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

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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

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.

Finally I use the data produced in Chapters 3 and 4 to model the hazard of zoonotic spillover in Eastern Sierra Leone. I adopt a BART to produce a multi-species distribution model to predict the occupancy of different species across the region and information on antibody prevalence to model the occurrence of the pathogen of interest.

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:** This chapter consolidates data from the two previous chapters to produce a hazard map of *Lassa mammarenavirus* spillover in Eastern Sierra Leone.
- **Chapter 6:** 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 that are directly or indirectly transmitted from animal **hosts**. Transmission events from animal populations into human populations are termed **spillover events**, these can lead to sustained **outbreaks** within human populations that can progress to localised **epidemics** or global **pandemics**. These pathogenic organisms may, or may not, cause clinical disease in their animal hosts. For example, *Lassa mammarenavirus*, 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 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 in addition to in

infected 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 distinction exists between zoonotic infectious diseases that regularly spillover into human populations from wild or domestic animals, with limited onward human-to-human transmission (i.e., Nipah and Lassa Fever), those that exhibit limited but sustained human-to-human transmission (i.e., Ebola and Monkeypox) and finally those that become adapted to human hosts and become infectious diseases of zoonotic origin (i.e., HIV and SARS-CoV-2) (Fine *et al.*, 1988; Legrand *et al.*, 2007; Jones *et al.*, 2008; Luby *et al.*, 2009; Lo Iacono *et al.*, 2015). Among the infectious diseases with limited human-to-human transmission (less than 10% of human cases lead to another infected human), there is an important caveat that there is evidence of important contribution of super-spreading events, where some infected humans lead to a disproportionally high number of secondary human cases (Lo Iacono *et al.*, 2015).

These different classes of zoonotic infectious disease often become conflated, in this thesis I will focus on zoonotic infectious diseases and not infectious diseases of zoonotic origin. Zoonotic infectious diseases with limited human-to-human transmission following spillover from animal hosts typically remain geographically constrained to their endemic region, defined by host animal ranges, pathogen extent or both. A recent exception to this has been the 2022 international Monkeypox pandemic. Monkeypox, caused by the *Monkeypox virus*, is endemic to Central and West Africa, with regular spillover events into human populations. These events can lead to large outbreaks in this region, for example in Nigeria in 2017 and multiple outbreaks in the Democratic Republic of Congo since 2000 (Ogoina *et al.*, 2019; Titanji *et al.*, 2022). In early 2022 a number of cases were detected globally in individuals with history of recent travel, cases were disproportionately identified in a community of gay, bisexual and other men who have sex with men, the maintenance of transmission chains in this community was found to be as a result of network structures of these communities (Vivancos *et al.*, 2022; Endo *et al.*, 2022).

While the global Monkeypox outbreak and ongoing SARS-CoV-2 pandemic are important examples of zoonotic infectious diseases causing epidemics outside of their endemic regions these are relatively rare events to spillover events within the endemic regions [need references to support or dispute this]. These episodes act to highlight the ongoing hazard of spillover and reinforce the importance of ongoing surveillance of zoonoses in endemic zones.

1.1.1 Surveillance of endemic zoonotic infectious diseases

Detection of outbreaks of zoonotic infectious diseases relies primarily upon clinical case detection of infected humans rather than evidence of infection 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. In West Africa, detection of outbreaks of 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 which can aid in risk stratification of patients that present with symptoms consistent with these diseases [references, such as Happi 2022, Leski 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, the availability of these assays is less in other countries within the endemic region.

1.1.2 Predicting changing zoonotic spillover risk

One purpose of surveillance in animal species is to inform risk prediction models of outbreaks of known zoonotic infectious diseases and novel pathogens.

1.1.3 Rodent borne zoonotic infectious diseases

1.1.4 Sampling rodent hosts

The remainder of this thesis will focus on the West African region and more specifically on Lassa Fever as a case study [?too early to focus down].

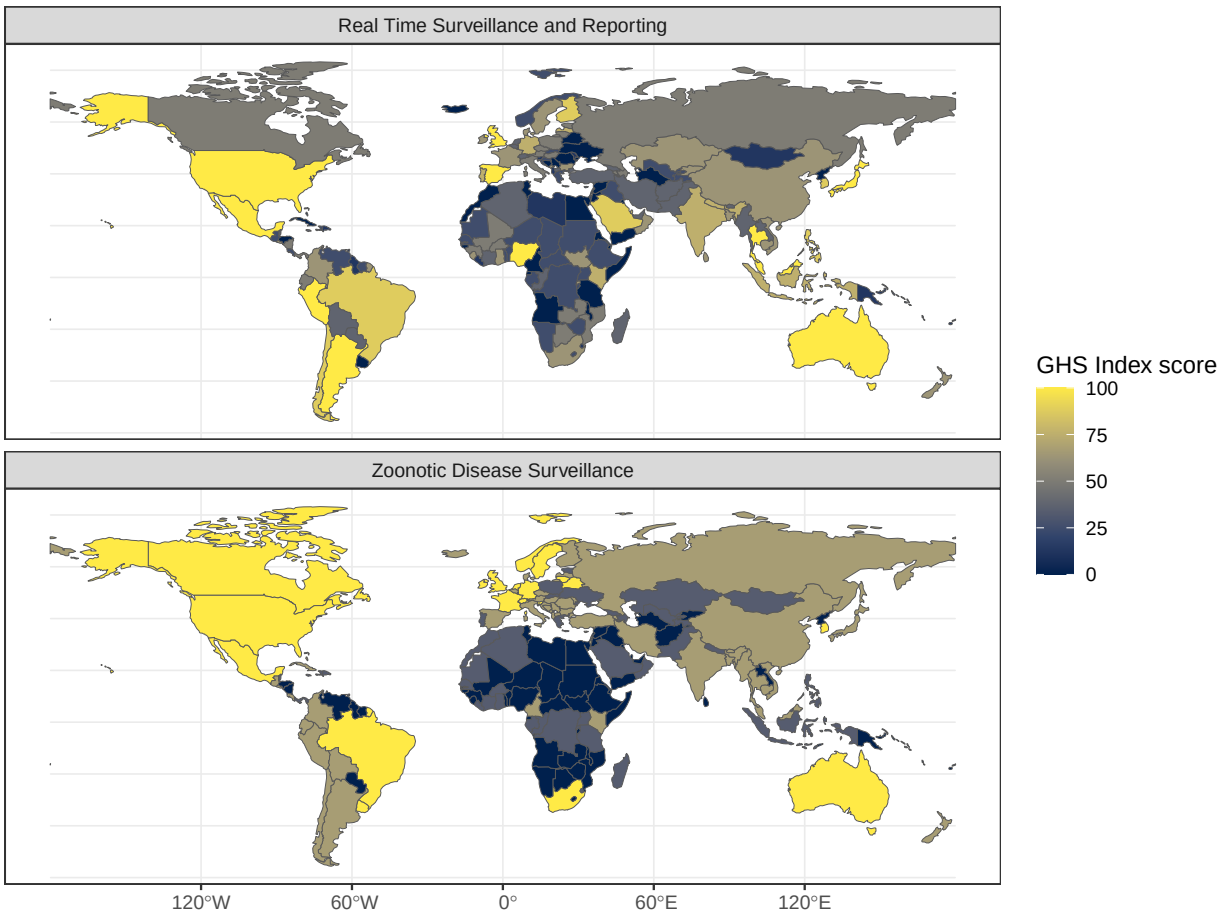

Figure 1.1: Global Health Security Index country scores for the sub-domains of (top) 2.3) Real-time surveillance and reporting and (bottom) 1.2.2) Surveillance systems for zoonotic diseases/pathogens. Real time surveillance and reporting for epidemics of potential international concern is rated highly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

1.2 *Lassa mammarenavirus* and Lassa Fever

1.2.1 *Lassa mammarenvirus* epidemiology

1.2.2 Lassa Fever epidemiology

1.2.3 Lassa Fever treatment

1.2.4 Lassa Fever in Sierra Leone

1.3 Rodent hosts of *Lassa mammarenavirus*

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1.3.2 Heterogeneity of rodent abundance

1.4 Systems approaches to endemic zoonoses

1.5 Aims and objectives of the thesis

1.5.1 Aim

1.5.2 Objectives

1.6 Summary

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

2.1 Preamble

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2.3 Introduction

2.4 Methods

2.4.1 Data sources

2.4.2 Host and pathogen trapping data

2.5 Analysis

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

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.

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 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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