# Introduction

## Zoonotic infectious diseases

Zoonotic infectious diseases are diseases of humans caused by pathogens transmitted either directly (e.g., bites and scratches) or indirectly (e.g., via vectors, environmental or food contamination) from animal hosts. Specifically, a “zoonoses” is any disease or infection that is shared between animals - including livestock, wildlife, and pets - and people, either through direct or indirect pathways (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. 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). Zoonotic pathogens do not always cause clinical disease in their animal hosts, for example, *Lassa mammarenavirus* (LASV), the causative agent of Lassa fever in humans is not thought to cause significant clinical disease in rodent host species’ as measured through organ dysfunction, weight loss or behavioural change (Safronetz et al. 2022). Meanwhile, in humans LASV infection can lead to severe clinical symptoms and death (change reference) (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 (Haider et al. 2017; Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus 2008).

Zoonoses display a range of patterns of spillover from wild or domestic animals and transmission in human populations. 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). Ebola virus disease (*Sudan ebolavirus* and *Zaire ebolavirus*) and mpox (formerly Monkeypox caused by the *Mpox virus*) in contrast exhibit sustained human-to-human transmission following spillover, but due to the transmission dynamics of these pathogens, outbreaks are generally constrained to local epidemics (Legrand et al. 2007; Fine et al. 1988). Finally, some pathogens may be better adapted, to transmission among humans due to their pathogen properties or similarities between human physiology or immunology and their primary vertebrate reservoir. These 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) (Ye et al. 2020; Marx, Apetrei, and Drucker 2004). Spillover may not be be limited to a single direction of animal to human transmission and “spillback” can play potentially important roles in maintaining pathogen endemicity with subsequent “secondary spillover” into human populations alternatively spillback can lead to morbidity and mortality in animal populations (Fagre et al. 2022).

These different patterns of spillover are observable through phylogenetic analysis of viral sequences from human populations. 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 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 transmission among local human populations (Isidro et al. 2022). wherein contrast phylogenetic analysis of LASV sequences indicate the most common recent ancestor of viruses circulating in Nigeria is >1000 years prior, while sequences from Guinea and Sierra Leone suggest a more recent introduction of 220 and 150 years respectively (Andersen et al. 2015). These findings are consistent with repeated spillover events into human populations from pathogens circulating within a single or multiple reservoir species. 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 (Dudas et al. 2018; Lloyd-Smith et al. 2009). The example of LASV highlights the present 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 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.” (“One Health CDC” 2022). This framework is particularly useful when considering how spillover of zoonoses occur in a context of ongoing climate, landuse and biodiversity change.

## Global change and zoonoses

Anthropogenic climate change is hypothesised to modify the risk of zoonoses to human populations through several mechanisms (B. A. Jones et al. 2013; Daszak, Cunningham, and Hyatt 2001). 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). Environmentally transmitted zoonoses such as Leptospira will 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 (Farooq et al. 2022; Hoover and Barker 2016).

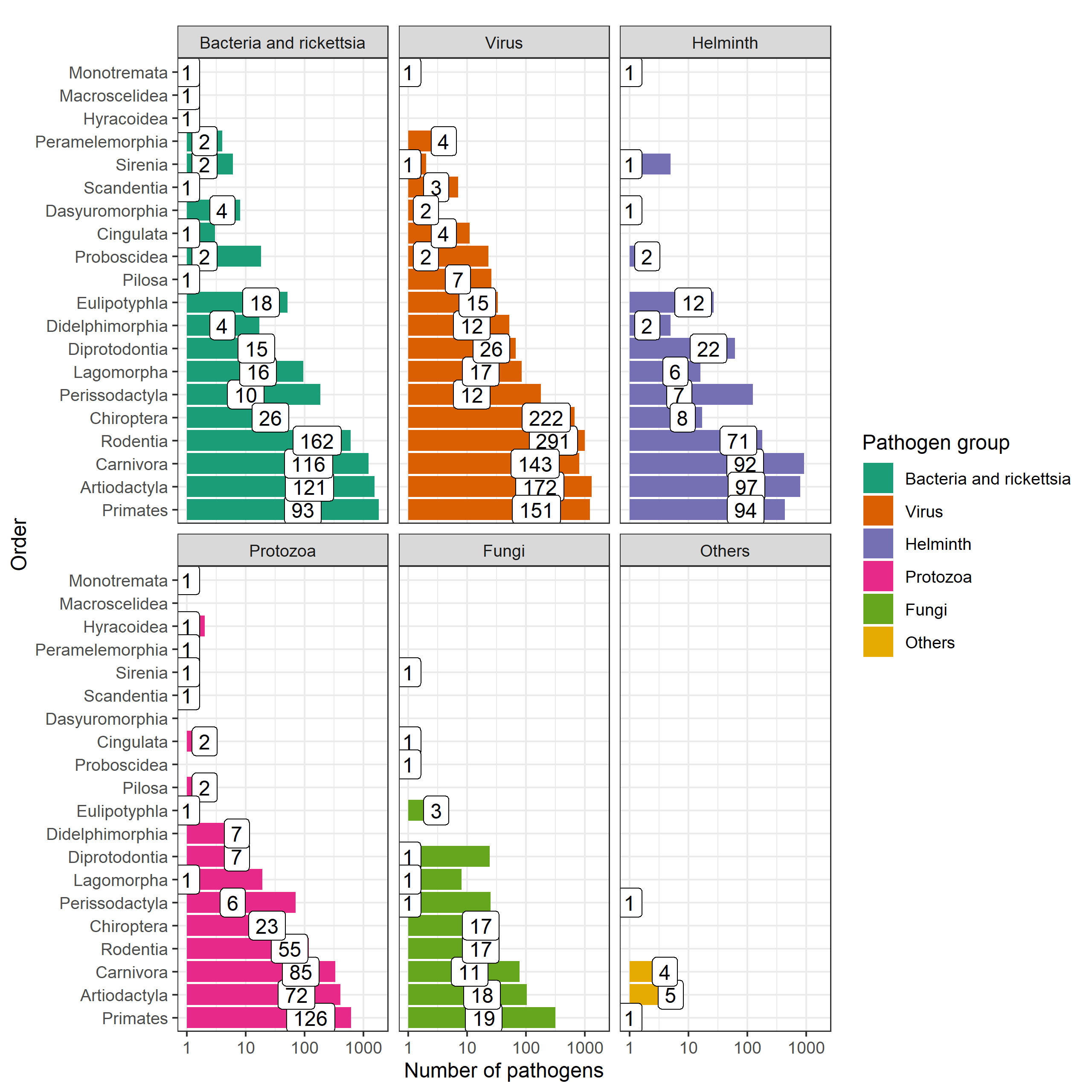
Climate change is occurring in step with anthropogenic landuse change. Human driven conversion of natural landscapes towards human dominated use occurs at both a local and global scale through direct and indirect human actions (i.e., agricultural development, natural resource extraction, and urbanisation) (Gottdenker et al. 2014). The association of landuse 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 landuse change, has been hypothesised to 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 and Daszak 2013). Additionally, heightened interactions between wildlife and domesticated animals 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) (Plowright et al. 2015; Epstein et al. 2006). In tandem climate and landuse change also modify species’ home ranges. As a consequence, contact events between current hosts of zoonoses and potential future hosts of a pathogen are produced, increasing the potential for cross-species pathogen transmission and the subsequent expansion of a zoonoses’ endemic range (Carlson et al. 2022). This has been observed in 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 also modulates zoonosis spillover risk, with several mechanisms proposed. The “Dilution effect” - initially applied to the Lyme disease (*Borrelia burgdorferi sensu lato*) system which comprises several vectors and animal hosts - hypothesises that in settings of low species diversity (measured as species richness) infection rates increase in a host species, the inverse being that higher levels of animal biodiversity reduces 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 this is a general property of zoonosis systems, as several studies have suggested the inverse. This mechanism, termed the “Amplification effect” occurs when increasing biodiversity, particularly through introduction of a new host, or a 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, 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, Franklinos, et al. 2020). A synthesis of the effect of landuse change on biodiversity across multiple scales and zoonosis systems observed that species richness of zoonotic pathogen host species increased but not non-host species, along an anthropogenic landuse gradient (Gibb, Redding, et al. 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 may potentially have a greater impact on the risk of zoonosis spillover than in settings of low diversity of zoonotic pathogens.

## Zoonoses discovery

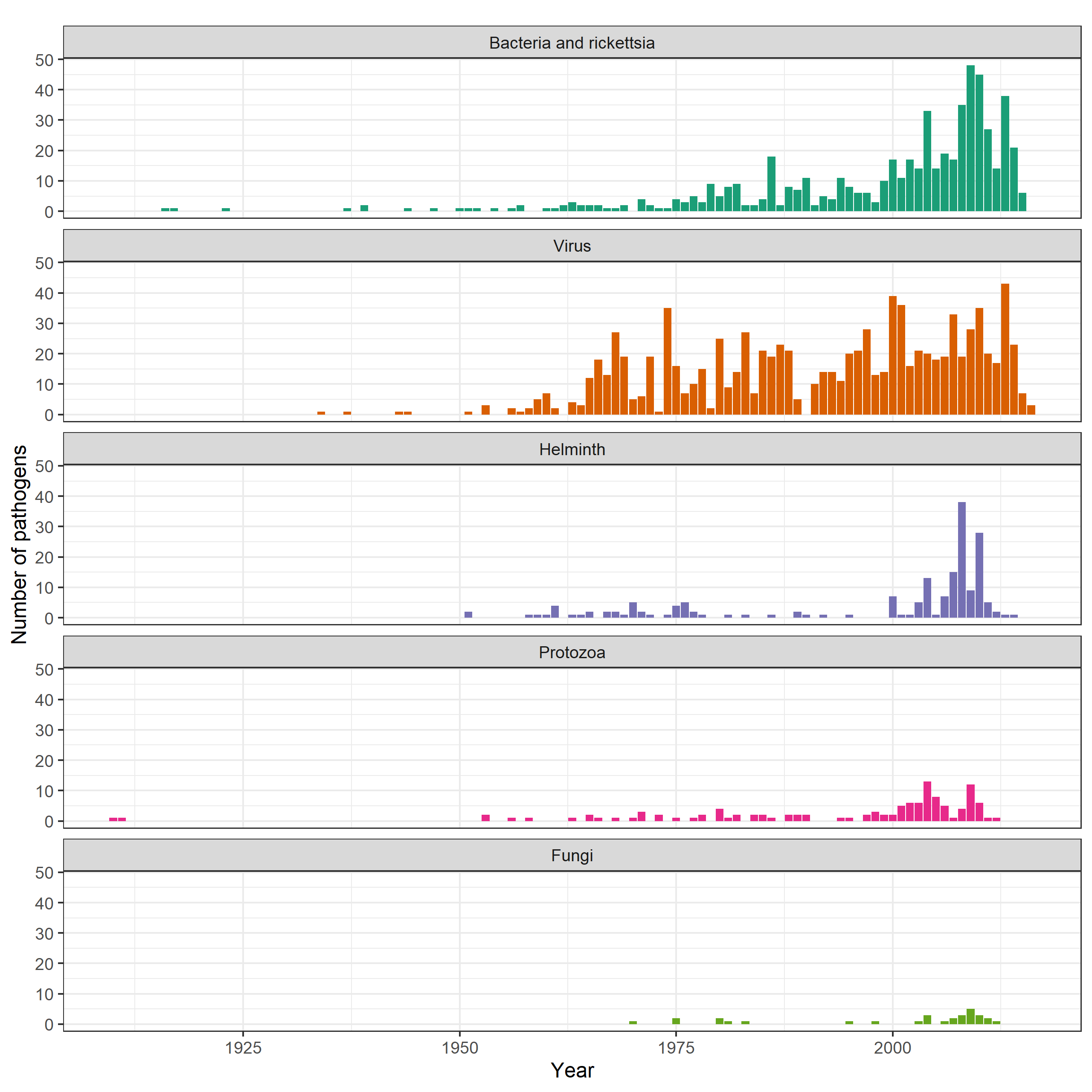
The majority of microorganisms are non-pathogenic to humans or animals and provide vital ecosystem services andthe small subset of microorganisms (<1%) that are pathogenic are typically able to replicate in multiple hosts (Editors 2011; Cleaveland, Laurenson, and Taylor 2001; Mark E. J. Woolhouse, Taylor, and Haydon 2001). For example, 60% of emerging human infectious diseases are associated with known zoonoses, a human infectious disease being a zoonoses is therefore not rare (K. E. Jones et al. 2008). Discovery of these zoonoses is variable across mammalian taxa, with sampling effort increased in orders with increased human interaction, i.e., primates and livestock species. A recently compiled dataset (CLOVER), contains an increased number of described pathogens in Primates, Artiodactyla (ungulates) and Carnivora alongside Rodentia and Chiroptera (Gibb, Albery, Becker, et al. 2021; Gibb, Carlson, and Farrell 2021). @ref(fig:host-pathogen-associations) shows the number of known pathogens in these mammalian orders. Of these, Rodentia contain the greatest number of pathogens known to be zoonotic (85) (Han, Kramer, and Drake 2016).



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.

The discovery of zoonoses are biased by both our ability to detect them and the sampling effort of animal species for pathogens (Grange et al. 2021; Gibb, Albery, Mollentze, et al. 2021). The discovery rate of viral zoonoses, an important subset of all zoonoses, has increased with improvements in the technical means to identify them (Mark E. J. Woolhouse et al. 2008). The rate of discovery has exceeded prior expectations of viral biodiversity, but, continues to remain taxonomically and geographically biased, limiting inference able to be drawn from current datasources (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 @ref(fig:rodent-pathogen-discovery).

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Discovery of pathogens in Rodentia, the order containing the greatest number of zoonotic pathogens, has increased over time. Data obtained from CLOVER.

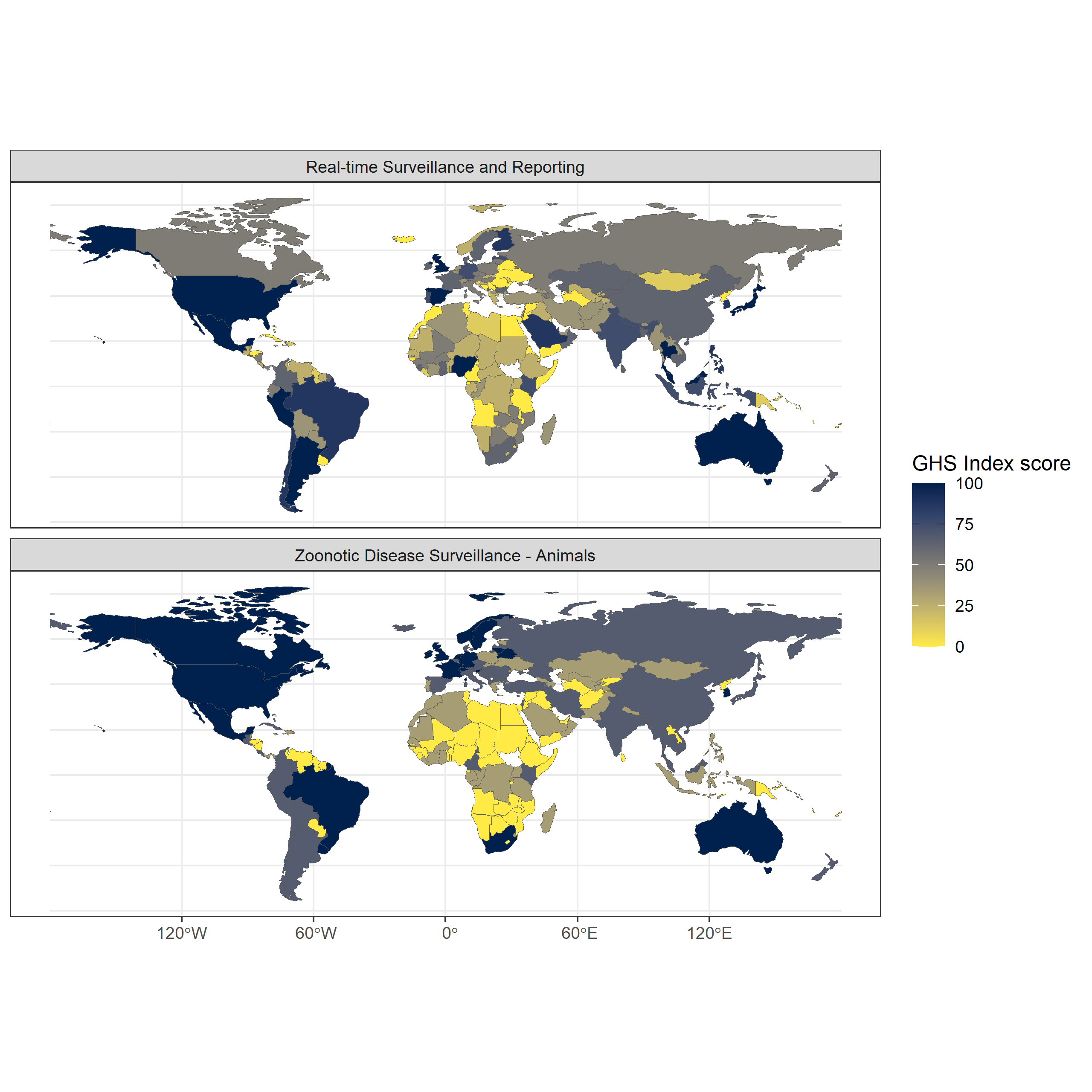
Zoonoses are known to exist in the majority of terrestrial mammal orders (21/27) with the number of hosts of zoonotic pathogens strongly positively associated with the species richness of these orders (Han, Kramer, and Drake 2016). Two mammalian taxa,Rodentia and Chiroptera, are associated with the greatest 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,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 (Olival et al. 2012; Wolfe, Dunavan, and Diamond 2007; Luis et al. 2013; Mollentze and Streicker 2020). Geographic hotspots of zoonotic disease risk are therefore predicted to occur where mammalian host species richness is greatest, e.g., 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 (Haggblade, Diarra, and Traoré 2022; Maconachie 2012; Walther 2021; Nicholson, Tucker, and Ba 1998; Bongaarts 2009). It has also been the location of several recent zoonosis epidemics and outbreaks, for example, the 2014 Ebola epidemic and ongoing Lassa fever outbreaks.

## West Africa as a hotspot of zoonosis risk

While the number of zoonotic infectious disease outbreaks and, human morbidity and mortality associated with them, has been observed to rise in West Africa this must be viewed in the local context of anthropogenic change described above, particularly as the number of people at risk of infection continues to increase (Makoni 2020). Alongside these global changes, pathogen discovery, improved access to diagnostics, increasing healthcare access and improved reporting will together result in an apparent increase in the burden of zoonotic infectious diseases in the region. An example of intensifying pathogen discovery is the PREDICT programme, conducted between 2009 and 2020, it 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 including the detection of Marburg virus for the first time in Sierra Leone, West Africa (“About PREDICT. School of Veterinary Medicine” 2019; Amman et al. 2020). Projects such as this can importantly change our understanding of the 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) have expanded the availability of testing for this disease. Prior to 2005 molecular diagnosis of Lassa fever infection was not possible in the country 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, any trends in the number of reported cases of this disease from Nigeria need to be considered in light of this (Dalhat et al. 2022).

Current detection of zoonotic infectious disease outbreaks generally rely 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 systems have implemented active surveillance systems through testing of animal populations in West Africa. Elsewhere, for example 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 an emerging outbreak of a zoonotic infectious disease (Global Health Security Index 2022). Figure @ref(fig:global-zoonotic-disease-surveillance) shows results from two components of this assessment, highlighting that few African countries have widely implemented real-time surveillance or zoonotic disease surveillance in animals. Real-time surveillance is rated as poor, 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 diseases 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).



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.

## Rodent borne 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 (D’Elía, Fabre, and Lessa 2019; Ecke et al. 2022; Han, Kramer, and Drake 2016). 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).

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 may 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 (Morand et al. 2019; Iacono et al. 2016).

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 (Fichet-Calvet et al. 2008; Leirs et al. 1997). This may impact the generalisability of studies conducted in within a rodents range when attempting to understand the risk of rodent borne zoonosis spillover.

## 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 particular risk of emergence and outbreaks in West Africa and the role of rodents in zoonotic infectious disease transmission. The remainder of this introduction will focus on the case study of this thesis, Lassa fever, in West Africa and more specifically Sierra Leone.

### *Lassa mammarenavirus* and Lassa fever

*Lassa mammarenavirus* an enveloped, bisegmented, single stranded RNA virus of the Arenaviridae family 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 infection is caused by spillover of the virus from infected rodents and their excreta, with a limited role of human-to-human secondary transmission (J. B. 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 this virus (Grobbelaar et al. 2021; Bellocq et al. 2020; Colangelo et al. 2013).

*Lassa mammarenavirus* has four confirmed lineages (I-IV) and three additional lineages (V-VII) based on geographic and phylogenetic analysis (Y. 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 Ivory Coast and lineage VII contains recently sampled sequences from Togo (Ehichioya et al. 2019; Andersen et al. 2015; Manning, Forrester, and Paessler 2015; Whitmer et al. 2018). 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 (Ehichioya et al. 2019; Andersen et al. 2015). 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.

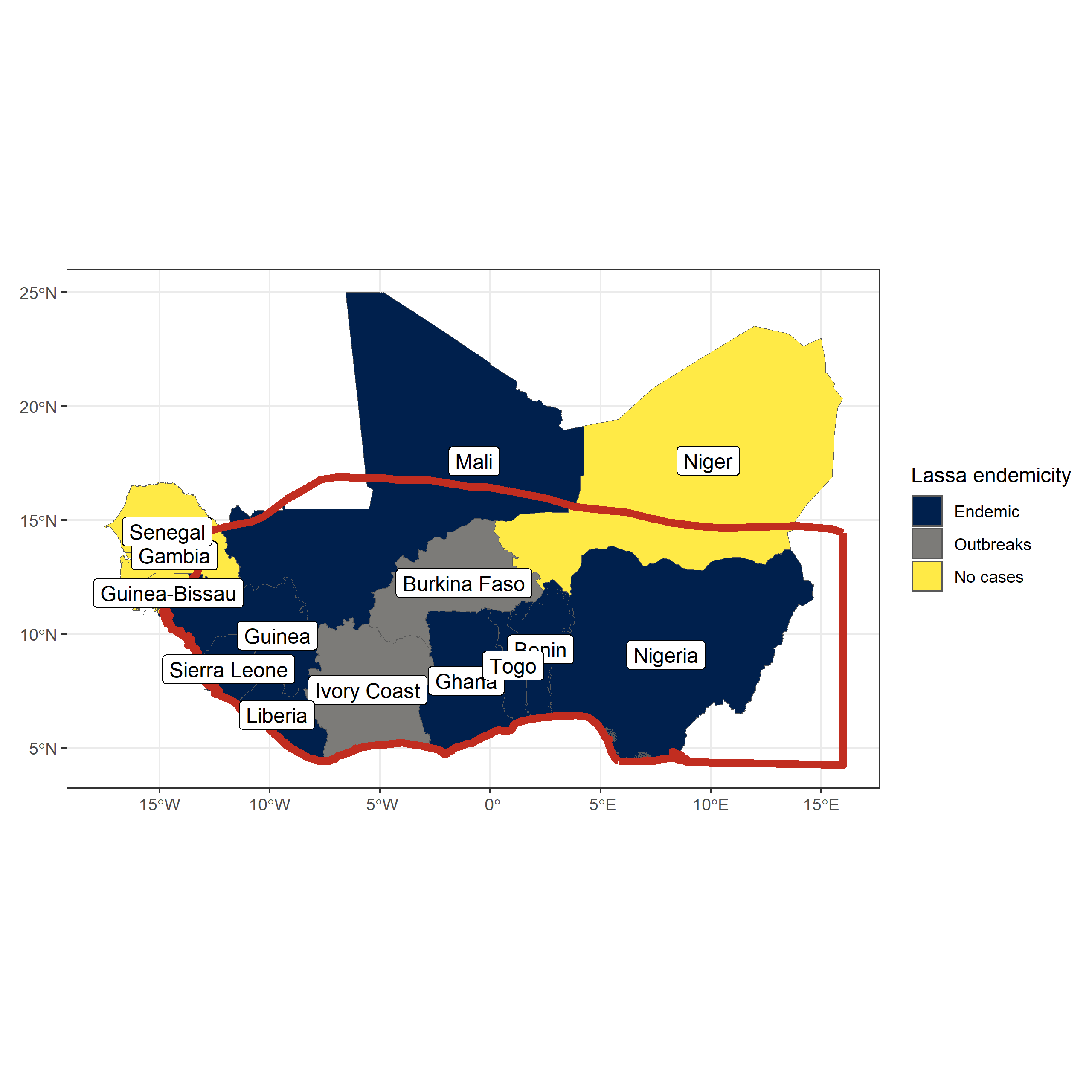
Among infected humans, with clinical symptoms, the viral incubation period is between 7 and 18 days (J. B. McCormick et al. 1987). Initial symptoms are non-specific with fever, weakness, malaise, cough, sore throat and a typically frontal headache (Knobloch et al. 1980). The majority of symptomatic patients 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 (J. B. 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 syndome 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 (J. B. 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 questionnable (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 2022, 2020; International AIDS Vaccine Initiative 2023; Themis Bioscience GmbH 2022).

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. I conducted a review 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, producing an estimated case-fatality rate of 16.5% (+/- 5%) among confirmed cases (Simons 2022). 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, 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, the majority of mildly symptomatic cases will have a dramatically reduced probability of mortality and will lower the case-fatality rate.

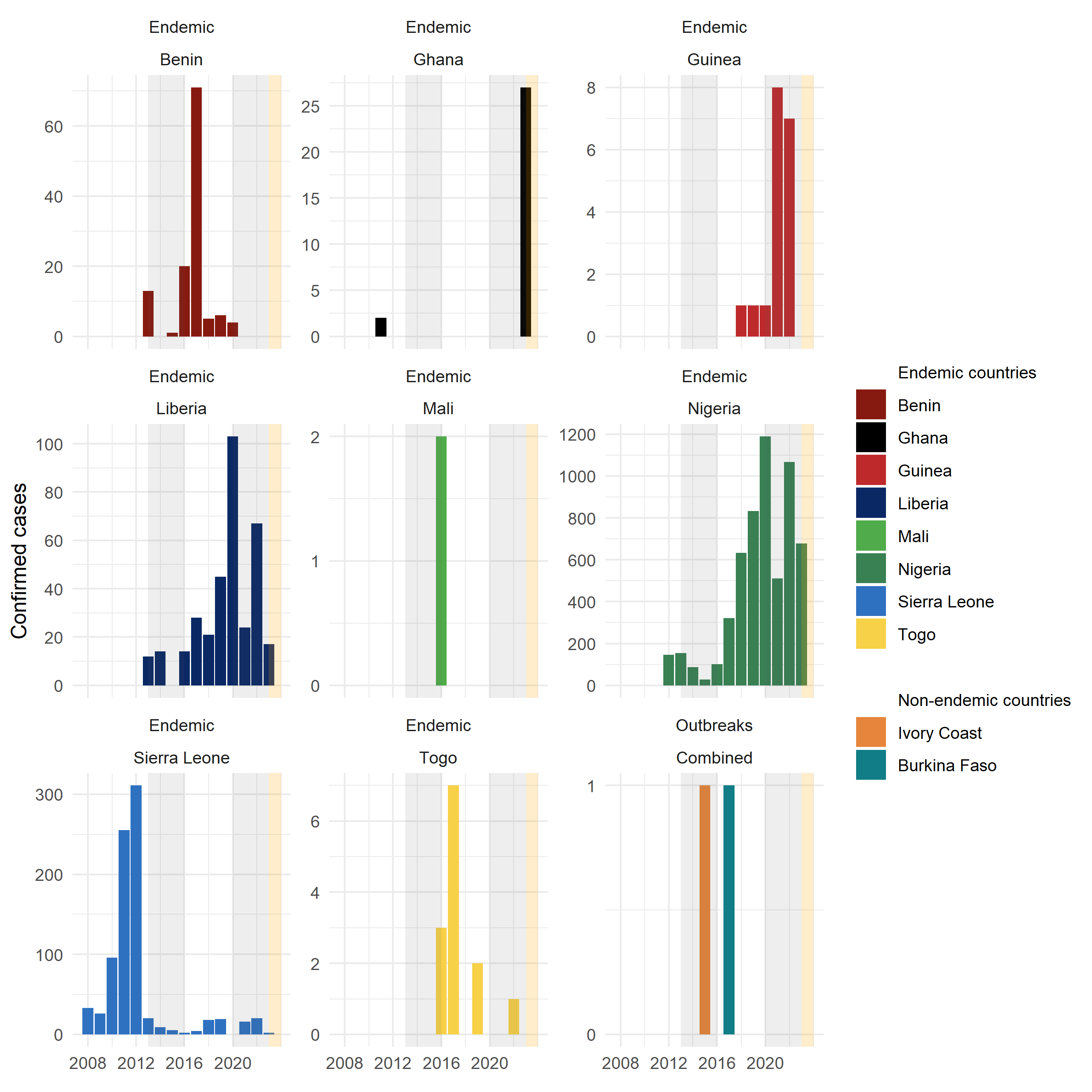
Survivors of symptomatic Lassa fever may have lasting effects of the disease. Sensorineural hearing loss is reported to occur in up to a third of Lassa fever survivors and potentially causes significant social and public health burden in the region that have not been well studied (Mateer et al. 2018). 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 (A. L. Li et al. 2020; Ezeomah et al. 2019). Most hospitalised patients, following recovery, rapidly clear viral RNA. Most patient sera is 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 in this cohort (Thielebein et al. 2022).

### Lassa fever epidemiology

Annual Lassa fever incidence is unknown, with estimates ranging between 150,000 to 4,300,000 cases per year cases annually (J. B. 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) (World Health Organisation 2022). Sporadic cases in Burkina Faso and Ivory Coast have also been reported (@ref(fig:lassa-endemic)). The endemic region is consistent with the expected 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).

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, it’s 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.

Nigeria and Sierra Leone have historically reported the greatest number of Lassa fever cases (@ref(fig:lassa-cases)). Potentially this is driven by increased availability of testing for acute cases in these countries. Human seroepidemiological surveys in Guinea, Mali and Ivory Coast, countries that have generally reported few acute cases, report seroprevalence in excess of 20% suggestive of undetected localised transmission of Lassa fever (Kerneis et al. 2009; Bausch et al. 2001; Sogoba et al. 2016; Safronetz et al. 2017; Akoua-Koffi et al. 2006). 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 contrast there has been a dramatic fall in cases reported from Sierra Leone, whether these represent changes in the underlying spillover risk is currently unclear.



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.

The number of reported confirmed cases of Lassa fever in endemic countries is likely 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 (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 2022).

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 is also suggestive 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 awaited (Penfold et al. 2023).

### 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 (Simons et al. 2023). 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 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). Describe life history. Describe breeding patterns in Tanzania. Potentially not the same in West Africa.

Describe locations of this species and interactions with invasive rodents and other native rodents. The potential importance of this for viral transmission.

Describe the different clades and other arenaviruses and how that may limit expansion outside of West Africa.

Figure of seroprevalence among sampled *M. natalensis* and other species.

Describe other native rodent species.

Describe invasion of mus and rattus.

Describe limited systematic rodent sampling.

Describe that we cannot truly understand what the effects of changing systems will be on rodent occurrence and abundance due to data sparsity.

### Predicting current and future Lassa fever risk

Describe current understanding of spatial risk

Describe potential future spatial risk

Limitations and biases

Summary paragraph

## 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

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