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

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1 Introduction

1.1 Zoonotic infectious diseases

Zoonotic infectious diseases are infections caused by pathogens that can cause clinical disease in humans that are directly or indirectly transmitted from animal hosts. A "zoonosis" is any disease or infection that is naturally transmissible from vertebrate animals or an animal reservoir to humans, either directly or indirectly [reference WHO https://www.who.int/news-room/fact-sheets/detail/zoonoses]. Direct transmission includes, bites and scratches (i.e., *Rabies lyssavirus* and *Bartonella hanselae*) while indirect transmission can occur through 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?**). Transmission events from vertebrate animal populations into human populations are termed spillover events, which can, under certain circumstances, lead to sustained outbreaks within human populations that can 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 by organ dysfunction, weight loss or behavioural change, while 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).

A zoonosis may display different 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 at frequent intervals but cause 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*) generally exhibit sustained human-to-human transmission following spillover from wild or domestic animals, but due to the transmission dynamics of these pathogens, outbreaks are typically constrained to local epidemics (Fine *et al.*, 1988; Legrand *et al.*, 2007). Finally, some pathogens may be better adapted to transmission among humans through 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 spillover event through 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) (Jones *et al.*, 2008).

While the 2022 mpox outbreak and ongoing SARS-CoV-2 pandemic are important examples of zoonoses causing epidemics and pandemics beyond their host species regions, these remain relatively rare events when compared to recurrent spillover events within endemic regions. For example, phylogenetic analysis of circulating mpox and SARS-CoV-2 lineages of human infections indicate a most common recent ancestor **X** years prior. 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. These patterns are supportive 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. This highlights the ongoing hazard of local spillover into human populations in endemic regions and reinforces the importance of ongoing surveillance of 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 usefule when considering how spillover of zoonoses occur in a setting of ongoing

climate, landuse and biodiversity change.

2. Why do we care?
   + History of infectious diseases
   + AIDS, Ebola, COVID-19
   + Global health equity
   + Globalisation and Biosecurity
3. Where do they happen?
   + Reporting of zoonotic infectious diseases
   + Unrecognised spillover
   + Combination of both hazard and risk
   + Socio-economic factors, a complex system
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   + Surveillance
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   + Rate of discovery
   + Surveillance bias
   + Reporting bias
   + Global change
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   + Immunology
   + Host ranges
   + Biodiversity and dilution
   + Human-host interactions
7. Why should we care about rodents?
   + Commensalism
   + Abundance
   + Known zoonoses

8. What do we know about the pathogens?
    + Bacteria inc. AMR
    + Parasites
    + Funghi
    + Viruses
9. Why do we care about viruses?
    + Mutation and diversity
    + Treatment options
    + Transmission potential
    + Health burden
10. What is Lassa fever?
    + Describe virology and ecology
    + Strains
11. What do we know?
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    + Ecology
    + Viral lifecycle
    + Risk factors of human infection + Lassa fever pathology + Sequaelae of human infection
12. What don't we know?
    + Current risk
    + Effective prevention and vaccines
    + Effective treatment
    + Range expansion

1.1.1 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

1.1.2 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].

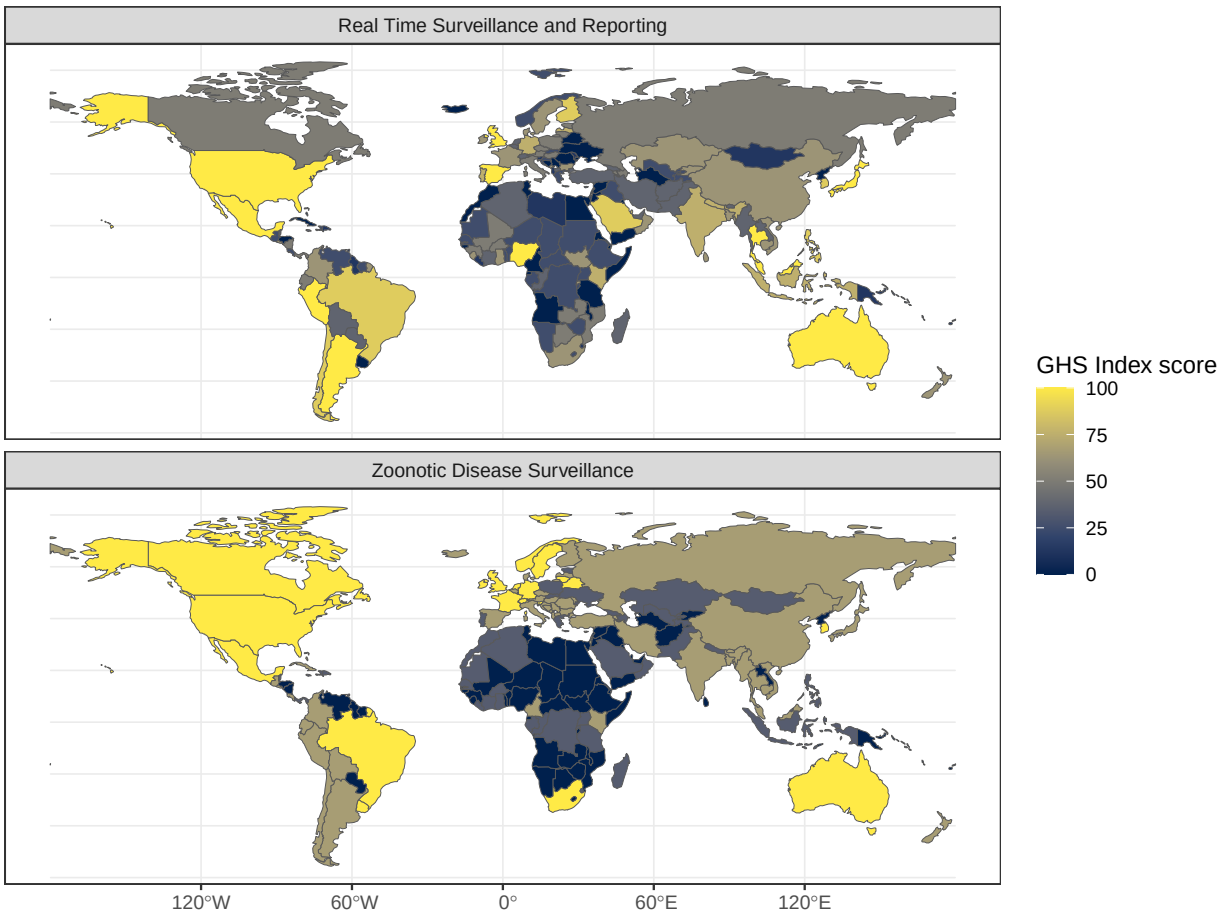

Figure 1.1: Global Health Security Index country scores for the sub-domains of (top) 2.3) Real-time surveillance and reporting and (bottom) 1.2.2) Surveillance systems for zoonotic diseases/pathogens. Real time surveillance and reporting for epidemics of potential international concern is rated highly 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.

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 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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1.1.3 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.

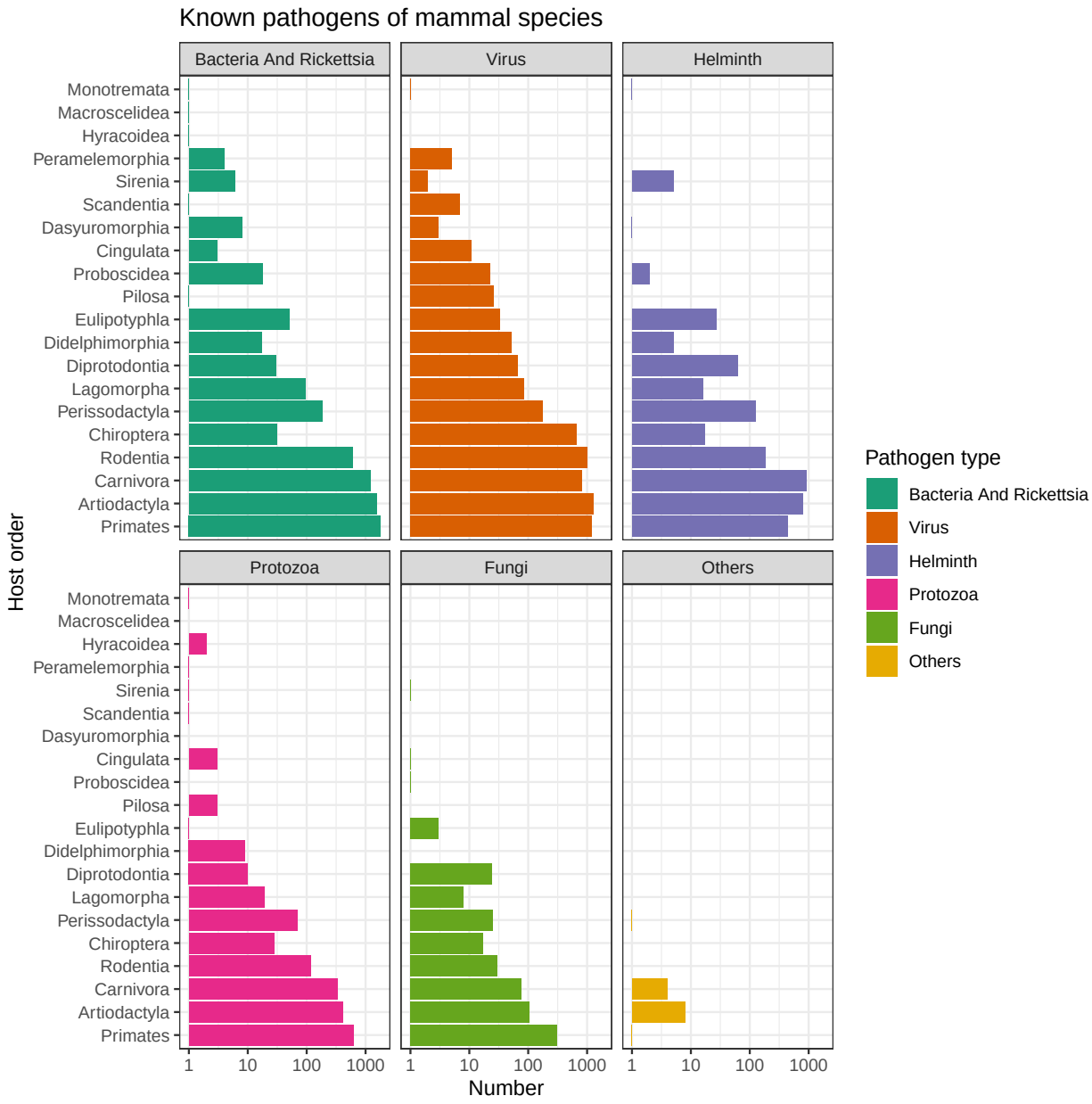

Figure 1.2: The sampling of the global host-pathogen system is incomplete, and sparse. A recent effort to combine available data sources shows highlights the better understanding of pathogens of several mammal taxa. Focussing on Rodentia we can also observe temporal biases to pathogen identification.

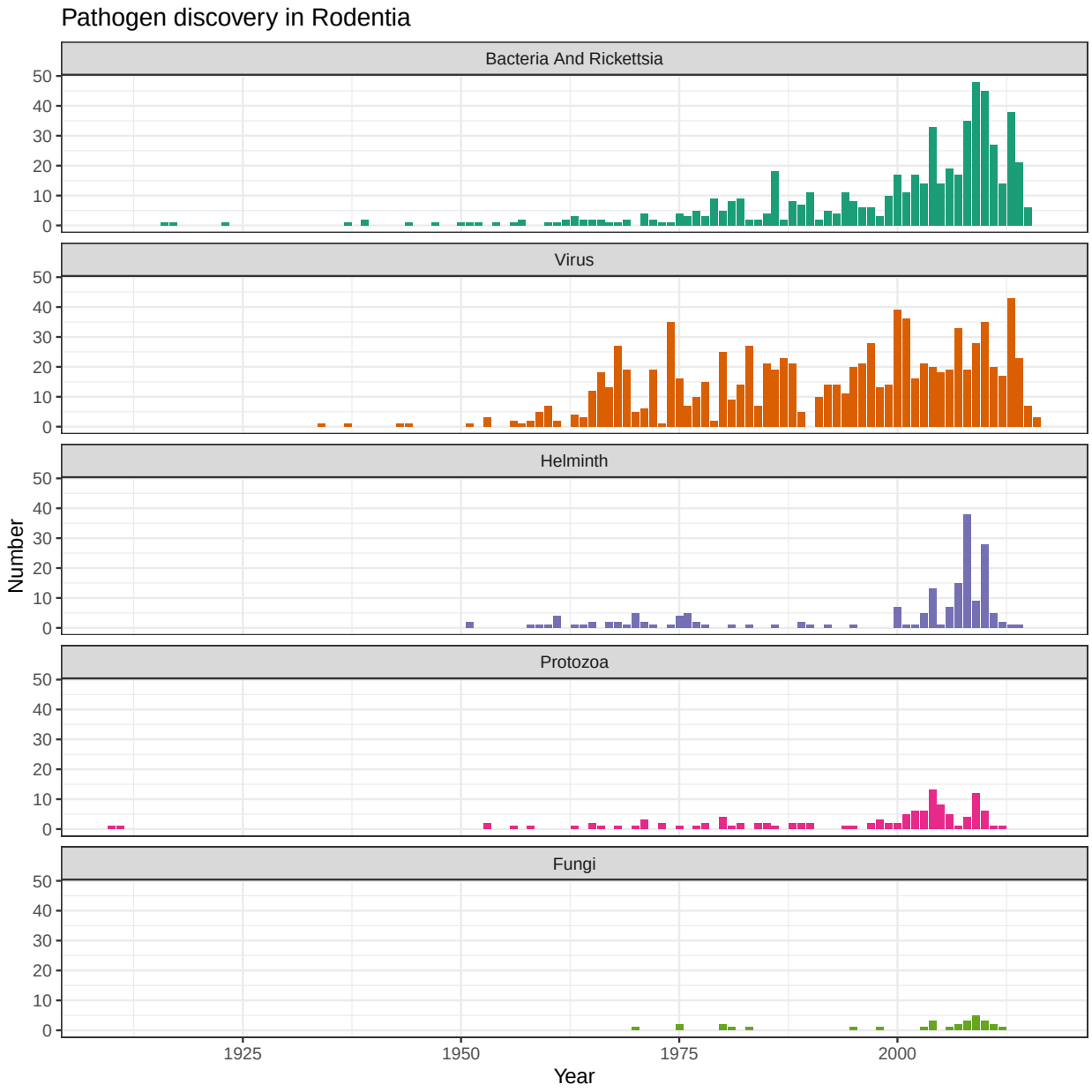

Figure 1.3: The sampling of the global host-pathogen system is incomplete, and sparse. A recent effort to combine available data sources shows highlights the better understanding of pathogens of several mammal taxa. Focussing on Rodentia we can also observe temporal biases to pathogen identification.

This 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. 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.

1.1.4 Sampling rodent hosts

Figure of rodent zoonotic pathogens from CLOVER dataset

1.2 *Lassa mammarenavirus* and Lassa fever

1.2.1 *Lassa mammarenvirus* epidemiology

1.2.2 Lassa fever epidemiology

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1.5.2 Objectives

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2.4.2 Host and pathogen trapping data

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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.

Placeholder

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

5 Model chapter.

6 Discussion chapter.

6.1 Contribution to understanding biases in currently available data

6.2 Integrating species assemblages into the hazard of zoonotic pathogen spillover

6.3 Understanding the epidemiology and risk of Lassa Fever

6.4 Future directions

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