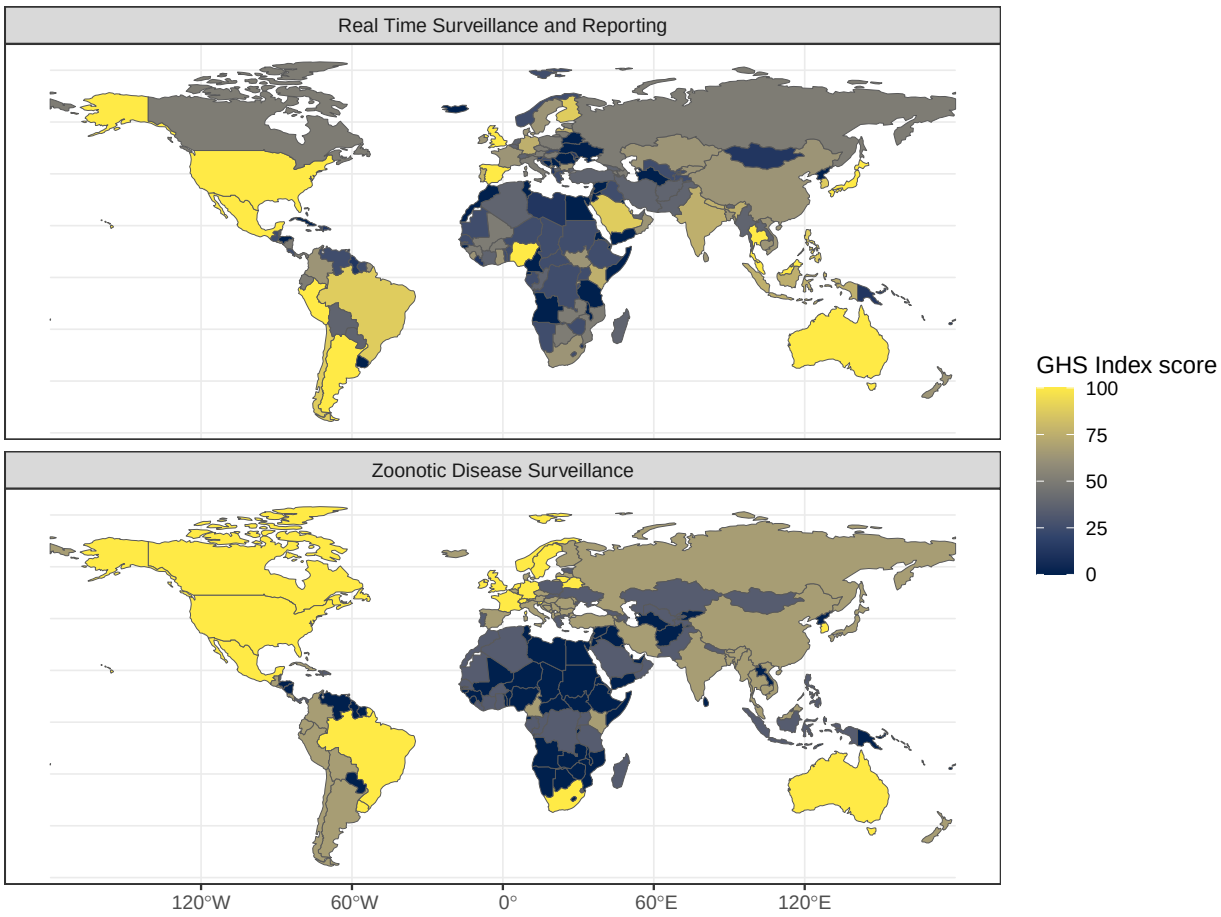

Figure 1.1: Global Health Security Index country scores for the sub-domains of (top) 2.3) Real-time surveillance and reporting and (bottom) 1.2.2) Surveillance systems for zoonotic diseases/pathogens. Real time surveillance and reporting for epidemics of potential international concern is rated highly in several North and South American countries and countries in East and South East Asia and Oceania. Zoonotic disease surveillance is rated highly in European, North and South American countries and Oceania. Generally surveillance for zoonotic infectious disease is limited across much of Africa.

species range. There are several important examples that show violation of these simplifying assumptions. These examples typically come from host species with large home ranges but it is likely that this assumption does not hold true for most host-pathogen systems. For example *Lassa mammarenavirus* infection among its primary rodent host species has only been observed in its westernmost range, similarly for *Nipah henipavirus* which is observed only in the northern range of its primary bat host species (Figure **??**).

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1.5.7 Rodent borne zoonotic infectious diseases

I have previously included examples that apply from multiple taxa of host species. For the remainder of this thesis I will focus on rodent borne zoonotic infectious diseases and will subsequently focus down on the case study of this thesis *Lassa mammarenavirus* in Sierra Leone.

The cause of this heterogeneity of pathogen prevalence and therefore spillover hazard within a hosts range is multifactorial. First, presence of additional microorganisms that are non-pathogenic to humans within a host species' range may provide cross immunity that prevent expansion of the zoonotic pathogen species into a wider area. Second, host species may be comprised of multiple clades which may have immunological differences which prevent efficient transmission of a pathogen adapted to one of the clades. Third, environmental suitability for the pathogen may vary across the host species range, this is of particular importance for pathogens that have environmental stages in the chain of transmission. Finally, presence of a pathogen in a host species may be dependent on the presence of other species or intermediate hosts for the pathogen that do not exist throughout the primary hosts range. Further, within a hosts range their occurrence and abundance may vary. For example in a species rich environment where a single host species conveys the hazard of spillover increased competition from conspecifics may reduce the host species' abundance in the landscape effectively "diluting" the hazard of spillover. Further, reduced biodiversity in a location may lead to non-host species not being present in a landscape, features of hosts that may contribute to their host status may also make them more resistant to factors that can drive local extinction and so these species are more likely to exist in species depauparate environments, increasing the hazard. Clearance of forest landscapes for monoculture agriculture may also lead to increased resources leading to increased populations of host species and increasing the scope for pathogen transmission among the species where previously this would not be sustained.

This heterogeneity will combine to modulate the hazard of zoonotic pathogen spillover from infected hosts into human populations. However, this is only a single layer of the risk of zoonotic pathogen spillover. The existence of the hazard in time and space alone will not necessarily lead to infection and disease in humans.

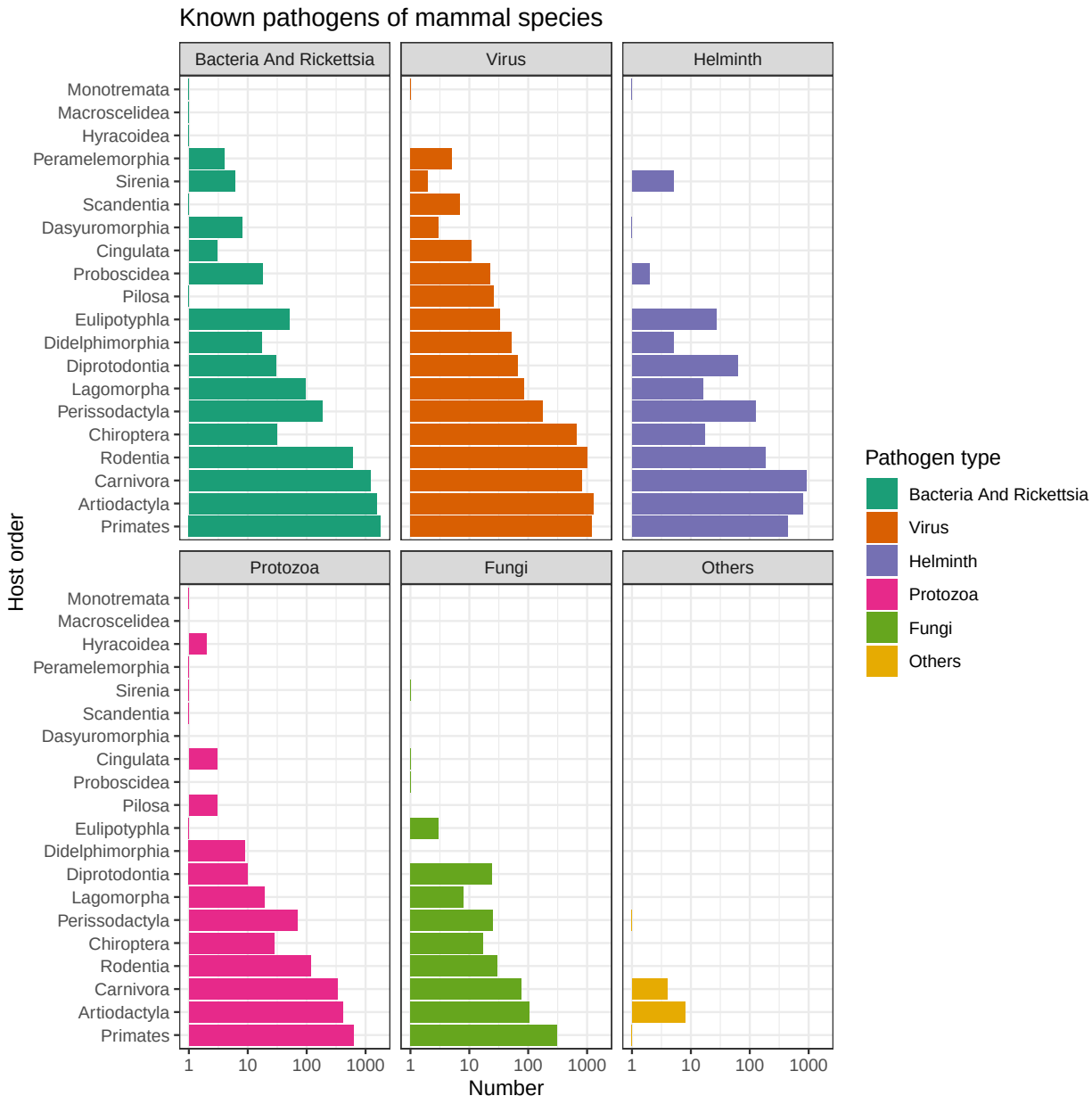

Figure 1.2: The sampling of the global host-pathogen system is incomplete, and sparse. A recent effort to combine available data sources shows highlights the better understanding of pathogens of several mammal taxa. Focussing on Rodentia we can also observe temporal biases to pathogen identification.

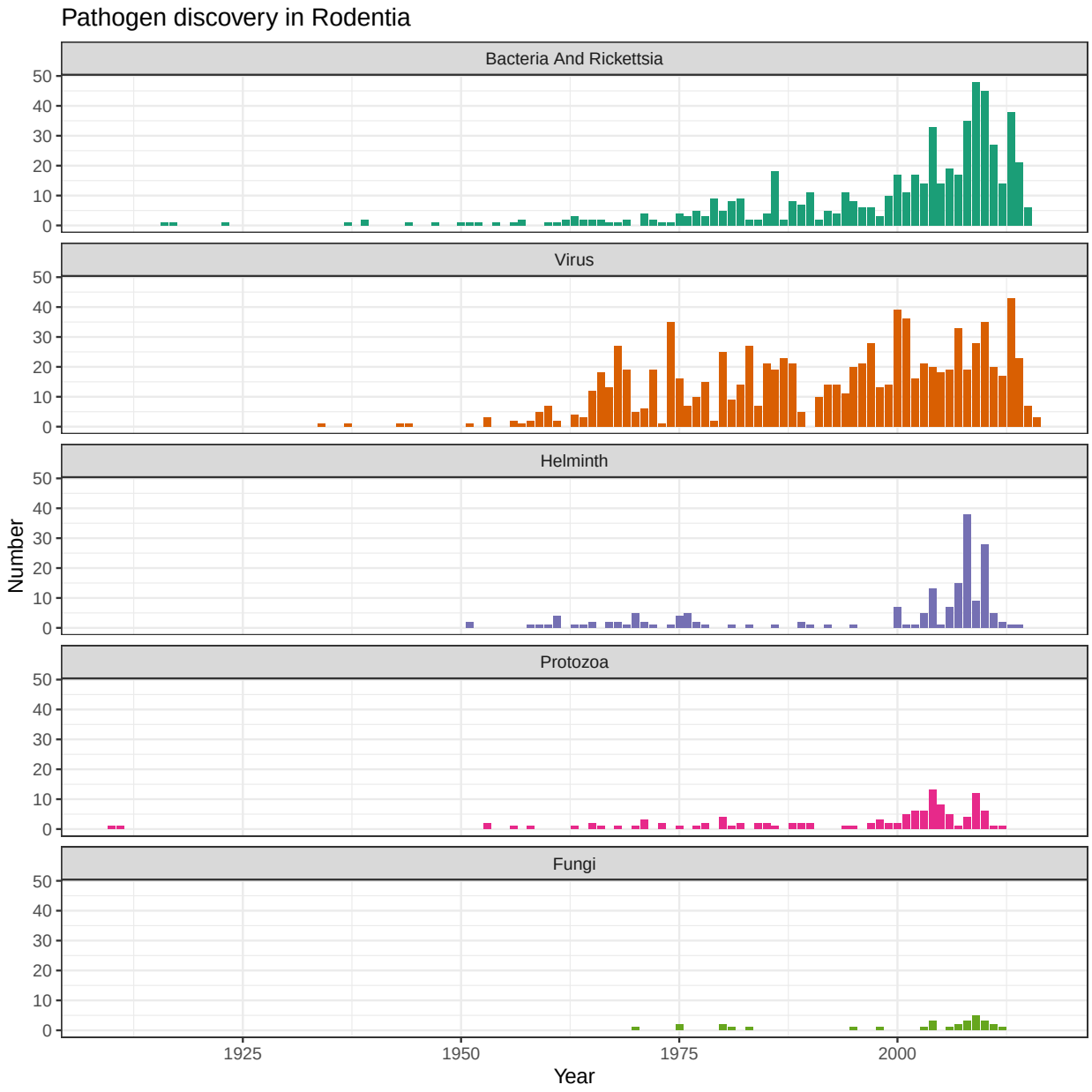

Figure 1.3: The sampling of the global host-pathogen system is incomplete, and sparse. A recent effort to combine available data sources shows highlights the better understanding of pathogens of several mammal taxa. Focussing on Rodentia we can also observe temporal biases to pathogen identification.

This additional level is termed the risk and overlays the baseline hazard. Several factors may increase or decrease the risk of spillover. Human activity such as hunting for food may increase the risk of contact with an infectious host. Human activity in locations within close spatio-temporal windows as infected hosts may increase the risk of infection (i.e. using the same water sources). These also bring in societal levels of risk due to food security, access to clean water etc. Land use change may lead to infectious hosts accessing areas of human habitation or food storage as resources become less accessible in non-disturbed regions. Construction of human buildings in areas of habitation of the host species may lead to the host nesting in human domiciles for shelter.

1.6 Aims of the thesis

The first aim of this thesis is to synthesise information on rodent and pathogen sampling from rodent trapping studies across West Africa to quantify the biases in currently available data. I hypothesise that rodent and pathogen sampling is spatially and taxonomically biased which will have implications on inference able to be drawn from currently available data about the hazard of zoonosis spillover risk across the region. I test the null hypothesis that rodent and pathogen sampling is conducted randomly in space across the region and propose an alternative hypothesis that rodent sampling is spatially clustered. I describe the occurrence of known and potential hosts of zoonosis from presence and absence data and compare this to currently available resources and produce host-pathogen associations from these data.

The second aim of this thesis is to investigate the association of rodent species diversity and landuse type in a Lassa fever endemic region of Eastern Sierra Leone. I hypothesise that known hosts of Lassa fever occur preferentially in human dominated landuse types with higher rodent species diversity in less disturbed landuse types. I test the null hypothesis that the probability of occurrence of rodent species does not change across landuse types and propose an alternative hypothesis that hosts of Lassa fever have a higher probability of occurrence in human dominated landuse types.

The final aim of this thesis is to recreate Lassa fever transmission networks among rodent species. Using rodent trapping data

1.7 Summary

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

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

2.6 Results

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

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

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

2.7 Discussion

2.8 Summary

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

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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

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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 Discussion chapter.

5.1 Contribution to understanding biases in currently available data

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

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