Spillover and emergence of bat-origin viral infections

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This dissertation is submitted for the degree of
Doctor of Philosophy

April 2021

For dad and my papas.

Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration with the following exceptions:

- I developed the model, performed the analysis, and wrote the text of Chapter 2, which is adapted from a similar publication [1]. Other named coauthors on the associated publication collected the serological data and performed preliminary data cleaning and analysis, as well as contributed ideas or supervision to the analysis and helped revise the text. The data and custom code package used in this analysis are both freely available online [2, 3].

- I conducted the quantitative literature review described in Chapter 3 with advice from the coauthors listed on the associated publication [4]. I gathered, read, and analysed the papers that comprise the review and wrote the majority of the associated manuscript. The coauthors involved helped with manuscript conception and revision, as well as interpretation of the results relevant to their areas of expertise.

- I performed all spillover estimation analysis described in Chapter 4. However, I discussed and refined the analysis and interpretation thereof with the coauthors listed on the associated publication; the idea was also developed collaboratively [5]. We have elaborated on the implications of the findings of this chapter elsewhere [6–8]. The code for this analysis is freely available online [9].

- I developed the model, performed all analysis, gathered data, and wrote nearly all of the text of Chapter 5; a preprint of Chapter 5 including source code is available online [10, 11]. Other named coauthors on the associated preprint also helped conceptualise the idea, gathered or provided data, provided analytical help or oversight (especially for geospatial analyses), provided specific expertise, and helped revise the text. Any paragraphs written in substantial part by other coauthors are clearly marked where they appear.

Although some material within this thesis has been previously published, I have adjusted the language to make roles clearer and at times to note (in footnotes) discrepancies between

my past and present perspectives. In general, where I have conducted the bulk of the analysis, I have used the pronoun "I." Where conclusions were made with the assistance of coauthors, I have kept the pronoun "we." Additional authorship notes are given as footnotes within the text of this document where appropriate.

This dissertation is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution.

This dissertation does not exceed 60,000 words excluding figures, photographs, tables, appendices, and bibliography.

Emma Elizabeth Glennon
April 2021

Acknowledgements

The thoughts I express in this thesis are the product of discussions and shared experiences around the world. Firstly, I would like to acknowledge the lives and work of those for whom progress and knowledge come too late. I am deeply grateful to those who have fought and died before me—and will fight with and after me—to count and repair the senseless injustices of these historic times.

I would also like to thank the innumerable colleagues, friends, activists, and others whose works, teachings, and companionship have helped me to grow personally and intellectually over the last four years. I am especially grateful to the whole Goma team, including Aminata, Esther, Richy, Nailah, Noé, Pascale, Denis, Emanuele, Prabasaj, Fabrice, and Loveena for teaching me more over six weeks than I ever thought possible; to Alex, Kirk, Maureen, Tamika, Hamish, and the many others in Australia who helped me reconnect to the world (and cuddle a few flying foxes); to all of my students; and to my family and ancestors who have guided me all this time.

Most personally, my thinking on these issues has been shaped by mentors, colleagues, and supervisors including Olivier Restif, Freya Jephcott, James Wood, and Alison Peel, as well as by everyone who has shared with me conversations, guidance, and critical feedback on particularly difficult sections of this document (although many of these sections have not survived to the corrected manuscript), including Margaret Comer, Adia Benton, Ignacia Arteaga, Edyth Parker, Samuel Mumford, Justin Feldman, Abigail Cartus, Eugene Richardson, Colin Carlson, Lioba Hirsch, Jessica Breakey, Stephanie McKay, Melody Schreiber, Kevin Kay, Alexandra Phelan, Marike Andreas, and Samuel Glennon. I am also grateful to the Gates Cambridge Trust and the examiners and anonymous reviewers who have provided funding and feedback to see this work through.

I am personally grateful to everyone who has supported me as a person over the last few years, especially those who have held me safe and accountable. Annika, Jacqueline, Ben, Kevin, and Joanna created the most supportive (if most disorganised and incident-prone) neighbourhood I could have dreamed of, not to mention Cambridge Community Kitchen, ACORN, and so many other pockets of indispensible community support. Charlie has always being there for a home-cooked meal and a much needed walk along the river. Dima, Masha,

Andy, and other fellow travellers have saved me in the moments I seemed to be alone. So many others have been part of my community over the past few years that I hesitate to name anyone, but here are a few whose support, company, and example have shaped my life in Cambridge (in no particular order): Freya, Edyth, Miriam, Eddie, Ben, Elf, Ishmael, Danny, Alex, Naomi, Laura, Edward, John, Dan, Katy, David, Andromachi, Fig, Krittika, Eric, Nick, Ashleigh, Yung-In, Mike, Harum, Jess, Cansu, Jerelle, Mimi, Eky, Badger, Ellie, Akshath, Joy, Claire, Songbird, Andrew, Angela, Zuheir, Holly, Jake, Dino, Indigo, Siddarth, Janosz, Mia. Memories from these years have already been such a sustaining joy—who could have ever known how long or how deeply I might need a portable packet of dad jokes, affections, and affirmations in November, 2019? I especially extend my gratitude to anyone whose influence on this work I have failed to name (or have yet to understand).

I can't pretend the past few years haven't had their challenges, and so for a few people I'm grateful most of all—thank you especially to Sam and Lion for helping me come through in one piece. And what could I possibly say about Margaret, my lockdown partner in chaos? I hope the next few years provide us both as many stories and comforts as challenges; now is the time to learn to live across borders. Finally, my sister, Suzannah, would like my readers to know that she takes credit for every good idea in this document, and that I would be nothing without her. She isn't completely wrong. Thank you for the shelter, the adventures, the puppy time, and the wisdom that only a sister can give.

Abstract

This thesis describes four years of research to quantify and characterise the system dynamics of bat-origin viral emergence events. Chapters 2–5 are comprised of four quantitative analyses: a compartmental model comparison of stochastic henipavirus serological dynamics in captive bats (*Eidolon helvum* in Ghana), a quantitative literature review of domesticated animals as bridging hosts of henipavirus and filovirus spillover, a statistical model of Ebola spillover observation probabilities, and a Bayesian model of syndromic differentiation of and surveillance for haemorrhagic fevers. By adapting, extending, and developing new analytical methods to infer the ecological and epidemiological dynamics of bat-origin viruses, I demonstrate through these chapters that 1) spillover of Ebola virus and other rare zoonotic pathogens is more common than typically accounted for, especialy when resulting in small outbreaks and singleton spillovers, 2) many gaps exist in knowledge of the emergence risks posed by henipaviruses and filoviruses, including fundamental aspects of viral dynamics in reservoir hosts and the roles of domesticated animals as potentially bridging or amplifying hosts, 3) common febrile illnesses and underdeveloped health infrastructure combine to create a primary barrier to detection of rare disease, and 4) many of the observation biases involved in spillover research and outbreak detection are mutually compounding and self-reinforcing. I synthesise these findings in Chapter 6, attempting to reconcile the many uncertainties in the quantitative study of zoonotic spillover and emergence with the urgent need for action to prevent and mitigate future epidemics. I conclude by emphasising the importance of core health infrastructure, as well as global redistribution of the means of good health and greater political engagement by scientists with the social forces that shape unequal distributions of disease.

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Chapter 1

Introduction

1.1 Motivation and aims

Zoonotic diseases—those resulting from an animal pathogen "jumping" to a human host, in a process known as spillover—make up the majority of emerging infectious diseases [12]. Viruses that circulate naturally in other animals are often (at least at first) poorly evolutionarily adapted to people [13–16], which can contribute to extremely high mortality rates such as those caused by infection with Ebola virus or rabies [17, 18]. Perhaps more importantly, our "host" systems are often poorly adapted to them, across many ecological and social scales. Without diagnostic tools, vaccines, or treatment options, emerging viruses easily evade control where systems of care, especially core public health infrastructure, are inadequate. As a result, zoonotic epidemics are often devastating at levels from the local (such as a small, violent outbreak of Ebola or Nipah virus) to the global (such as the current coronavirus disease 2019, COVID-19, pandemic).

Among zoonotic pathogens, bat-origin viruses have been implicated frequently in recent memory; this category is likely to include ebolaviruses, Nipah virus, Hendra virus, and the coronavirus (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19). During the original preparation of this thesis alone, between September 2016 and September 2020, there were more than 2000 deaths from 4 reported Ebola outbreaks (all originating in the Democratic Republic of the Congo),[1] [20], a deadly Nipah virus outbreak in a densely populated district in southern India (more than 1000 km from the closest previously reported Nipah outbreak) [21], and 7 reported Hendra virus (HeV) spillover events resulting in the

[1] I demonstrate in Chapter 4 that the true number of Ebola virus spillovers in this time is likely to be several times higher than what has been reported, and in Chapter 5 I expand and complicate that analysis. This tally is complicated by more recent outbreaks in 2021, which may have started with viral recurrence among cases infected years previously [19].

deaths of 7 horses [22]. Furthermore, the COVID-19 pandemic continues to change life as we know it around the world; as of February 2021, COVID-19 has already infected more than 100 million people around the world, killing more than two million [23, 24]. Although the reservoir host of SARS-CoV-2 has not yet been established, the virus is closely related to known bat coronaviruses, and many of the epidemiological and social dynamics surrounding its early spread closely mirrored that of SARS-CoV in 2002–2003 [25–27].[2] It remains extremely plausible that SARS-CoV-2 could have emerged (or a future coronavirus could emerge) from bats, which host a variety of SARS-like coronaviruses [33–36]. However these origin stories unravel in the coming years, bat-origin zoonotic viruses clearly pose an immediate and ongoing risk to human life.

In addition to the evident present toll of these viruses, there is substantial evidence that spillover risks are increasing along with ecological degradation and climate change. Long-term changes in the ecology of bat species have been associated with several catastrophic changes in climate and land use patterns. Heat stress is increasingly threatening flying fox populations across Australia [37]; the (southern hemisphere) summer of 2018–19 saw the largest known die-off of flying foxes in Australia, with as much as a third of the entire *Pteropus scapulatus* population dying from extreme heat within a two-day period [38]. One year later, bushfires sparked the "Black Summer," in which ash and smoke blanketed the skies of most of New South Wales and much of Australia's eastern and southern coasts [39]. The bushfire season killed 33 people and destroyed more than 3000 homes; it also burned over 100,000 km^2 of land including thousands of square kilometers of prime habitat for both bats and people [39]. Meanwhile, the state of Kerala in southern India has seen unusually extreme cycles of flooding and drought; combined with continued deforestation this extreme weather may have contributed to the spillover of Nipah virus in Kerala, seen for the first time in 2018 [40, 41].

Although there is some debate about the attribution of specific outbreaks, as well as whether bats represent ecologically or immunologically "special" reservoir hosts of zoonotic viruses [42–45], a positive relationship between zoonotic spillover from bats and their changing ecosystems is well documented. Contributing ecological factors to bat-origin spillover likely include reservoir climate-driven host shifts [46, 47], urbanisation and displacement of both bats and people [48, 47], availability of suitable feeding/roosting sites (and consequent changes in migratory behaviour and metapopulation dynamics) [49–51], and general health among bats subject to stress caused by loss of nutritional and other resources [52, 53]. Each

[2] The coronavirus that causes Middle East Respiratory Syndrome, MERS-CoV, is also closely related to bat coronaviruses and can infect bats, but is now endemic in camels [28, 29]. The importance of bats as a MERS-CoV reservoir remains unclear [30, 31]. It is therefore worth treating the "probable bat origin" of the current coronavirus epidemic with some caution [26, 32].

of these plausibly contributes to increasing rates of zoonotic spillover in general and from bats specifically [12, 47]. Although the theoretical basis and balance of these factors at a global scale is still an active area of investigation [54], the high and increasing risk of novel spillover of unknown zoonotic viruses in bat reservoir hosts is generally accepted [55–58].

In this thesis, I attempt to illuminate the ecological and epidemiological processes that create zoonotic epidemics. In the analysis chapters (2–5), I seek to describe and quantify aspects of the risk of bat-origin viral spillover and emergence. As with other rare and difficult-to-observe phenomena, spillover events and early-stage outbreaks typically result in sparse and incomplete data. The lack of appropriate data makes quantification difficult and accurate risk assessment seemingly impossible; the scientific understanding of zoonotic risk is characterised more by knowledge islands than knowledge gaps. Nonetheless, by modelling ecological and epidemiological processes causally related to spillover—from the circulation of zoonotic viruses among bats to the detection of small Ebola outbreaks and spillover events among people—I am able to use additional types of data to illuminate some of the most uncertain, and even unmeasureable, aspects of spillover. For example, in Chapter 4 I synthesise data on the sizes of reported Ebola outbreaks with an epidemiological model of the process by which a spillover becomes a local outbreak; this allows me to demonstrate the frequency with which spillovers are likely to have gone undetected by health systems. I also make use of data on henipaviral antibody titres in fruit bats, on disease distributions and clinical presentations in people (for a range of diseases, but particularly Ebola virus disease and other potentially haemorrhagic fevers), and on the existing corpus of scientific literature. In so doing I develop quantitative methods to examine what is known and what remains unknown about henipavirus and filovirus emergence. By leveraging data at a variety of ecological scales and epidemiological stages, I demonstrate that scientific knowledge of spillover is subject to persistent, self-reinforcing observation biases that lead to the underestimation of zoonotic hazard posed by wildlife reservoir hosts. Furthermore, I demonstrate that viral emergence post-spillover is strongly limited by core public health capacity in ways also subject to self-perpetuating observation biases.

1.2 Modelling dynamics of spillover and emergence

Mathematical models are useful tools for describing and making inferences about dynamic systems, particularly those like infectious disease with nonlinear and partially observed component processes. Both spillover and infectious disease emergence are typically observed through the outcome of human disease, while other crucial components of the disease system (e.g., animal infections, social contact networks, preexisting levels of immunity to

infection) are rarely measured directly. By accounting for interactions between observed and unobserved components of disease, mathematical models allow inference about the entire dynamic system, including these underlying states and their mechanisms of influence on human disease. Herd immunity and other network protection effects, disease amplification in vulnerable populations, stochastic effects such as metapopulation disease spread and local extinction, and host-level disease properties such as duration of immunity are just a few of the processes and traits dynamic models can be used to clarify.

Harnessing the inferential power of models requires making assumptions about underlying disease processes [59]. One of the most common mathematical models of infectious disease, for example, the "susceptible-infected-recovered" or SIR model, assumes that hosts progress through three disease states and that all infection is immunising. Misapplication of an SIR model to data from a disease with transient immunity might result in accurate short-term inferences, but any long-term predictions are likely to be inaccurate as population immunity wanes more quickly than an SIR model assumes. At present, too little is known about bat immunology or within-host pathogen dynamics to make robust assumptions about the nature of reservoir circulation of, for example, henipaviruses in fruit bat hosts [60]. In Chapter 2, I therefore use a wide range of possible assumptions to explore the likely nature of henipaviral circulation in captive *Eidolon helvum*; by developing and fitting a wide range of models with diverse assumptions about the nature of immunity and transmission I am able to analyse the consequences of these assumptions rather than rely on any one particular specification of the host-pathogen system. Although this comparison and reconciliation of multiple competing models avoids some of the crudest assumptions of the SIR model, it nonetheless—like all mathematical representations of real-world processes—rests on other assumptions. I describe core assumptions in each analysis chapter, and I elaborate on their reasonableness and implications in Chapter 6.

Models (such as SIR-derived models) that categorise individuals by disease state are a particularly common class of model, but many other mechanistic and statistical models can be equally informative about aspects of disease spillover and emergence. Spillover is the product of both ecological hazard (i.e., risk of pathogen shedding from non-human animals) and human social patterns (e.g., human-animal interactions and behaviours that may modify them). Furthermore, the *observation* of spillover events for any zoonosis depends on the transmissibility of disease from person-to-person, clinical presentation, and local public health infrastructure and disease surveillance capacity. Spillover risk can therefore be assessed by modelling the links between observed human infection and (true, unobserved) spillovers, as well as by modelling how macro-scale ecological risks of the precursors to spillover change over space and time. In Chapters 4 and 5, I model different aspects of the

relationship between spillover and the emergence and detection of early stage outbreaks. This allows for a theoretical and empirical exploration of the process by which spillovers become outbreaks, highlighting barriers to outbreak detection as well as the limitations of the data historically produced by the processes of spillover, emergence, and detection.

One of the most useful features of modelling is its ability to extend, infer, interpolate, and otherwise produce a more complete scientific picture from incomplete data. Fitting a model (that is, systematically adjusting/selecting parameters to minimise model predictions' disagreement with data) allows, for example, exploration of the drivers and determinants of noise or variation in the data; use of stochastic models can clarify expectations regarding noise as produced by a stochastic dynamic process vs. the effects of observation. That is, even apparent imperfections and inconsistencies in data provide information that can be harnessed to clarify disease mechanisms through careful modelling, rather than treated (as in many static statistical frameworks) as simple random error. Similarly, modelling known mechanisms of disease processes allows inference of unobserved quantities, such as (in Chapter 4) outbreaks that have not been reported but can be inferred from the properties of observed data and the processes that produced observations. This property is particularly useful in the analysis of emerging zoonoses, the scientific picture of which (as compared to other infectious diseases of people) is characterised by uncertainty, incompleteness, observation and sampling biases, and rapid change.

1.3 Document outline

I begin in Chapter 2 by investigating the ecological factors that underlie spillover risk from an important and unusually well-studied henipavirus reservoir host, *Eidolon helvum*. Despite the importance of viral circulation in reservoir hosts as a precursor to spillover, the mechanisms of henipaviral transmission and persistence among bats are poorly understood. To address this gap, I systematically explore a range of plausible hypotheses about the within- and between-host dynamics of henipavirus infection in *E. helvum* by constructing a generalised SEIR (susceptible, exposed, infectious, recovered) modelling framework. This framework encompasses 46 sub-models and a wide range of possible infection and immunity scenarios. I use likelihood-based methods to fit these models to nine years of longitudinal data on henipavirus serology from a captive colony of *E. helvum* bats in Ghana. I demonstrate that reinfection is necessary to explain observed dynamics; that acute infectious periods may be very short (hours to days); that immunity, if present, may be expected to last about 1–2 years; and that intermittently recurring long-term infection is a plausible explanation for observed antibody dynamics. Although some quantitative inferences are sensitive to assumptions about

serology, these qualitative predictions are robust to a diverse range of assumptions about the nature of infection dynamics in fruit bat hosts of henipaviruses. This approach helps clarify mechanisms of viral persistence and circulation in wild bats, including estimated ranges for key parameters such as the basic reproduction number and the duration of the infectious period.

Domesticated animals occupy a unique ecological role in the history of many zoonoses, offering links of close contact between wildlife and people as well as opportunities for viral amplification in intensive agricultural settings. Despite this potentially critical role, domesticated animals rarely feature in research about wildlife zoonoses and their pathways to spillover. In Chapter 3 I demonstrate and contextualise this research gap by compiling current knowledge on the role of domesticated animals as hosts of henipaviruses and filoviruses. I use a systematic literature search of these virus-host interactions in domesticated animals to identify 72 relevant studies, which I categorised by year, location, design and type of evidence generated. I include a short case study on filoviruses in Africa, comparing research efforts in domesticated animals and bats with the distributions of documented human cases. I demonstrate major gaps in our knowledge of the potential ability of domesticated animals to contract, spread, or amplify these zoonoses.

Outbreak detection is an essential step for quick and effective outbreak response, but it is difficult to know how often outbreaks go undetected. The history of Ebola outbreaks, including their sizes and times to detection, suggest small and early-stage outbreaks are especially likely to go unconfirmed and unreported by the literature. In Chapter 4, I attempt to quantify this effect by estimating Ebola virus disease (EVD) detection rates as a function of number of cases in an outbreak cluster. Using three independent datasets available on the distributions of secondary infections during EVD outbreaks across West Africa, in a single district (Western Area) of Sierra Leone, and in the city of Conakry, Guinea, I first simulated realistic outbreak size distributions and compared them to reported outbreak sizes. These three empirical distributions lead to estimates for the proportion of detected spillover events and small outbreaks of 26% (range 8–40%, based on the full outbreak data), 48% (range 39–62%, based on the Sierra Leone data), and 17% (range 11– 24%, based on the Guinea data). I conclude that at least half of all spillover events have failed to be reported since EVD was first recognized. I estimate the probability of reporting a single-case spillover event at less than 10%.

A major challenge to the identification of Ebola and other rare zoonotic outbreaks is their existence against a background of more common endemic illnesses. Combined with resource limitations including a lack of universal access to care or confirmatory diagnostic testing, this context of more common disease can make the signs and symptoms of Ebola cases

and clusters more difficult to identify. In Chapter 5 I attempt to model this effect to better understand the strengths and limitations of syndromic surveillance for haemorrhagic fevers. I develop an algorithm for probabilistic identification of potentially haemorrhagic febrile outbreaks, test its application to a syndromic database of 87 febrile outbreaks, and apply it to discuss theoretical and methodological aspects of syndromic surveillance. Using published data on symptom presentation and incidence of 21 febrile syndromes in sub-Saharan Africa, I show that Ebola virus disease, Marburg virus disease, and yellow fever represent a cluster of syndromes that are syndromically distinguishable from most other endemic febrile diseases. However, even when syndromic surveillance considers wide ranges of symptoms, these rare haemorrhagic fevers remain easily obscured by more common diseases, especially typhoid fever and dengue haemorrhagic fever. Furthermore, even large clusters (20+ cases) of filoviral diseases cannot be routinely distinguished by the symptoms present in their case definitions alone; I show these case definitions are insensitive to rare fevers across most of the region. Finally I demonstrate the possibility of "hidden hotspots" where Ebola virus is likely to spill over from wildlife and also go undetected due to existing vulnerabilities, such as underdevelopment of economic and health infrastructure. Such places may represent both the locations of past unobserved outbreaks and potential future origins for larger epidemics, as well as sites characterised by complex vulnerability to infectious disease more generally.

In Chapter 6 I synthesise these findings, then discuss how the evidence I have generated in Chapter 2–5 has contributed to the development of our understanding of the origins of emerging infectious diseases from bats. I highlight in particular what remains unknown or unknowable about zoonotic disease emergence, as well as how observation biases and feedback loops create an "epistemic bubble" in the quantitative study of this complex process. Finally, I use these findings to argue that despite scientific challenges, much of disease emergence is preventable if we address its social and political determinants: i.e., racial capitalism and the resulting maldistribution of access to the means of good health. In the recent history of disease emergence, quantitative science—an incremental project inherently dependent on flawed data and shaped by external priorities—has often served as an apparatus of distraction and justification for political inaction around disease. With references to the histories of Ebola and COVID-19, I close by discussing both these technocratic distractions and the urgent changes truly necessary to prevent zoonotic pandemics.

Chapter 2

Viral reservoir ecology

2.1 Background

2.1.1 African henipaviruses

Pathogen circulation in reservoir hosts is an essential precursor to spillover, but its ecological aspects are often poorly understood relative to post-spillover processes. Bats are an especially important clade to study, as they host a uniquely rich set of viruses—more viruses per species than even rodents [61], including many important emerging zoonoses [62, 43].[1] Bats host at least six of the World Health Organization's top ten named priority pathogens with potential to create a public health emergency [63]. The ecological mechanisms that allow for the circulation of such otherwise virulent viruses in their reservoir hosts, however, are poorly understood despite their enormous consequences for human health.

Authorship note: As noted in the Declaration of this document, most of the text in this section is excerpted or adapted from a previously published article [1]. All text is in my own words. All uses of the pronoun "I" refer to methods I carried out independently, while uses of the pronoun "we" indicate contributions of the co-authors on the relevant paper. I wrote the bulk of this chapter in 2017–2018, and the literature and my personal opinons have both evolved since; I have highlighted such differences in a few footnotes and added a few more recent sources, but this chapter is incompletely updated to the state of knowledge in late 2020.

[1] Whether bats are "special" as reservoir hosts of zoonotic viruses is a complex question [42, 43, 45], but since I originally wrote this I no longer think viral richness in bats itself indicates an important source of uniquely dangerous spillover hazard [44]. I suspect instead (although more evidence would be needed to confirm) their apparent importance as a reservoir may be partly rooted in their uniquely social ecology (connectivity, gregarity, reciprocality/complex social power structures, much like people), other life history traits (such as their longevity), and their extreme sensitivity to the current climate and ongoing environmental changes [42, 45].

Henipaviruses are hosted by fruit bats and include Hendra virus (HeV) in Australia and Nipah virus (NiV) in Asia [64–66], which are among the bat-borne pathogens considered by the WHO and others to have the highest pandemic potential. Both HeV and NiV cause almost annual outbreaks in horses and people, respectively. Human fatality rates are greater than 50% [67]. Spillover has occurred both directly from bats to people (e.g. NiV) [68–71] and indirectly via amplifying or bridging hosts, namely pigs for NiV and horses for HeV [72, 73, 4]. Henipaviruses have also been detected in fruit bats in Africa [74, 75], and antibodies to them have occasionally been detected in people and pigs, although no human cases have yet been documented [76–78]. The nature of henipavirus circulation in the reservoir—including the possibility that these viruses can persist in individual hosts and be impacted by environmental forces—has strong implications for the risk and drivers of spillover to people [71, 79, 50].

The hypothesis that henipavirus infections may be recurrent (i.e., oscillating between latent or otherwise inactive infection and acute infection) in their bat hosts has been gaining support (reviewed in [60]). Evidence includes simultaneous viral shedding of henipaviruses from a large number of individuals in a single roost during presumed times of physiological or nutritional stress [80, 81]; serological conversions of bats that had previously exhibited apparent clearance [82]; ongoing henipaviral circulation in small island populations [83, 84]; and long-term persistence of circulating henipaviruses in small, closed populations [85]. However, our incomplete understanding of bat immunology and the difficulty associated with isolating henipaviruses from bats has rendered it challenging to determine what these observations mean in terms of bats' immunity, clearance, and transmission of these pathogens [60]. Simple models of plausible latent, recurring infection (e.g., the "susceptible-infected-latent-infected," or SILI, model) have been analysed theoretically but not empirically applied to this system [60, 86].

Rather than comparing alternative, arbitrary models of bat-virus dynamics, I systematically explored a comprehensive set of hypotheses about the cycle of henipavirus infection and immunity in bats. I expanded upon the classical compartmental SEIR ('susceptible-exposed–infectious–recovered') framework to cover a comprehensive range of models of infection dynamics, including features of recurrence, reinfection, non-infectious infection. Critically, I made few assumptions about the timing of, recovery from, or immunity granted by a noninfectious state. I allowed this state to represent a variety of qualitatively different types and stages of infection, including an incubation period, exposure that may lead to asymptomatic infection, and lifelong or temporary latent infections, all while allowing standardization, e.g., by R_0 or equilibrium dynamics. I statistically fit 46 variants of this generalised model to a longitudinal serological dataset of a breeding, captive colony of

Eidolon helvum held in Ghana for nine years. In line with empirical evidence [84], I included a seasonal birth pulse, maternally-derived immunity and a simple age structure into this set of models. I used the results of the cross-model comparison to predict the most likely within-host dynamic features—including cycles of recurrence and reinfection, clearance of infection, and probable parameter values—of African henipaviruses infections in their bat reservoir hosts.

2.1.2 Dynamic model specification

Mechanistic models of biological processes, especially infectious disease dynamics, allow for such diverse and important insights as thresholds for herd immunity [87], ecological drivers of outbreaks [88], and strategies for disease control [89, 90]. However, development of such models relies upon strong assumptions of underlying mechanisms, such as whether or not infection generates immunity in the host. Invalid assumptions about these properties can lead to model predictions that are misleading, arbitrary, and/or irreproducible. This limitation is especially evident for those diseases we know the least about—emerging epidemics [91, 92], poorly understood endemic diseases [93], and wildlife diseases [94]—limiting the application of models to these systems despite their potential to help build hypotheses, guide data collection, and accelerate research [95]. For such infections, it may not be possible to choose an appropriate model based on prior knowledge of host-pathogen interactions. SIR and similar models are likely to be inappropriate defaults in these contexts.

In the case of outbreaks of unknown aetiology or infectious diseases with unknown epidemiological properties, modellers often assume simple "susceptible-infected-recovered" (SIR) or "susceptible-exposed-infected-recovered" (SEIR) dynamics, i.e., that infection results in acute disease, recovery from which grants a host lifelong immunity [59]. For many epidemic diseases, these models are good approximations that can provide strong insights [96, 97]. SIR dynamics, however, represent only a small subset of infection types; many known diseases are better described by models accounting for asymptomatic infections [98], chronic or persistent infections [99], incomplete or waning immunity [100], or slowly progressing infection [101].

Application of a misspecified model may result in biased inferences. Unobserved asymptomatic infections, for example, can cause an epidemic to decline more quickly than predictable from acute infections alone [102, 103] while failing to account for a disease's incubation period can cause underestimation of its basic reproduction number (R_0) [59]. Latent or chronic infections can facilitate the long-term persistence of rarely-transmitted pathogens such as human herpesviruses [104] as well as epidemic pathogens causing rare recrudescence events. At least five incidents of recrudescence occurred during the 2014–16

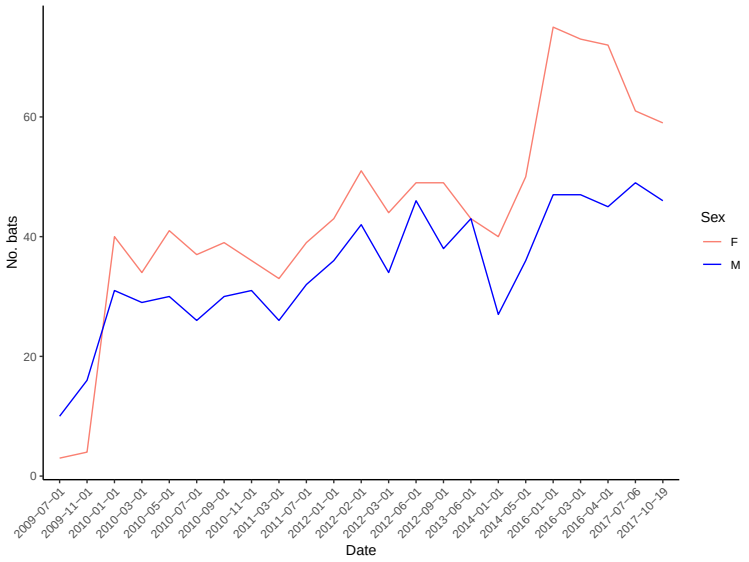

Fig. 2.1 Population counts of captive *Eidolon helvum* by sex and time point.

Ebola epidemic; although they did not lead to secondary infections, such events have the potential to act as reintroductions [105]. I developed the generalised mechanistic model presented below in order to adjust to this complexity and understand the potential consequences of the establishment of SIR and similar models as default models of unknown viral dynamics.

2.2 Materials and methods

2.2.1 Data

Individual-level serological data were collected longitudinally from a captive colony of *E. helvum* (straw-coloured fruit bats) established in Achimota forest, Accra National Zoo in Accra, Ghana as previously described [85]. The colony is separated from the surrounding forest by a solid roof and two layers of wire mesh, and captive bats have been isolated from all other bats since colony establishment. After the initial capture of 77 wild *E. helvum* by January 2010, the bats have been breeding in captivity, and since 2012 the population has oscillated between approximately 100 and 120 individuals (Figure 2.1). Each bat in the colony has been tagged, with blood collected from each tagged bat 1–5 times per year since the establishment of the colony, and seroprevalence has been assessed using a Luminex assay (Figure 2.2). Antibody levels were represented using the Mean Fluorescence Index (MFI), and the seropositivity cutoff was set at 110 MFI [85, 75]. Distributions of seroconversion

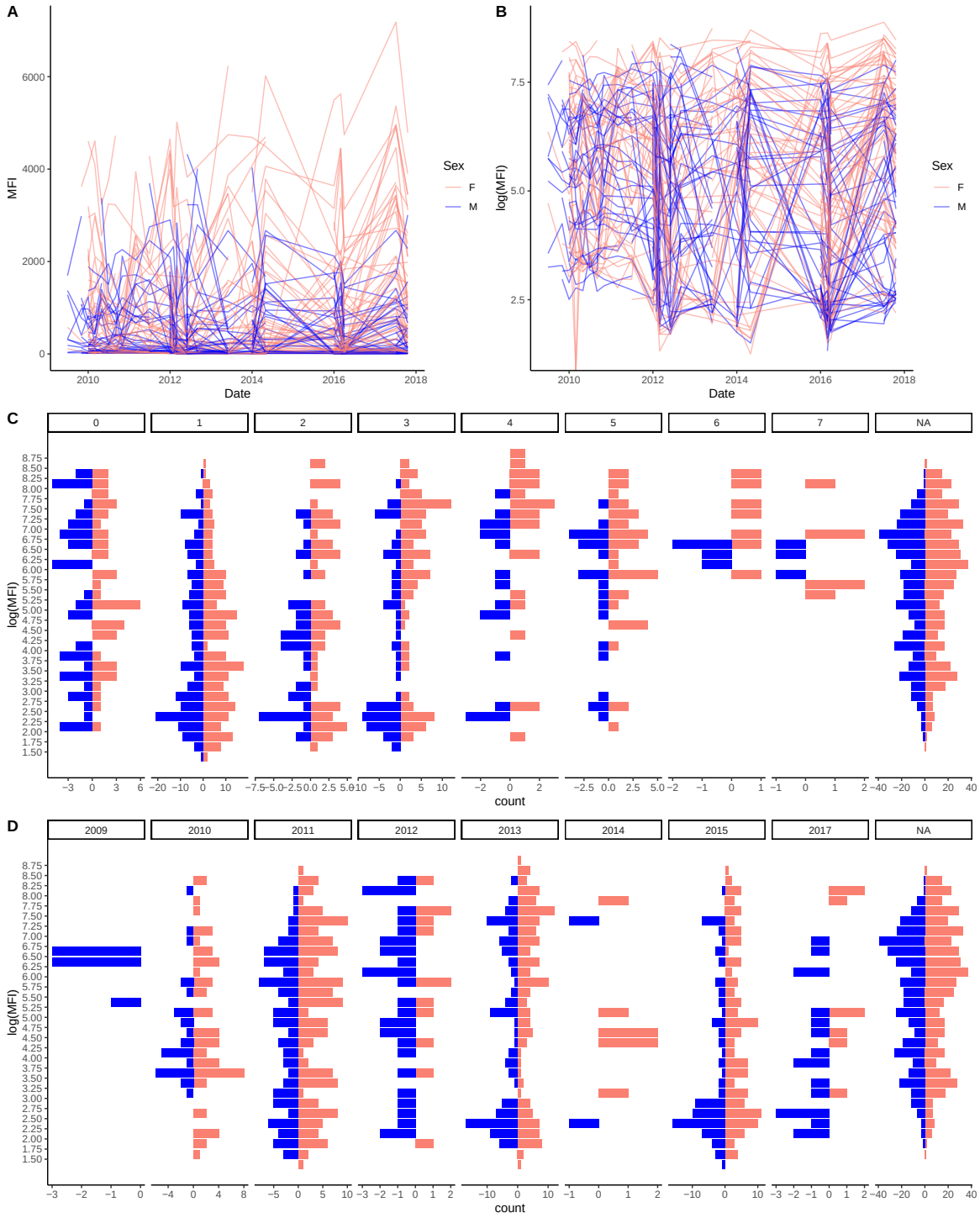

Fig. 2.2 Raw serology data for a capitive colony of *Eidolon helvum*. Mean Flourescence Index values for NiV-G Luminex assays over time per individual (A-B) and as a function of estimated age (C) or birth cohort (D). Colour (female in pink; male in blue) indicates sex for all subfigures. Only bats born in captivity have an estimated age; the recorded age for wild-caught bats is `NA`.

and seroreversion times used to fit the model were not strongly sensitive to the cutoff value (Figure 2.3).

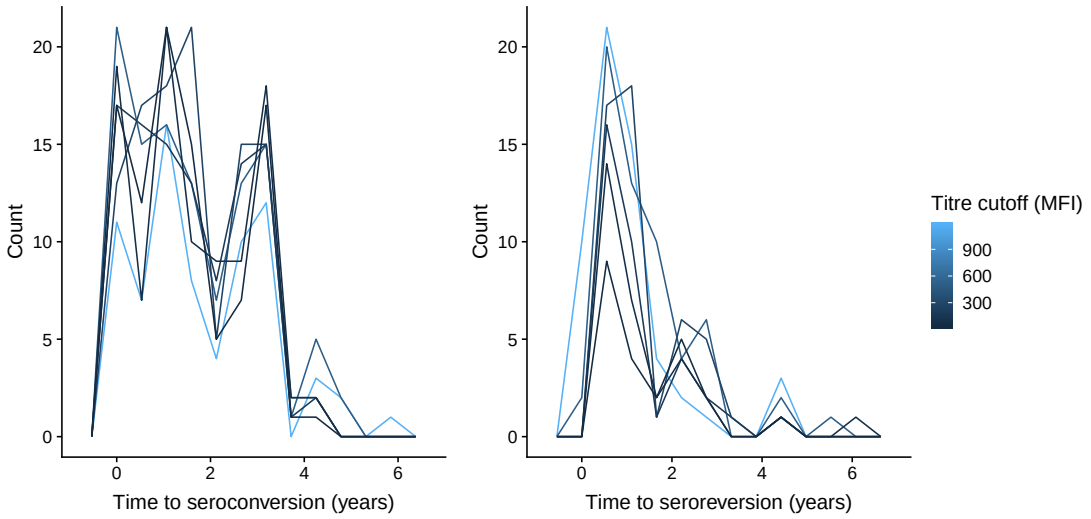

Fig. 2.3 Distributions of observed seroconversion and seroreversion times by MFI cutoff used to differentiate seropositive and seronegative individuals by Luminex assay.

2.2.2 Model development

Because within-host dynamics of henipaviruses in bats are so poorly understood, I opted to allow for multiple assumptions about the existence of immunity, heterogeneity in the form of infection, and ability of infections to clear or recur. I developed a framework that generalises the SEIR model, composed of a subset of all possible combinations of transitions among four state variables:

- **S**: susceptible and must undergo infection to become immune;
- **E**: infected but not infectious ('exposed')—incubating, asymptomatic, or latently infected;
- **I**: both infected and infectious, contributing to the overall force of infection;
- **R**: recovered/immune and must lose immunity to be reinfected.

Under the additional constraints that any one infection will either require an incubation period for all hosts or none, that infectiousness must be a possible outcome of noninfectious infection, that clearance of acute infections is either immunizing in all cases or none, and that

clearance of latent infection is either immunizing in all cases or none, there are 46 possible submodels comprised of subsets of transitions between these states.

Where $\beta \in \{\beta_1, \beta_2\}$ represents transmission, $\sigma \in \{\sigma_1, \sigma_2\}$ represents clearance of latent infection, $\gamma \in \{\gamma_1, \gamma_2\}$ represents clearance of acute infection, ρ represents reversion to latency, ε represents recrudescence from latency, and ω represents immune waning, the transition matrix can be written as in Equation 2.1, corresponding to the flow diagram in Figure 2.4.

$$\begin{array}{c} \text{state} \\ S \\ E/L \\ I \\ R \end{array} \begin{array}{c} \begin{array}{cccc} S & E/L & I & R \end{array} \\ \begin{bmatrix} & \beta_1 I & \beta_2 I & 0 \\ \sigma_1 & & \varepsilon & \sigma_2 \\ \gamma_1 & \rho & & \gamma_2 \\ \omega & 0 & 0 & \end{bmatrix} \end{array} \tag{2.1}$$

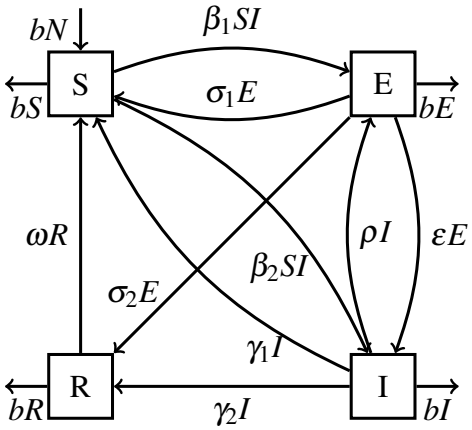

Fig. 2.4 Flow diagram representing states and all possible transitions in generalised SEIR model. Individual models are specified by setting a subset of transition rates to zero.

This framework consists of a wide range of 46 possible submodels. To refer to individual submodels, I define the following system of notation:

- All submodel representations indicate all possible transitions for a susceptible individual to take, starting from the susceptible compartment.
- As in more standard SI, SIR, or SEIR models, adjacent letters indicate one-way transitions from the compartment indicated by the first letter to the compartment indicated by the second letter (e.g., SI indicates the only possible transition is $S \to I$)
- As with SIRS and SEIRS models, transition from R to S returns an individual to a susceptible state and therefore indicates proceeding through the model compartments

as any other susceptible individual (e.g., SIRS indicates $S \to I \to R \to S \to I \ldots$ *ad infinitum*).

- Square brackets represent loops of latent and acute infection (i.e., transitions both from E to I, represented by $\varepsilon > 0$ and from I to E, represented by $\rho > 0$)). Individuals can flow from the last compartment within the set of brackets to either the first compartment within the brackets or the first compartment to the right of the brackets (e.g., S[IL] indicates that $S \to I$, but once infected, $I \to E \to I \to E \ldots$ *ad infinitum*. S[I(R)L] indicates $S \to I$, but once infected, an individual may either transition to E (latent infection) or may recover with lifelong immunity; recovery with lifelong immunity is always a possibility after acute infection, but not directly from latent infection.)

- Parentheses indicate one of two possible routes for the proceeding compartment (e.g., SE(S)I indicates that $S \to I$, but once exposed individuals can either become acutely infected or return to susceptibility, as in a non-immunising asymptomatic infection).

The framework therefore includes standard SIR/SIRS and SEIR/SEIRS dynamics and several possible models where individuals may be symptomatic or asymptomatic (e.g., SE(RS)IRS, in which exposed individuals may recover immediately or undergo acute infection, or SE(S)IRS, where exposure neither leads necessarily to acute infection nor to immunity). Several possible 'loops' of latent infection are also possible, with a variety of possible exits. For example, in all models with $\sigma = 0$, infection can only clear when it is acute, not when it is latent—this might be a good representation, e.g., of human diseases which require treatment (and treatment-seeking behavior) for full clearance. When $\gamma = 0$, by contrast, infection can only clear from the latent stage. When $\gamma = \sigma = 0$, infection is lifelong and recurring in all cases.

Because these models all share a general transition matrix, R_0 is the same function of parameters for each, which can be determined from the next generation matrices, where T represents the rates of entrance into infected states and Σ represents rates of exit from infected states [106]:

$$T = \begin{pmatrix} 0 & \beta_1 N \\ 0 & \beta_2 N \end{pmatrix} \tag{2.2}$$

$$\Sigma = \begin{pmatrix} -\sigma - m - \varepsilon & \rho \\ \varepsilon & -\gamma - m - \rho \end{pmatrix} \tag{2.3}$$

$$\lambda_{max}(-T\Sigma^{-1}) = R_0 = \frac{\beta_2 N(\varepsilon + \sigma + m) + \varepsilon\beta_1 N}{(\varepsilon + \sigma + m)(\gamma + \rho + m) - \varepsilon\rho} \tag{2.4}$$

Various parameters and combinations of parameters create mechanistic features in our submodels. These features have the following parametric definitions, where OR is an inclusive or (i.e., at least one of the conditions is met):

- Recurring infection: $\rho > 0$ AND $\varepsilon > 0$. Once infected, individuals may progress through cycles of acute and latent (i.e., noninfectious) infection without needing exposure from another infected individual.
- Lifelong immunity: ($\gamma_2 > 0$ OR $\sigma_2 > 0$) AND $\omega = 0$. Infected individuals may recover with immunity, and this immunity never wanes.
- Temporary immunity: ($\gamma_2 > 0$ OR $\sigma_2 > 0$) AND $\omega > 0$. Infected individuals may recover with immunity; this immunity will eventually wane until individuals are susceptible again (or die).
- No immunity: $\gamma_2 > 0$ AND $\sigma_2 > 0$. infected individuals either never recover or immediately return to susceptibility upon recovery from infection.
- Clearance without immunity: $\gamma_1 > 0$ OR $\sigma_1 > 0$. Infected individuals may return directly to a susceptible state without passing through an immune state.
- Clearance from E: $\sigma_1 > 0$ OR $\sigma_2 > 0$. Noninfectious infected individuals may directly become immune or susceptible.
- Clearance from I: $\gamma_1 > 0$ OR $\gamma_2 > 0$. Infectious individuals may directly become immune or susceptible.
- Reinfection: $\sigma_1 > 0$ OR $\gamma_1 > 0$ OR (($\gamma_2 > 0$ OR $\sigma_2 > 0$) AND $\omega > 0$). Individuals may lose their infection and, whether or not they ever have immunity, return directly to a susceptible state.
- Non-infectious infections/asymptomatics: $\beta_1 > 0$ AND ($\sigma_1 > 0$ OR ($\sigma_2 > 0$ AND $\omega > 0$)). Individuals may be exposed and infected, then clear infection (whether they develop immunity or return to a susceptible state directly) without ever being infectious.

This flexible, generalised model provides a framework for systematically considering many hypotheses about the dynamics of a poorly understood pathogen. Representing a wide and easily standardised range of possible mechanisms for disease circulation and persistence, it may allow model selection and comparison in a much more systematic way than more common approaches to early model applications.

2.2.3 Application to *Eidolon helvum*

I used the generalised SEIR model framework presented in Section 2.2.2 with minor adjustments to more account for captive colony demographic processes. To allow for maternal immunity and emulate age structure, I incorporated a simple age- and sex-stratified structure into the model. This structure included newborn (up to 6.7 months to correspond to estimates of maternal antibody waning [84]), juvenile (up to 1 year), adult male, and adult female classes. Newborns and juveniles have a higher mortality rate than adults, corresponding to previous estimates [107]; newborns are born with maternally derived immunity if and only if born to an immune mother [85]. Births occur according to a yearly birth pulse as previously developed [108]. Newborn, juvenile, and adult age classes are related to dynamic characteristics and do not correspond exactly to morphologically-assessed age categories [109]. Newborns in the model are instead characterised by potential maternal immunity and correspond to individuals typically labelled neonate or (young) juvenile, while our adult age classes are characterised by higher annual survival rates than juveniles and include both adult and sexually immature (i.e., subadult) individuals between approximately 1 and 2 years of age. I calculated R_0 based on the adult mortality rate.

The deterministic version of the full model including age structure is represented by the following differential equations, where parameters are used as in Table 2.1, and M, F, J, and N represent adult male, adult female, juvenile, and newborn individuals, respectively (although the Ma compartment itself represents maternally immune newborns):

$$
\begin{aligned}
b(t) &= ce^{-s\cos^2(\pi t-\phi)}\\
\frac{dS_F}{dt} &= \mu\frac{S_J}{2} - (m\frac{N}{k} + (\beta_1+\beta_2)(I_F+I_M+I_N+I_J))S_F + \sigma_1 E_F + \gamma_2 I_F + \omega_2 R_F\\
\frac{dE_F}{dt} &= \mu\frac{E_J}{2} - (m\frac{N}{k} + \sigma_1+\sigma_2+\varepsilon)E_F + \beta_1(I_F+I_M+I_N+I_J))S_F + \rho I_F\\
\frac{dI_F}{dt} &= \mu\frac{I_J}{2} - (m\frac{N}{k} + \gamma_1+\gamma_2+\rho)I_F + \beta_2(I_F+I_M+I_N+I_J))S_F + \varepsilon E_F\\
\frac{dR_F}{dt} &= \mu\frac{R_J}{2} - (m\frac{N}{k} + \omega)R_F + \sigma_2 E_F + \gamma_2 I_F\\
\frac{dS_M}{dt} &= \mu\frac{S_J}{2} - (m\frac{N}{k} + (\beta_1+\beta_2)(I_F+I_M+I_N+I_J))S_M + \sigma_1 E_M + \gamma_2 I_M + \omega_2 R_M\\
\frac{dE_M}{dt} &= \mu\frac{E_J}{2} - (m\frac{N}{k} + \sigma_1+\sigma_2+\varepsilon)E_M + \beta_1(I_F+I_M+I_N+I_J))S_M + \rho I_M\\
\frac{dI_M}{dt} &= \mu\frac{I_J}{2} - (m\frac{N}{k} + \gamma_1+\gamma_2+\rho)I_M + \beta_2(I_F+I_M+I_N+I_J))S_M + \varepsilon E_M\\
\frac{dR_M}{dt} &= \mu\frac{R_J}{2} - (m\frac{N}{k} + \omega)R_M + \sigma_2 E_M + \gamma_2 I_M\\
\frac{dMa}{dt} &= 2bR_F - (\omega_m + m_j\frac{N}{k})Ma\\
\frac{dS_N}{dt} &= 2b(S_F+E_F+I_F) - (\omega_m + m_j\frac{N}{k} + (\beta_1+\beta_2)(I_F+I_M+I_N+I_J))S_N + \sigma_1 E_N + \gamma_2 I_N + \omega_2 R_N\\
\frac{dE_N}{dt} &= -(\omega_m + m_j\frac{N}{k} + \sigma_1+\sigma_2+\varepsilon)E_N + \beta_1(I_F+I_M+I_N+I_J))S_N + \rho I_N\\
\frac{dI_N}{dt} &= -(\omega_m + m_j\frac{N}{k} + \gamma_1+\gamma_2+\rho)I_N + \beta_2(I_F+I_M+I_N+I_J))S_N + \varepsilon E_N\\
\frac{dR_N}{dt} &= -(\omega_m + m_j\frac{N}{k} + \omega)R_N + \sigma_2 E_N + \gamma_2 I_N\\
\frac{dS_J}{dt} &= \omega_m(S_N+Ma) - (\mu + m_j\frac{N}{k} + (\beta_1+\beta_2)(I_F+I_M+I_N+I_J))S_J + \sigma_1 E_J + \gamma_2 I_J + \omega_2 R_J\\
\frac{dE_J}{dt} &= \omega_m E_N - (\mu + m_j\frac{N}{k} + \sigma_1+\sigma_2+\varepsilon)E_J + \beta_1(I_F+I_M+I_N+I_J))S_J + \rho I_J\\
\frac{dI_J}{dt} &= \omega_m I_N - (\mu + m_j\frac{N}{k} + \gamma_1+\gamma_2+\rho)I_J + \beta_2(I_F+I_M+I_N+I_J))S_J + \varepsilon E_J\\
\frac{dR_J}{dt} &= \omega_m RN - (\mu + m_j\frac{N}{k} + \omega)R_J + \sigma_2 E_J + \gamma_2 I_J
\end{aligned}
$$

Symbol	Parameter meaning	Value constraints	Source
R_0	Basic reproduction number	0.25+	fit for all models
β_1	Transmission rate to E	–	calculated from R_0
β_2	Transmission rate to I	–	calculated from R_0
ω	Immune waning rate	0+	fit for relevant models
ρ	'Latency' rate (I→E)	0+	fit for relevant models
ε	Incubation/recurrence rate (E→I)	0+	fit for relevant models
σ_1	Clearance rate (→S) from E	0+	fit for relevant models
σ_2	Recovery rate (→R) from E	0+	fit for relevant models
γ_1	Clearance rate (→S) from I	0+	fit for relevant models
γ_2	Recovery rate (→R) from I	0+	fit for relevant models
ϕ	Birth pulse timing	4.5	[85]
s	Birth pulse synchronicity	14.3	[110]
c	Birth pulse scalar	1.53	calculated to balance deaths
m	Adult death rate	0.186 year^{-1}	[107]
m_j	Newborn and juvenile death rate	0.796 year^{-1}	[107]
ω_m	Maternal antibody waning rate	1.79 year^{-1}	[84]
μ	Juvenile maturation rate	2.27 year^{-1}	for one-year juvenile stage
N	Population size	13–123	exact sample numbers
k	Population carrying capacity	100	estimated to match observed population oscillations (100–120)

Table 2.1 Parameter names and values used in all models. The parameters β_i, σ_j, and γ_k can each occur in two forms where (i, j, and k are each in $1,2$), but only one of each pair is nonzero for any submodel. The birth pulse timing parameter ϕ corresponded to a birth pulse peak occurring in April in Accra, Ghana [85]. The R_0 range included subcritical values due to the small population of the captive colony.

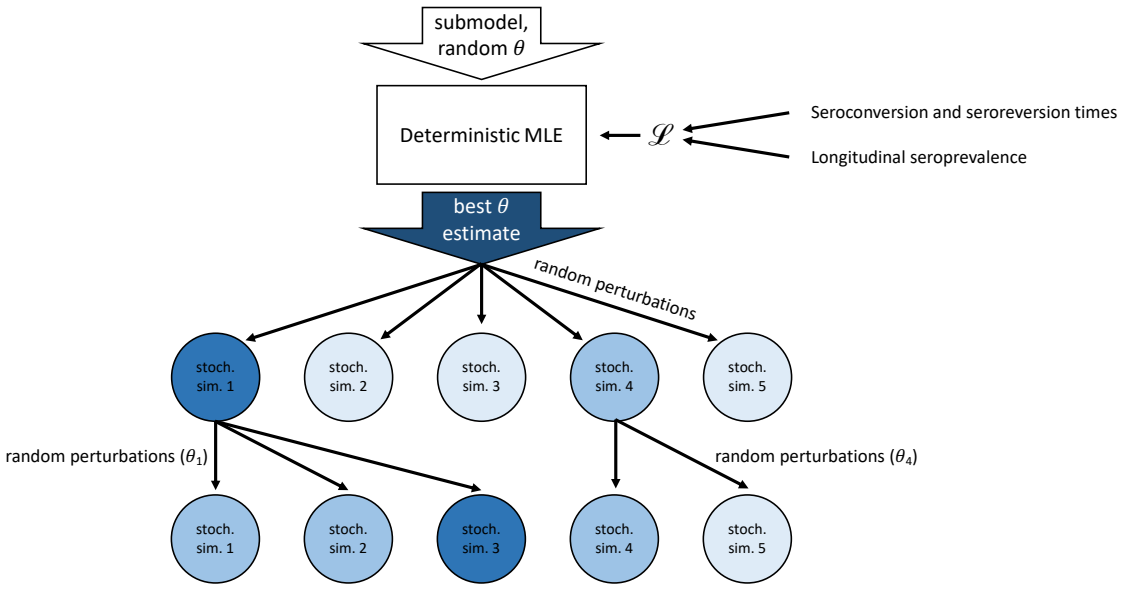

Fig. 2.5 Diagram of model fitting procedure for a single submodel with five particles and two iterations. The first stage of fitting is maximum likelihood estimation of the deterministic version of the submodel, where the likelihood function incorporates two types of data: estimates of seroconversion and seroreversion times, and sampled seroprevalences over time. The best parameter estimate (θ) is perturbed slightly for each particle (circles) then used to simulate the stochastic version of the submodel once per particle. The likelihoods of each simulation are calculated (here, darker colours represent higher likelihoods), and the parameters from the highest likelihood particles (here, particles 1 and 4) are sampled in proportion to their likelihood-based weights. These are perturbed again and used in a new round (i.e., iteration) of sampling.

2.2.4 Fitting models to data

To account for both the goodness-of-fit of model trajectories and their chances of persisting in this small, closed population, I fit models to the data in two stages (Figure 2.5). In both stages, I used a likelihood function that accounts for overall observed seroprevalence and observed distributions of seroconversion and reversion times, with the first stage using the deterministic variant of each model. In the second stage, I fit the stochastic variant of each model to additionally account for the chance of stochastic persistence in this small, isolated population. The two stages were:

1. Maximum likelihood optimisation of the deterministic variant of the model with a burn-in time of 300 years and initial parameters sampled from a Latin hypercube sample ($n = 100$) due to the frequency of parameter values resulting in a likelihood of zero.

2. Iterated particle filtering, following a similar algorithm to [111]. Instead of only iterating across time points and taking the likelihoods of observed cross-sections, I also iterated across individual seroconversion and seroreversion times and took the likelihood of each (100 iterations on 10000 particles with a cooling factor of 1% per iteration). I fixed the initial state sizes (at 5 each initial infected adult males and adult females, with other compartments fixed to their values after 300 years of the best-fitting deterministic model) and allowed the simulations to run for 8 years to assess persistence; I assumed the final year represented equilibrium and calculated seroconversion likelihoods based on the mean number of infecteds across the final year of simulation. Subsequent iterations involve:

   (a) Calculating the likelihoods of all 10000 simulations of the previous iteration (likelihood and AIC caluclated independently for each particle).

   (b) Sampling starting parameter sets proportional to weights calculated from those likelihoods.

   (c) Perturbing those starting parameter sets with an initial standard deviation of half the initial parameter value (with a minimum standard deviation of 0.1 for R_0). This standard deviation "cooled" by a factor of .01 per iteration.

   (d) **Finally simulating exact stochastic trajectories** of each model using an adaptive τ-leaping algorithm. I implemented adaptive tau-leaping [108] using the Rcpp package [112]. I set maximum and minimum time steps (10^{-3} days $\leq \tau \leq$ 0.5 days) for tau leaping. By default, time was incremented by the maximum $\tau = 0.5$ days unless there were fewer than 10 individuals in any compartment;

in these cases, τ was set to the $\min(\frac{1}{\{r_-\}})$ where $\{r_-\}$ is the set of rates causing depletion in the compartment.

Once a time step τ was chosen, events occurred based on random events $\sim Pois(\{r\}\tau)$. If these events would have caused any compartment to become negative, τ was repeatedly halved until it fell below the minimum threshold, at which point the simulation incremented by a single event according to the Gillespie stochastic simulation algorithm.

Due to uncertainties about the mechanisms of antibody responses in bats [60, 113], I performed this analysis under two different assumptions about serological status. In the first, I assumed that all non-susceptible individuals are seropositive (i.e., the E, I, and R compartments). In the second, only the R compartment was seropositive. I refer to these sets of assumptions as EIR+ and R+, respectively.

The likelihood function for each of these stages was based on cross-sectional seroprevalences, the probabilities of different seroconversion/reversion pathways within each model, and the expected time for an individual to traverse that pathway; I fit these components both to population-level seroprevalence at each sampling point and to the range of possible timings of all observed seroconversion/reversion events (i.e., a uniform distribution of times between the minimum and maximum possible times based on the sampling dates). Additional information on the likelihood function can be found in Appendix A.

2.2.5 Model comparison

For each set of assumptions (i.e., EIR+ and R+), I created a composite model by averaging parameters by Akaike weight (derived from Akaike information criteria, AIC) for that assumption [114]. I calculated a vector of model weights (W) for any one assumptions set as the mean of weights across 1000 quantiles:

$$W = \frac{1}{1000}\sum_{i=1}^{1000} w(\Delta_{[i/1000]}),$$

where Δ for any model represents ΔAIC, w is the vector of Akaike weights for all models m (with $M = 46$ models) $w_m = \frac{e^{-\Delta_m/2}}{\sum_n^M e^{-\Delta_n/2}}$, and $i/1000$ is the relevant quantile.

I also used the Akaike weights to estimate the relative importance for each model parameter and several model features comprised of parameter and model specification combinations, such as recurrent latent infection. For each set of assumptions, I calculated relative importance for each possible parameter and feature as the summed weight of all models containing the relevant parameter(s).

2.3 Results

2.3.1 Model comparison

Top-fitting models were able to reproduce observed patterns of seroprevalence, seasonality, and distributions of seroconversion/seroreversion times (Figure 2.6). The two sets of serological assumptions (EIR+ and R+) resulted in different top models according to AIC (Figure 2.6A), although both predict recurrent cycles of acute and latent infection and spontaneous clearance of latent infection:

- E, I, and R seropositive (EIR+): S[E(S)I] (Akaike weight of 0.64): model with initial exposure that can either clear without acute infection or may result in acute infection. Once acute, may recur through cycles of latent infection or may clear.
- R only seropositive (R+): S[E(S)I]RS (Akaike weight of 0.55): as in EIR+ model, but acute infection may result in temporary immunity.

Many model structures were unable to adequately predict both observed serological patterns and viral persistence in the captive colony under certain serological assumptions. For example, under the EIR+ assumption, SI/SEI (i.e., lifelong infection), S[IE]R/S[EI]R (i.e., recurrent latent infection with eventual lifelong immunity), and S[EI]/S[IE] (i.e., lifelong recurrent infection) models all resulted in a likelihood of zero when applied to our longitudinal dataset. This was often, but not always, because these models cannot produce both seroconversion and seroreversions (e.g., under the EIR+ assumption, only models where infected bats can eventually return to susceptibility can produce seroreversions).

Under the assumption that antibodies represent immunity (i.e., R+) all likely models include two types of infection cycles: recurrent latent infection and reinfection following viral clearance (Figure 2.7). Under the EIR+ assumption, potential models were more varied, but rarely included sterilizing immunity (i.e., any R compartment) and often included potentially recurrent latent infection.

2.3.2 Parameter estimates

Under the EIR+ assumption, several key parameter estimates were consistent across models, especially R_0 (Figure 2.8-A) and the immune waning rate ω. Most high-likelihood values of R_0 fell between 2 and 4, with a composite mean of 3.0. However, the R+ assumption resulted in extremely high R_0 values (up to about 200; Figure 2.8-C). The composite mean R_0 values for this assumption was 112.3.

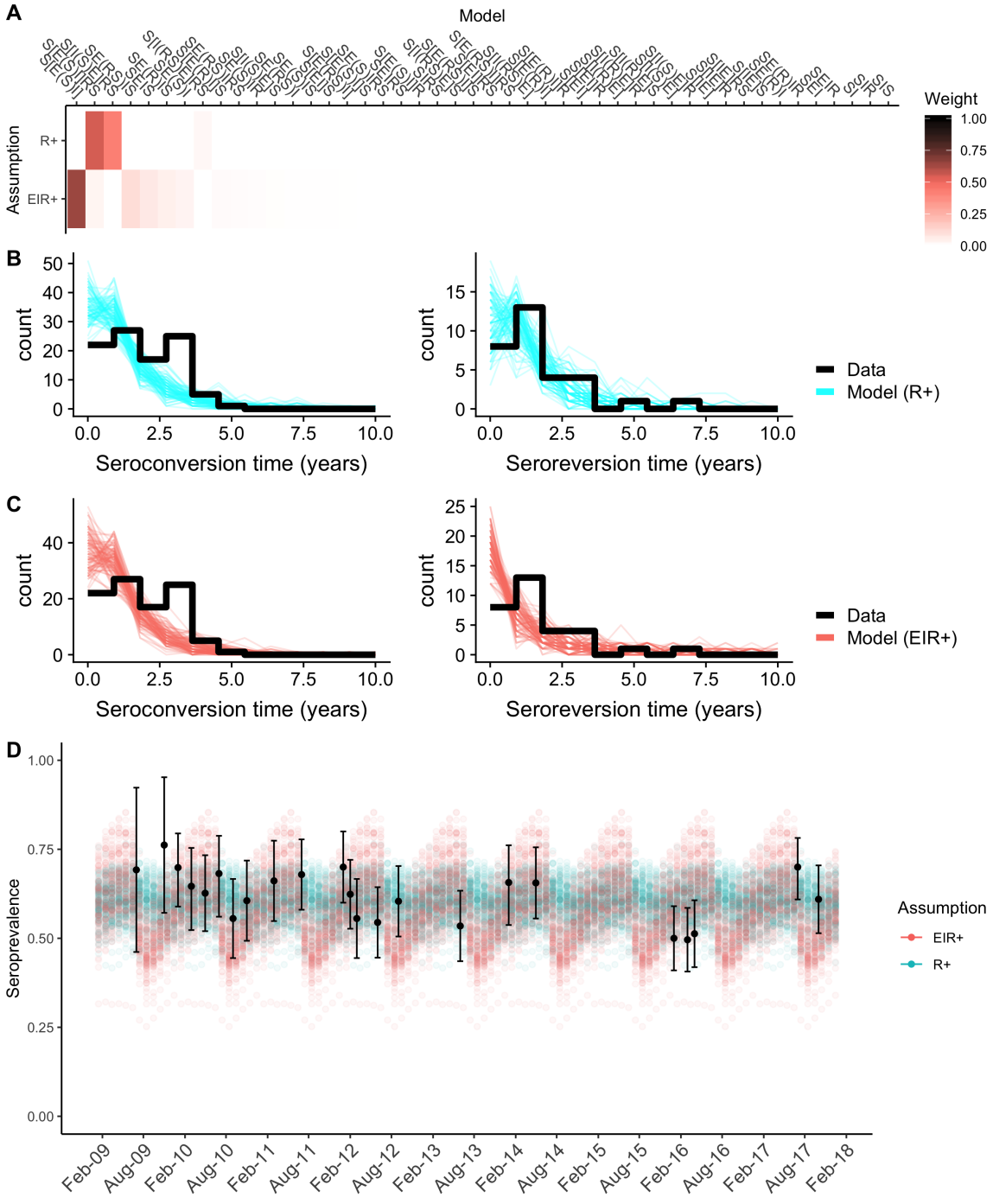

Fig. 2.6 Model fits under different serological assumptions. A. Akaike weights for each model and assumption. B–C. 100 simulated sets of predicted vs. observed seroconversion and seroreversion times under the R+ assumption (blue) and the EIR+ assumption (pink). D. 100 stochastic simulations of the best-fitting model under each set of assumptions (EIR+ in pink; R+ in blue). Each simulation used parameters sampled according to particle weights. Measured seroprevalences and 95% binomial confidence intervals are shown in black.

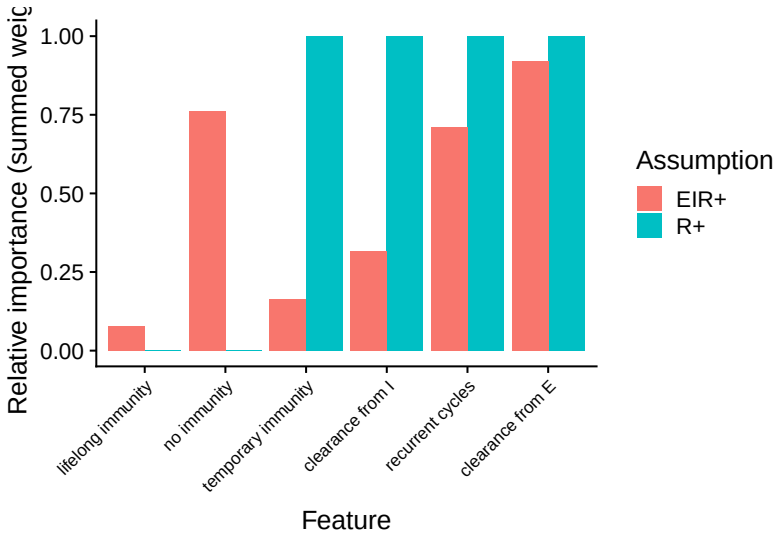

Fig. 2.7 Relative feature importance (i.e., summed Akaike weights of models incorporating each feature; see Supplemental Text 2.4 for feature definitions) under each set of assumptions about serological status (EIR+ and R+).

Estimated immune waning times were remarkably consistent across all models and both sets of assumptions (Figure 2.8). Under the EIR+ assumption, all but one model predicted immunity lasting either 1–2 years or lasting lifelong (10+ years) or longer on average. Under the R+ assumption, predicted immunity lasts just under 1 year for all probable submodels.

While recurrence and reinfection after viral clearance were supported in nearly all high-likelihood models, the balance of these mechanisms differed by serological assumption (Table 2.2 and Figures 2.9–2.10). However, under both assumption sets seroconversion and seroreversion processes were best supported by frequent cycles of recurrent infection and occasional clearance.

Result	EIR+		R+	
	Top model	Composite	Top model	Composite
Representation	S[E(S)I]	–	S[E(S)I]RS	–
R_0	2.0	3.0	66.7	112.3
Shedding duration	1.0 months	2.7 days	1.6 weeks	4.5 hours
Latency/incubation period	2.1 hours	1.8 hours	3.0 hours	2.9 hours
Immunity duration	–	88 years	2.3 years	1.3 years

Table 2.2 Top and weighted composite models under each set of serological assumptions. All top and composite models include reinfection, recurrence, and non-infectious infections. Composite models are mean parameters weighted by submodel Akaike weights.

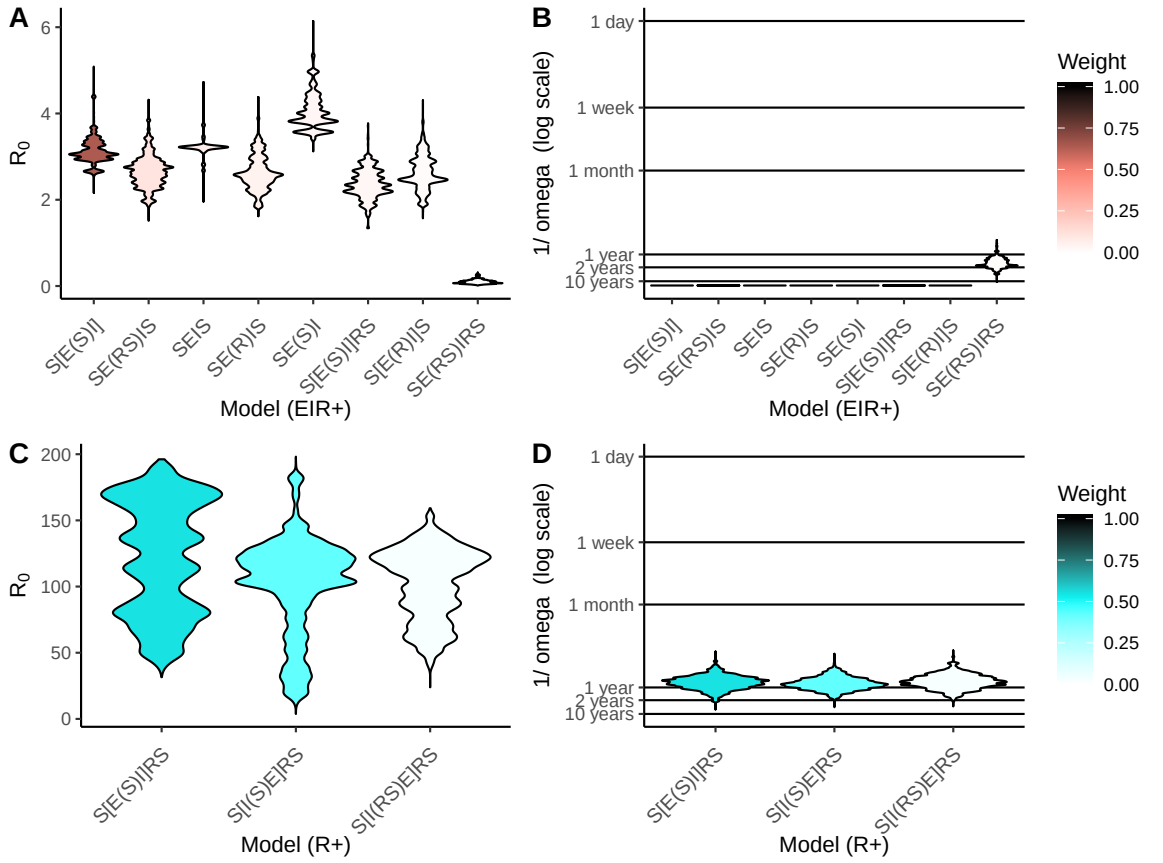

Fig. 2.8 Distributions of predicted parameter values for models with at least 1% Akaike weight under the EIR+ (A-B) and R+ (C-D) assumptions. R_0 values (A and C) and immune waning durations (B and D) are weighted by particle likelihood in last ten iterations of stochastic captive colony fitting procedure. Models are ordered according to decreasing weight. Most models under the EIR+ assumption result in identical predictions of lifelong immunity (B) because they do not include the relevant parameter (ω).

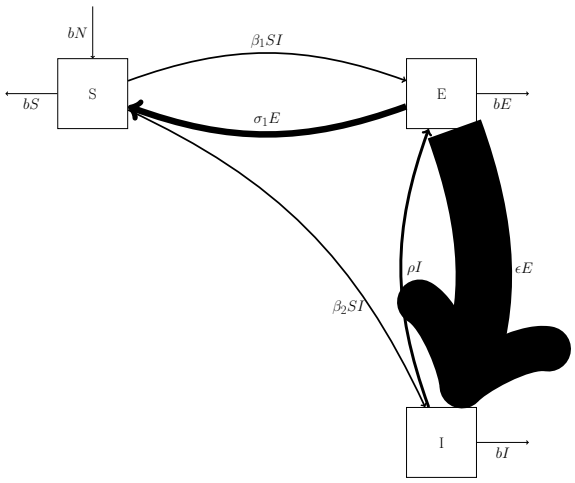

Fig. 2.9 Flow diagram of top model (S[E(S)I]) under EIR+ assumption, with line weights corresponding to the square root of fit parameter estimates.

Weighted estimates for other parameters were more variable (Figures 2.11–2.14) but exhibit several trends. For example, the duration of acute infection predicted under the R+ assumption is between hours to about one week under all but three models with nonzero likelihoods; these three models predict long infectious periods but are three of the four worst-fitting models. For both sets of assumptions, cycles of acute and latent infection are predicted to be very short (between hours and days).

2.4 Discussion

Observed patterns of seroprevalence, seroconversion, seroreversion and persistence of henipaviruses in a captive colony of *E. helvum* in Ghana were best explained by cycles of reinfection with occasional viral clearance, possibly alongside cycles of recurrent latent henipavirus infection and/or non-infectious infections. For the best-fitting model under the EIR+ assumption (i.e., individuals in the E, I, and R compartments are seropositive), a latently infected bat is about 75 times more likely to undergo at least one more short bout of acute infection than to spontaneously clear infection. This leads to an expected duration of infection (including both latent and acute stages) of about 4.5 years. For the best-fitting model under the R+ assumption (i.e., only individuals in the R compartment are

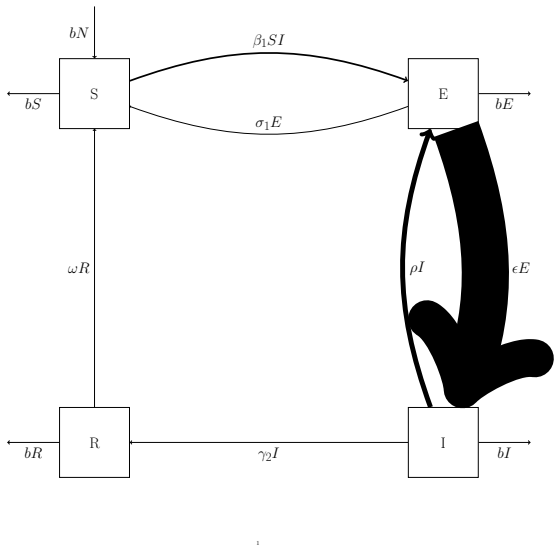

Fig. 2.10 Flow diagram of top model (S[E(S)I]RS) under R+ assumption, with line weights corresponding to the square root of fit parameter estimates.

seropositive), an acutely infected bat is about 40 times more likely to return to a latent state than to recover and develop temporary immunity, with an expected duration of infection of about 10 months. These expected durations are, however, highly variable even for a single parameter value, because there is a wide distribution of the number of infection cycles a single individual may experience. Minimum infection times are possible on the scale of about a day (between 1–3% of individuals under both sets of assumptions), while maximum infection times may last throughout a bat's expected lifetime (although with <0.1% probability). The variability in infection length and frequent support for multiple infection pathways may suggest high individual heterogeneity in response to infection; e.g., some individuals may be able to effectively suppress infections while others, perhaps in response to pregnancy or other sources of physiological stress [50, 115], experience acute infection or recurrence. Measuring differences in infection and antibody dynamics at the individual level could provide additional support for the existence of multiple infection pathways and could help disentangle these processes.

Both sets of serological assumptions (EIR+ and R+) consistently predict rapid cycles of acute and latent infection that correspond with the cyclic nature of seroprevalence in the observed data. This suggests viral shedding is sporadic, in accordance with observations of henipaviruses in nature, although we note that a transition time of a few hours is unlikely

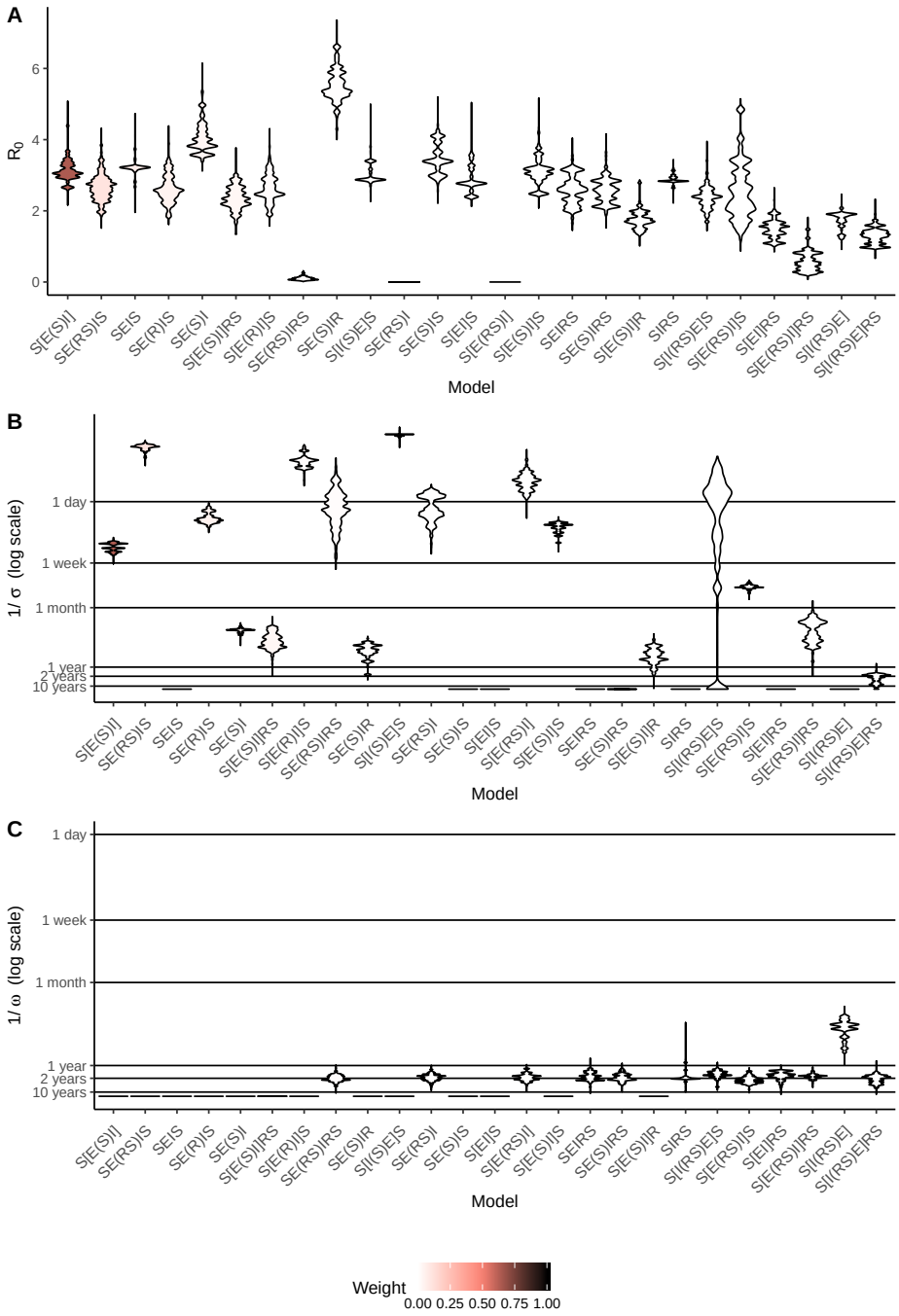

Fig. 2.11 Distributions of predicted parameter values under the EIR+ serological assumption. R_0 values (A), time to clearance from E ($1/\sigma$, B), and immune waning durations ($1/\omega$, C) are weighted by particle likelihood in last ten iterations of stochastic captive colony fitting procedure. Models are ordered according to decreasing weight.

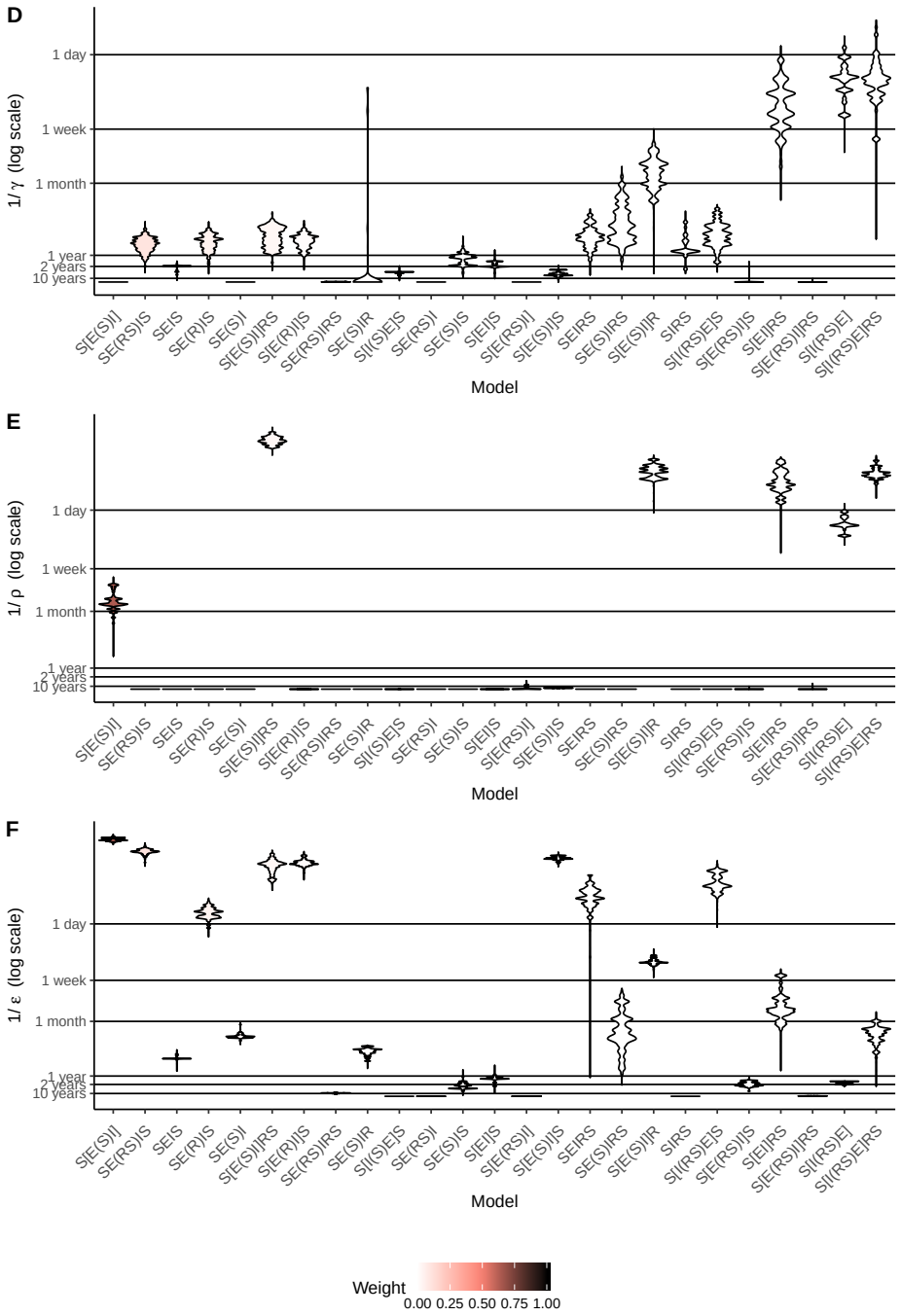

Fig. 2.12 Distributions of predicted parameter values under the EIR+ serological assumption (continued). Time to clearance from I ($1/\sigma$, D), incubation time or time to recurrence ($1/\rho$, E), and time to revert to latency ($1/\varepsilon$, F) are weighted by particle likelihood in last ten iterations of stochastic captive colony fitting procedure. Models are ordered according to decreasing weight.

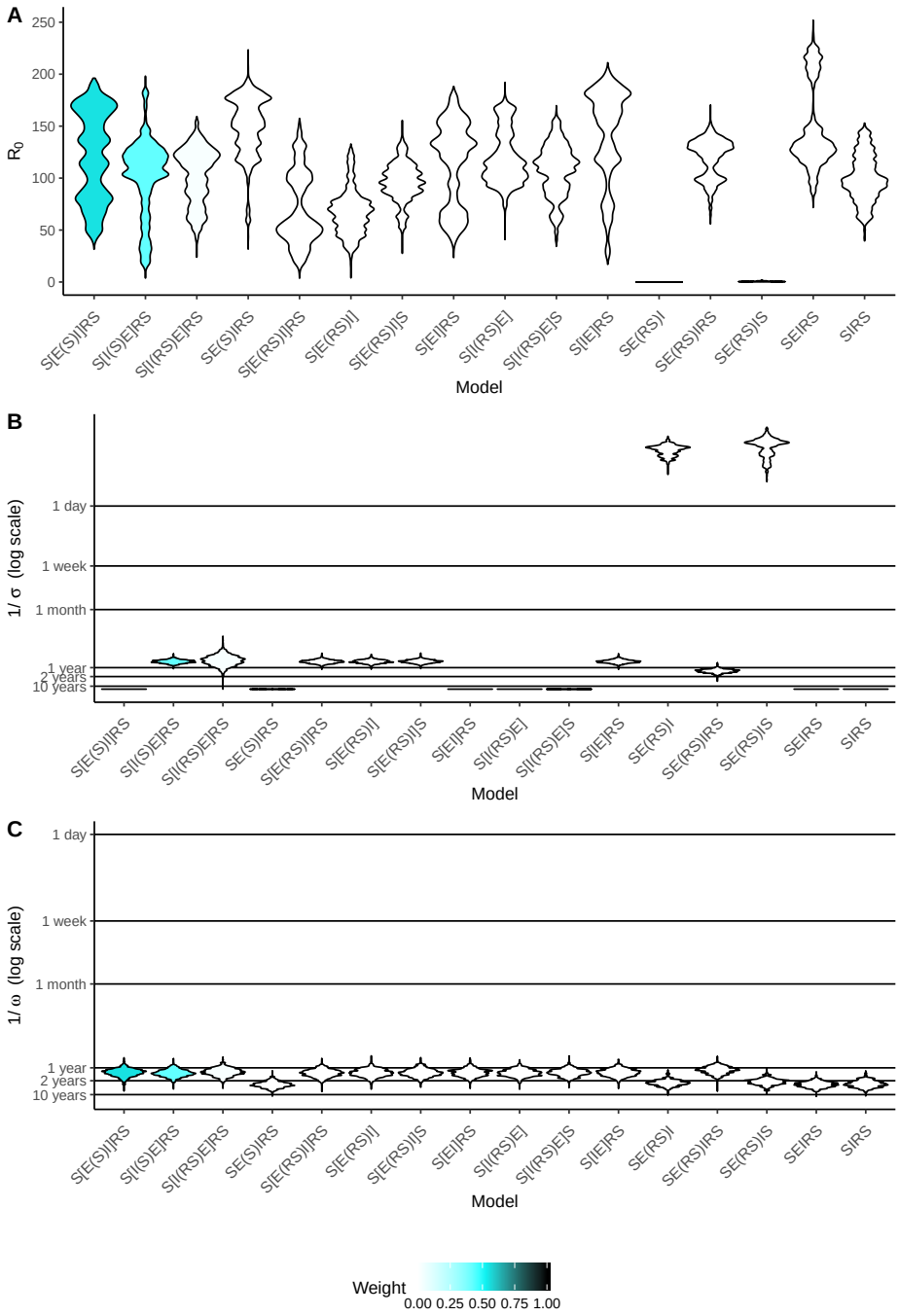

Fig. 2.13 Distributions of predicted parameter values under the R+ serological assumption. R_0 values (A), time to clearance from E ($1/\sigma$, B), and immune waning durations ($1/\omega$, C) are weighted by particle likelihood in last ten iterations of stochastic captive colony fitting procedure. Models are ordered according to decreasing weight.

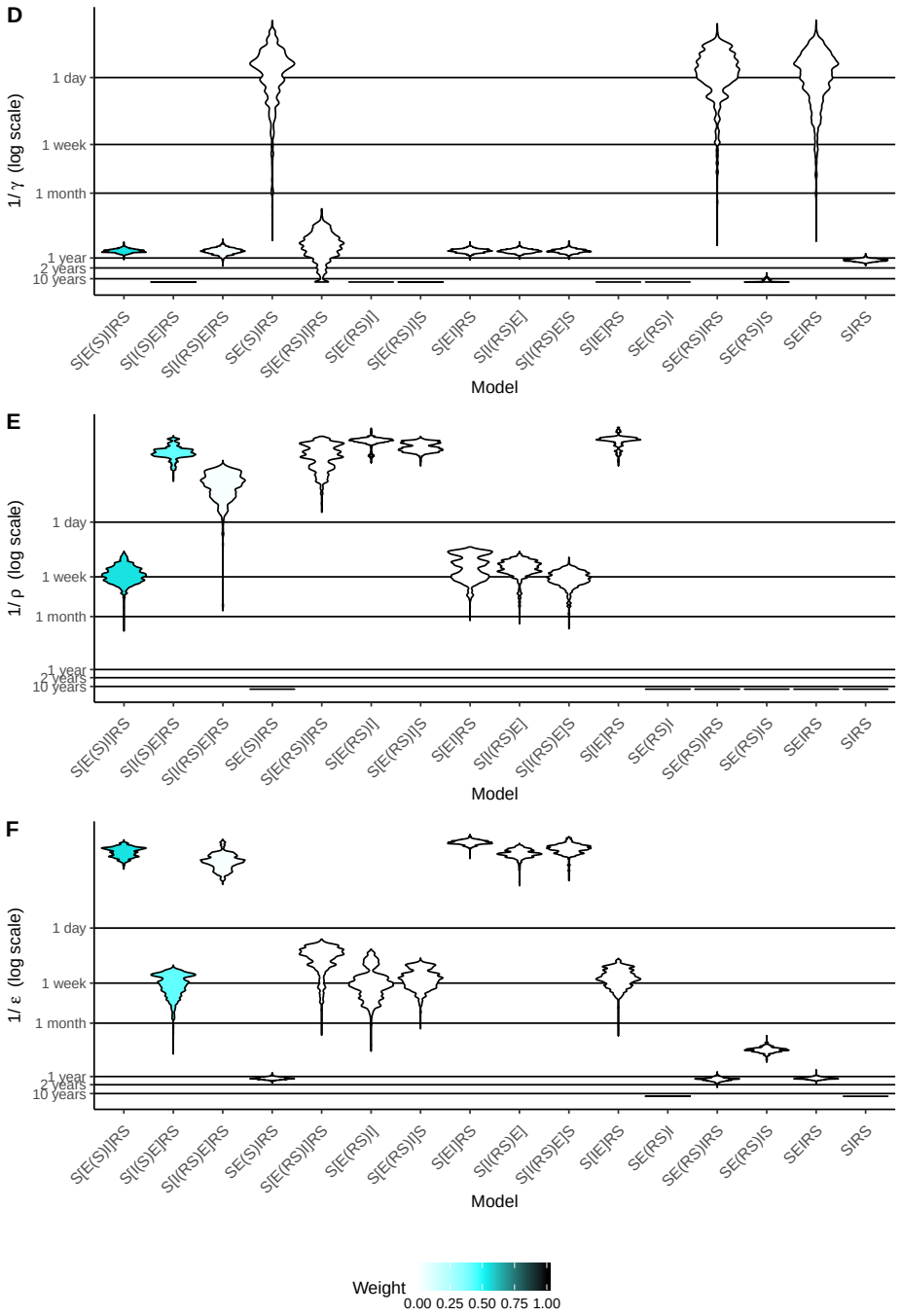

Fig. 2.14 Distributions of predicted parameter values under the R+ serological assumption (continued). Time to clearance from I ($1/\sigma$, D), incubation time or time to recurrence ($1/\rho$, E), and time to revert to latency ($1/\varepsilon$, F) are weighted by particle likelihood in last ten iterations of stochastic captive colony fitting procedure. Models are ordered according to decreasing weight.

to represent a true immune response [74, 80]. The likelihood function used in this analysis (Appendix A) may favour excessively short cycles of acute and latent infection because these can provide a wide range of probable serological transition times. Although experimental infection studies have failed to provide reliable data on the patterns and duration of henipavirus shedding [65], our results indicate that cycles of recurrent infection are able to reflect naturally observed variation in serological transition times (perhaps reflecting individual heterogeneity [116] or dose-dependency [117] in immune responses).

Observed patterns of seroprevalence, seroconversion, and seroreversion could not be explained by models with simple immunizing infection or recurrent latent infection alone. Especially under the R+ assumption, most models had likelihoods of zero, including many models with immune waning. SEIR models—which may apply to Marburg virus dynamics in fruit bats [110, 118, 119]—and SEI models with or without immunizing asymptomatic infections—which may explain rabies persistence in neotropical and temperate bats [120–122]—were notably incapable of explaining observed patterns of henipavirus serology in the captive E. helvum colony under either serological assumption. Even models of lifelong latent infection were unable to explain these patterns under our current model assumptions. This includes the S[IE] model which had been suggested (under the acronym of SILI) for henipavirus dynamics in fruit bats [60]. Thus, while our study supports the existence of recurrent infection in bats, it also suggests a need for additional features of the cycle of infection and immunity.

Variations both within and between assumption sets—including apparently unrealistic predictions—are informative about which dynamic features are required to explain observed patterns. The extremely high predicted R_0 values under the R+ assumption, for example, may suggest that long-term viral persistence in this small, closed population is unlikely within plausible parameter ranges if all seropositive individuals are immune. Indeed, the data implies that 60–70% of bats would be immune under the R+ assumption, which may require a very high value of R_0 for the virus to persist; these values allow some individuals to be infected long-term, maintaining infection in the population and avoiding stochastic extinction that is otherwise likely with only a few dozen susceptible individuals. However, due to the lack of prior constraints on the range of parameter values explored during the fitting process, we cannot rule out that there are other plausible parameter sets with lower R_0 values that were excluded by our likelihood-maximisation method.

One of the limitations of this analysis is the remaining uncertainty about the interpretation of serological data in the absence of virological data. Ideally, measurements of both infection and serological status could allow stronger inferences. However, while viral shedding in urine has been readily detected in wild bat populations, no consistent, accurate, and noninvasive

test of an individual's true henipavirus infection status currently exists. Some immunological differences between bats and other mammals may exist; as additional research clarifies the role of their antibody responses to infection, and henipavirus infection in particular, the appropriate set of serological assumptions may become clearer [119, 123, 42, 124]. In addition, this analysis relied on the classification of bats as either seropositive or seronegative, which is achieved by choosing a mean fluorescence index (MFI) cutoff for the Luminex serological assays. Because interpretation of bats' antibody responses to henipavirus infection remains uncertain [75], this may introduce some bias in our results. However, the distributions of seroconversion times and seroreversion times based on the data remains similar across a wide range of cutoff values (2.3).

Explicit modelling of antibody titres and measurement uncertainty (if necessary, with an assay that more consistently and directly maps to individual infection status) could improve inference but would require additional information about the role of antibodies in bats' response to henipaviruses. Modelling antibody titres instead of seropositive vs. seronegative status would also require more frequent sampling timepoints. Other limitations of our analysis include the assumption of a steady state within the colony. More longitudinal studies of bat henipavirus dynamics in wild populations could resolve these issues, although low rates of recapture make such studies difficult [125]. Finally, any additional bounds on our parameters could improve inferences. For example, constraining the duration of acute infection/viral shedding in particular could prevent any bias in our captive colony fitting algorithm shows toward short acute-latent cycle times.

Despite these limitations, this work has narrowed the range of plausible hypotheses for persistence and circulation of henipaviruses in a fruit bat reservoir host in Africa, using uniquely long-term and well-controlled data from a captive colony. Because the captive colony in this study has been isolated from wild bats, has had minimal human intervention, has a well-documented demographic history, and has demonstrated ongoing henipavirus circulation for almost a decade, it is an ideal system to study the long-term individual- and population-level dynamics of henipaviruses with minimal risk of an external force of infection. This generalised SEIR model framework has allowed comparison of a diverse range of models and parameters, representing many potential within-host mechanisms rather than assuming such mechanisms in the context of uncertain serological interpretation.

This expanded SEIR framework lends itself to exploring hypotheses for the hidden process of viral circulation in reservoir hosts more broadly. This framework could be useful for generating transmission and within-host hypotheses for other low-morbidity pathogens. Application of this framework to such pathogens may be particularly useful to develop testable predictions to target field-based and experimental work [95]. In the case of henipaviruses in

bats, models of reinfection following viral clearance and seasonally recurring latent infection have been considered as possible explanations of seasonal shedding [60]. Future work on the relationship between antibody presence and infection status, as well as examination of heterogeneity in responses to infection, could help disentangle these hypotheses further. While we cannot conclusively say which mechanism underlies this process, we have extended these explanations into a wider set of hypotheses, applied them to several types of real-world data, and supported the existence of certain dynamic features of henipaviruses in *Eidolon helvum*.

Chapter 3

The role of domesticated animals

3.1 Background

The list of bat-borne viruses known to cause morbidity and mortality in domesticated animals, wildlife, and people continues to grow [126]. Many such viruses have pandemic potential and cause severe disease in recipient hosts, raising concern for public health, agriculture, and conservation [62, 49]. The routes of associated spillover events vary widely: from sporadic bat-to-human Nipah virus (NiV) spillover events over at least the last 15 years in Bangladesh [69, 127] to the 1998-1999 pig-amplified NiV outbreak in Malaysia and Singapore, which resulted in the culling of over one million pigs and the deaths of more than one hundred people [128, 129]. In Australia, outbreaks of disease caused by Hendra virus (HeV), which together with NiV and the closely related Cedar virus comprises the genus *Henipavirus* [130], have resulted from bat-to-horse transmission with occasional spread among horses or transmission from sick horses to their veterinarians and handlers [131]. Henipavirus disease outbreaks have been characterized by stuttering chains of transmission, as have most recorded outbreaks of filovirus diseases caused by Marburg virus (MARV) and ebolaviruses [132, 49]. In contrast, the West African outbreak of Ebola virus disease (EVD) in 2013–16 was characterized by sustained human-to-human transmission on an apparently unprecedented scale. This outbreak, which caused a massive death toll and societal impact,

Authorship note: As noted in the Declaration of this document, some of the text below is excerpted or adapted from a previously published article [4]. All text is in my own words. All uses of the pronoun "I" refer to methods I carried out independently, while uses of the pronoun "we" indicate contributions of the co-authors on the relevant paper.

may have resulted from a single bat-to-human spillover event (although this does not mean it was caused only by this most proximate origin point) [133–136].

Domesticated animals used as food sources, companions, or workforce, are able to act as bridges for viral transmission between wildlife (including bats) and people [137]. Such animals link "the field" and "the home," often having closer physical contact with both wildlife and people than wildlife and people typically have with one another. The context of intensive agriculture, in which livestock are held in large, dense, and highly-connected populations, provides an ideal opportunity for viral amplification [138, 139], thereby increasing the risk of otherwise improbable spillover events to people as well as causing significant economic and animal health costs.

While clear examples of domesticated animals as bridging hosts are availble for henipaviruses, the potential role of domesticated animals as bridging species for most filoviruses is less clear. This lack of clarity can be attributed in part to the different ecological and social/agricultural contexts of regions of documented henipavirus and filovirus spillover events. For example, the kind of intensive livestock production that facilitated NiV spillover in Malaysia and possibly Reston ebolavirus (RESTV) spillover in the Philippines [140] is uncommon in sub-Saharan Africa, where most Marburg viral disease and EVD outbreaks have occurred [141]. Also, evidence for non-domesticated wildlife, such as apes and duikers, as bridging species for ebolaviruses has made study of domesticated animals as hosts a less urgent priority [142, 143]. Understanding the potential role of domesticated animals in filovirus transmission is important nonetheless, particularly given ongoing intensification of livestock production and its encroachment into new wildlife habitats in Africa [144–148].

The emergence of bat-borne henipaviruses and filoviruses has prompted frequent calls for a "One Health" approach to mitigating their risk to people and animals [49, 149–151], involving multidisciplinary collaboration to connect the health of wildlife, domesticated animals, people, and the environment. Despite the importance of such an approach to zoonoses with complex life histories, few studies have explicitly considered the role of domesticated animals in the spillover of bat-borne viruses. This omission creates a major gap in our understanding of the epidemiology and ecology of these viruses.

Here I systematically review the available literature on domesticated animals as hosts of two sets of bat-borne viruses with zoonotic potential: the henipaviruses NiV and HeV and the filoviruses MARV and ebolaviruses. I summarise the existing evidence for the abilities of domesticated animal species to host, sustain intraspecific transmission, and act as interspecific spillover species for each virus. In addition, we use our quantitative review to understand where research effort has focused and to identify understudied domesticated animal species, regions, and viruses, as well as more general knowledge gaps. Finally, I present a case study

of filoviruses in Africa considering the context of global capacity challenges, agricultural intensification, and zoonotic disease emergence.

3.2 Methods and materials

To assess the evidence for the abilities of domesticated animals to host and transmit henipaviruses and filoviruses, I conducted a quantitative literature review based on a Web of Knowledge search using the following terms and criteria:

```
(TS=(morbillivirus OR Nipah OR Hendra OR henipavirus OR Ebola OR
ebolavirus OR Marburg OR filovirus) AND TS=(pig OR swine OR porcine
OR cattle OR cow OR bovine OR sheep OR ovine OR goat OR caprine
OR horse OR equine OR camel OR dog OR canine OR cat OR feline OR
livestock OR domesticated OR pet OR poultry OR chicken OR galline
OR duck OR anatine OR buffalo OR bubaline OR donkey OR asinine)) AND
LANGUAGE:(English) AND DOCUMENT TYPES:(Article OR Note)
```

This search produced 1276 results as of March 27, 2017, of which 72 studies fit the following inclusion criteria:

1. They pertained to henipa- or filovirus infection in our selected set of domesticated animals (e.g., not only in rodents such as guinea pigs); this excluded articles that are about veterinary practice or animal behavior alone without specific reference to viral infection.

2. They were not comment, opinion, or review articles.

3. They had not been retracted nor followed by an expression of concern.

While reading the papers identified by this search, I found additional unpublished or informally published reports (e.g., on government websites). Results from these additional reports are not included in any summary statistics or figures, but they are noted (and identified as outside of our search) in the results and discussion sections where they provide relevant context.

I categorized Nipah viruses by clade (NiV-B for Clade I NiV originating in Bangladesh; NiV-M for Clade II NiV originating in Malaysia or elsewhere in Southeast Asia [152]) and ebolaviruses by species (e.g., *Zaire ebolavirus* (EBOV), *Reston ebolavirus* (RESTV)) where available; otherwise I used the narrowest classification provided by the study. Animal categories included were pigs, horses, cows, small ruminants (i.e., sheep and goats), dogs, cats, buffaloes, donkeys, and poultry (i.e., chickens and ducks). I included one entry in

our database per animal-virus pair; this resulted in some overlap in terms of both studies represented and outbreaks described.

For each domesticated animal-virus species pair within each study, I evaluated whether any evidence, even if limited, was sought or provided for the following traits or abilities of the host species: susceptibility, disease phenotype, a physiological or mechanical mechanism for virus transmission, demonstrated virus transmission to conspecifics, demonstrated inter-species virus transmission (and, where relevant, the other species infected), natural (i.e., non-experimental) infection, and a demonstrated role in zoonotic spillover during the course of an outbreak. I considered studies to provide evidence both for those abilities they directly tested and for those that were prerequisite for their findings (e.g., I considered studies describing HeV transmission between horses as evidence of the susceptibility of horses to HeV). Where possible, I recorded negative findings as distinct from a lack of findings.

I accessed global domesticated animal counts by country in 2014 from FAOSTAT [153]; this database includes official national data where available, supplemented by estimates from the Food and Agriculture Organization of the United Nations (FAO). I accessed filovirus disease outbreak data from the Centers for Disease Control and Prevention (CDC) to place research effort in Africa in the context of the distribution of past outbreaks [154, 155]. To compare research effort applied to domesticated animals with that applied to bats, I collected studies that fit criteria 2 and 3 above, applied to henipa- or filovirus infection in bats in non-controlled settings in Africa, as returned by the following search terms:

```
(TS=(Nipah OR Hendra OR henipavirus OR Ebola OR Marburg OR
filovirus) AND TS=(bat) AND TS=(Africa OR Algeria OR Angola OR Benin
OR Botswana OR Burkina Faso OR Burundi OR Cabo Verde OR Cameroon OR
Central African Republic OR Chad OR Comoros OR Congo OR Cote d'Ivoire
OR Djibouti OR Egypt OR Guinea OR Eritrea OR Ethiopia OR Gabon OR
Gambia OR Ghana OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar
OR Malawi OR Mali OR Mauritania OR Mauritius OR Morocco OR Mozambique
OR Namibia OR Niger OR Nigeria OR Rwanda OR Sao Tome OR Principe OR
Senegal OR Seychelles OR Sierra Leone OR Somalia OR Sudan OR Swaziland
OR Tanzania OR Togo OR Tunisia OR Uganda OR Zambia OR Zimbabwe)) AND
LANGUAGE: (English)
```

3.3 Results

3.3.1 Susceptibility, clinical signs, and natural infection

Available evidence for the capabilities of domesticated animal species to host, transmit, and contribute to the zoonotic spillover of henipa- and filoviruses showed considerable species biases (Figure 3.1). No MARV studies examined any domesticated animal as potential hosts. No studies examined camels, buffaloes, or donkeys as hosts of any henipavirus or filovirus. No studies investigated any relationships between cattle or poultry and ebolaviruses or directly tested the susceptibility of cattle or poultry to HeV. Experimental infection studies involving horses, goats, and sheep suggest they are not highly susceptible to EBOV infection [156]. All remaining animal-virus pairs demonstrated some level of susceptibility to henipaviruses or filoviruses (left column, Figure 3.1).

Of all domesticated animal species, pigs showed the most evidence for a significant role as amplifiers of zoonotic henipa- and filoviruses. They are demonstrated amplifiers of NiV-Malaysia (NiV-M), with serological studies of pigs, case-control studies of people, and successful control via culling all supporting their critical role in the 1998-1999 NiV outbreak in Malaysia and Singapore [129]. Pigs have also shown high seroprevalence against NiV-Bangladesh [157]. When experimentally infected with HeV, pigs demonstrate similar clinical signs, including fever and respiratory signs, as when naturally infected with NiV [158, 159]. About 5% of pigs blood-sampled from two villages in Ghana tested positive for non-neutralizing antibodies to henipaviruses, suggesting a broad geographical range of natural henipavirus infection in pigs [78]. When infected with the filovirus RESTV, which naturally occurs in the Philippines, pigs exhibit no clinical signs [140, 160, 161, 148]. Upon experimental infection with EBOV, however, pigs develop fever and pulmonary hemorrhage [162]. Mass mortalities of bush pigs in Gabon have been reported concurrent with EVD outbreaks in people and other wildlife, but infection in pigs was not confirmed in these cases [163].

Horses have exhibited susceptibility to NiV-M infection in experimental studies [128], and horses naturally infected with NiV in the Philippines have suffered acute neurologic disease, often characterized by circling, ataxia, and sudden death [164]. The horse is a well-known host of HeV in Australia, apparently following direct or indirect infection from bats in multiple outbreaks [65, 165]. Infection in horses remains rare, however, with cross-sectional studies of asymptomatic horses and (informally published) investigations of clinically ill horses rarely showing evidence of past or current infection [166–168]. HeV infection in horses results in a wide range of signs, often including severe respiratory and/or neurological disease such as pulmonary edema and vascular lesions in the lungs and brain [169]. High

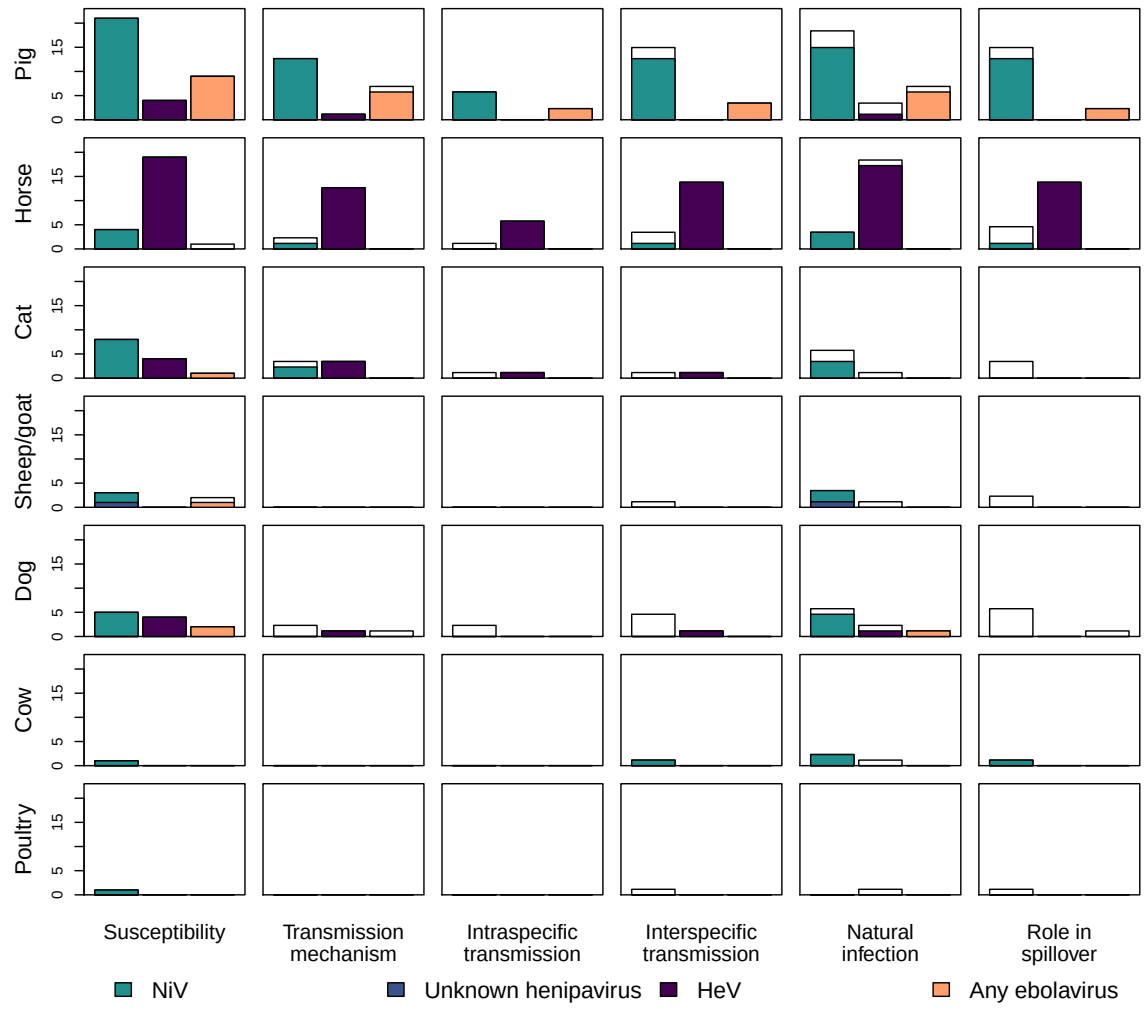

Fig. 3.1 Number of studies seeking (white) or providing (color) evidence of domesticated animal species as hosts of each of Nipah virus, unknown henipaviruses (stacked with Nipah virus for visibility), Hendra virus, and ebolaviruses. Marburg virus, camels, buffaloes and donkeys are excluded from the figure as no associated studies were identified. Types of evidence considered are: demonstrated susceptibility to each virus, demonstrated transmission mechanisms thereof, evidence of transmission between animals of the same species, evidence of transmission from a domesticated animal species to some other species, evidence of natural infection (e.g., immunity during an outbreak or in a natural setting), and evidence of a role of spillover to humans in a confirmed outbreak.

viral loads in response to HeV challenge have been confirmed experimentally [170]. The horse is not susceptible to EBOV disease [156].

There is serological evidence of natural NiV infection of goats, but not sheep, during outbreaks in both Malaysia and Bangladesh [129, 171, 157]. Non-neutralizing antibodies of an unknown henipavirus were reported from a sheep and a goat in Ghana [78]. No studies have examined or described henipavirus disease in these species. It appears that neither sheep nor goats are susceptible to ebolavirus disease; sheep exhibit a neutralizing antibody response to immunization with EBOV glycoprotein [172], and goats and sheep are insensitive to challenge with live EBOV [156].

Experimental infections of the domestic cat have demonstrated this species' susceptibility to HeV [173, 170, 174] and NiV [158, 175, 176]. Cats infected with henipaviruses develop severe respiratory disease, with typical signs including pulmonary edema and interstitial pneumonia [174]. Natural infection of cats with NiV has also been reported; several cats died after eating the meat of NiV-infected horses in the Philippines in 2014 [164], and seropositive cats were detected during the index outbreak in Malaysia in 1999 [128]. In contrast, sixty-four cats were blood-sampled following the first known HeV outbreak in Queensland, Australia, but serum neutralization testing provided no evidence of infection [166]. Of two cats sampled in Ghana during a wider study on henipavirus epidemiology, both tested seronegative to henipavirus [78]. The only investigation of the susceptibility of the domestic cat to any filovirus infection is an in vitro study [177]. This study assessed the glycoprotein-mediated entry of EBOV into primary feline cells, and found they were more susceptible to EBOV entry than canine cells, but less susceptible than human or primate cells [177]. We found no evidence that either natural or experimental infection of the domestic cat with EBOV or any other filovirus has been investigated.

Several studies have reported high seroprevalences to NiV in the domestic dog during disease outbreaks in Malaysia (where up to 57% of tested dogs were seropositive [178]) and the Philippines (where all four dogs with contact with sick horses were seropositive [164]) in the absence of clinical disease. Dogs experimentally infected with HeV show few to no clinical signs despite viral replication and the excretion of viable virus in oral secretions and urine [179]. To date, however, only two dogs have been demonstrated to be naturally infected with HeV [180, 181]; only one of these cases [181] was returned by our search. Both animals lived on farms in Australia where there were HeV outbreaks in horses, showed minimal clinical signs of disease, and were euthanized as a precaution to protect public health [180, 182]. Post mortem examination was reported for one of these dogs and revealed diffuse vasculitis throughout the body [181]. We could only find one investigation of filovirus

infection in the domestic dog. The authors of this study reported a high seroprevalence of EBOV-reactive antibodies in dogs in Gabon in the absence of clinical disease [183].

Minimal data exist for both poultry and cattle as hosts of henipaviruses and no data exist for either as hosts of filoviruses. Contact with sick cattle has been associated with NiV seropositivity among people in Bangladesh [171]. Chowdhury et al. [157] tested domesticated cattle in a NiV-prone region of Bangladesh for antibodies to NiV glycoprotein and found 6.5% seropositivity. This is the only attempt, to our knowledge, to test cattle for evidence of NiV infection. We identified two studies which examined NiV infection in poultry; one failed to find serological evidence of infection during NiV outbreaks among a small ($n = 10$) sample of unspecified bird species [171], and one demonstrated mortality in chicken eggs experimentally inoculated with NiV-M [184]. We found one study that looked for evidence of natural HeV infection in cattle and poultry (following the first known outbreak of this disease), and the authors failed to find serological evidence of infection in 276 sampled cattle or 21 combined turkeys, geese, and chickens [166]. No studies returned in our search have looked for evidence of susceptibility to, or infection with, filoviruses in either cattle or poultry, but one study that fell outside our search terms reported no evidence of EBOV infection in tissues from fewer than five chickens collected in the Democratic Republic of the Congo and Cameroon [185].

3.3.2 Intra- and interspecific transmission

All interspecific transmission routes for which we found evidence of domesticated animal involvement are summarized in Figure 3.2. Nipah virus circulation among pigs and transmission from pigs to people were well-documented in the 1998-1999 NiV outbreak in Malaysia and Singapore [186] but neither have been observed for HeV. Dogs and cats in contact with pigs became infected during this NiV outbreak [128]. Phylogenetic and serological evidence suggest that RESTV has circulated among pigs for decades [140], and farmers and slaughterhouse workers in contact with infected pigs in the Philippines have tested seropositive to RESTV antibodies, suggesting pig-to-human spillover [161, 187]. Experimental studies have demonstrated the ability of pigs to transmit EBOV to other pigs [162] and to macaques [188]. A 2014 NiV outbreak in the Philippines involved multiple horses and their handlers as well as people, cats, and dogs that consumed horse meat; epidemiological evidence from this outbreak is highly suggestive of horse-to-human spillover but is inconclusive about horse-to-horse transmission [164]. In addition to infecting their veterinarians and human handlers, HeV-infected horses have infected other horses with which they shared a stable as well as at least one dog [189, 190, 170, 191, 181]. This transmission was likely mediated by

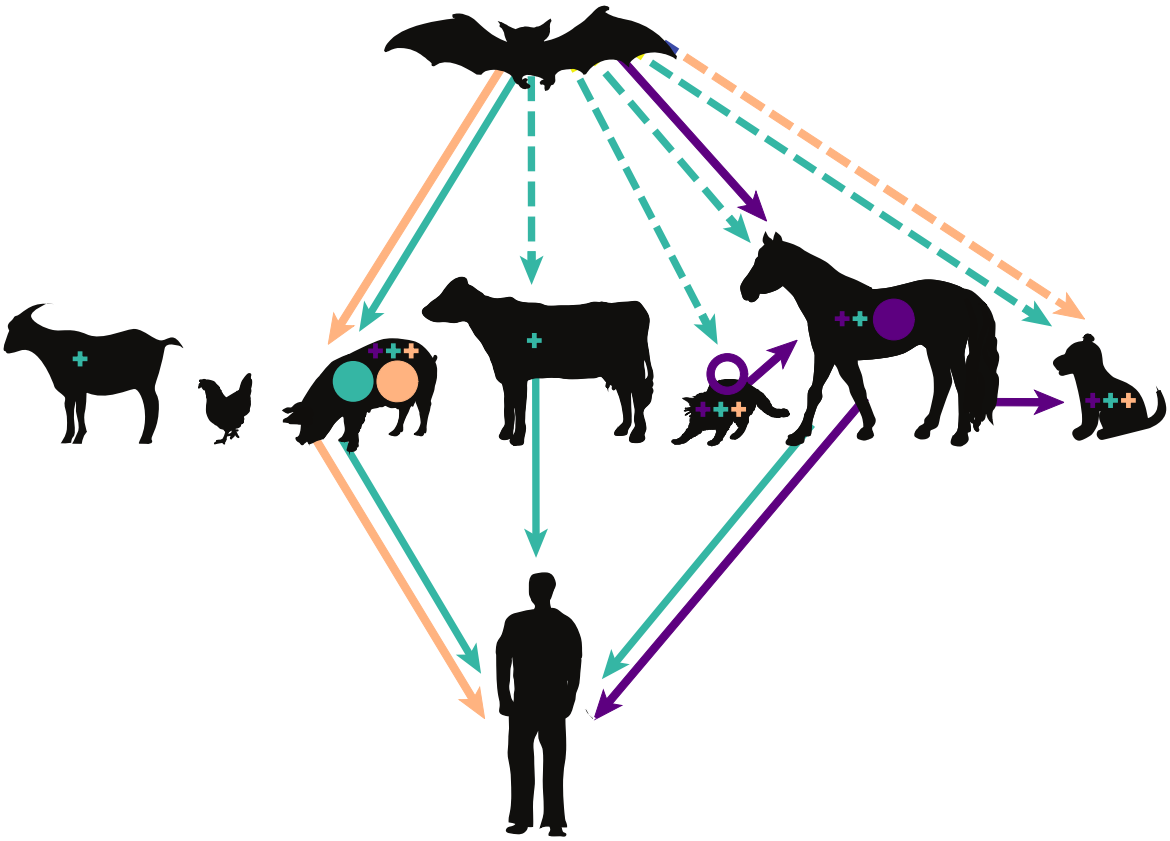

Fig. 3.2 Summary of suggested routes of interspecies transmission for NiV (green), HeV (violet), and ebolaviruses (orange) to and from domesticated animals. The species represented are goats, poultry, pigs, dogs, cats, horses, and cattle. Plus symbols indicate known susceptibility to infection of a domesticated animal species, while filled and open/dashed circles indicate intraspecific transmission in natural and controlled settings, respectively. Solid and dashed lines represent transmission that has been observed or suspected in natural and experimental conditions, respectively. Carrion, rather than direct transmission from bats, has been suggested as a source of EBOV infection in dogs [183]. NiV-associated mortality has been demonstrated in chicken eggs, but not in live chickens. Known or suspected direct transmission from wildlife to people is not represented. We found no evidence of transmission from other wildlife host species (e.g. EBOV from nonhuman primates) to domesticated animals.[1]

human handlers spreading the virus among horses or by environmental contamination, as outbreak reports suggest direct horse-to-horse transmission is relatively inefficient [191].

No intraspecific transmission has been demonstrated for any henipavirus among goats, sheep, poultry, dogs, or cattle, but we found almost no research effort in this area. There is limited evidence from a questionnaire survey, however, of an association between human NiV cases and exposure to sick cattle in Bangladesh [171], although none of the sick cattle were tested for NiV infection. Dogs have been shown experimentally to be able to transmit HeV to ferrets [179], and HeV-infected cats have infected other cats [173] and horses [170] in experimental settings. No transmission among adult cats or between cats and other species has been shown for NiV, although the isolation of NiV RNA from fetal tissues and placental fluid in an experimentally infected pregnant cat suggest vertical transmission may be possible [175].

No studies to our knowledge have tried to demonstrate the potential for intra- or interspecific ebolavirus transmission between domesticated animals (other than for pigs, as described above) and any other domesticated or wild species.

3.3.3 Research effort

A summary of all the studies investigating domesticated animals as hosts for a henipavirus or a filovirus returned by our search is shown in Figure 3.3. Pigs and NiV comprised by far the most frequently studied domesticated animal-virus pair (25% of pairs studied). Most of these studies involved either analysis of the 1999 Malaysian NiV outbreak or experimental infection studies in controlled settings. Few studies investigated cattle (3% of studies), poultry (3%), or sheep/goats (7%). We found no studies that investigated filovirus infection in either cattle or poultry. For both henipaviruses and filoviruses, we found no cross-sectional studies of poultry and no experimental studies of cattle. Henipaviruses are much better-represented targets of domesticated animal studies than filoviruses; no study from our search looked at domesticated animals as potential hosts of MARV, and only 19% of studies targeted ebolaviruses.

Excepting laboratory studies (for which locations were not always listed or relevant), Australia was the best-represented region, comprising 41% of geographically specific studies, followed by East and Southeast Asia with 36%, Africa with 18%, and South Asia with 4.5%. Only one study in East or Southeast Asia investigated ebolaviruses (specifically RESTV). Similarly, all but one study in Australia focused on HeV, and both studies in South Asia (for a total of eight species-specific investigations) focused on NiV in Bangladesh. At least five domesticated animal species were studied per region.

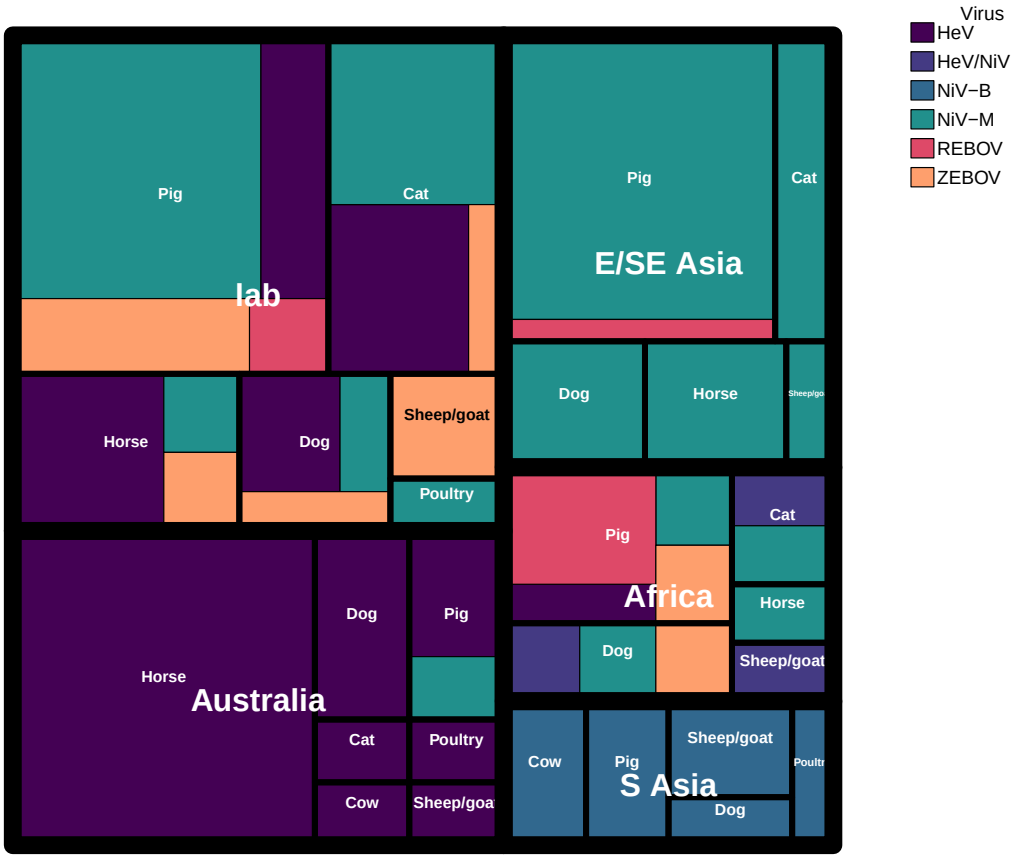

Fig. 3.3 Breakdown of studies returned in quantitative literature review by region, species, and virus studied, where the area of each box is proportional to the number of studies looking at a given animal-virus pair in each region. Some studies cover multiple host-virus pairs and are therefore represented by a greater total area.

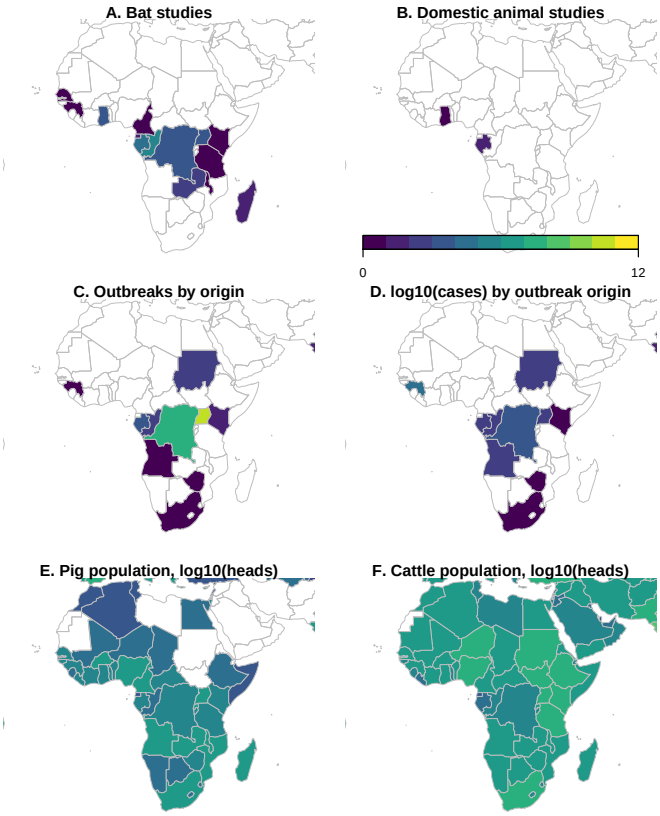

Fig. 3.4 Number of studies studying henipaviruses and filoviruses in bats (A) and domesticated animals (B); number of outbreaks (C) and confirmed human cases (D) of filoviruses by country of outbreak origin; and populations of (E) pigs and (F) cattle by country as reported by the FAO

3.3.4 Case study: filoviruses in Africa

Domesticated animals have received less attention as potential hosts of filoviruses than of henipaviruses. Fewer than one fifth of studies returned in this review focused on filoviruses—despite their profound impact on human health as demonstrated by the 2013–16 Ebola outbreak in West Africa [134, 135, 192]. Due to resource constraints and the importance of close-contact human-to-human transmission in outbreak settings, domesticated animals have been relatively low-priority targets of investigation [135]. Case investigations during outbreaks should continue to rule out known sources of EBOV transmission before investigating speculative sources such as domesticated animals, which have never been associated with previous outbreaks. A better understanding of the ecology of domesticated animals in relation to pathogen transmission will nonetheless be critical for long-term control of EVD in West Africa.

Research effort on filoviruses in African bats is fairly well spatially matched to countries where zoonotic spillover has occurred (see Figures 3.4-A through 3.4-D). Investigations of domesticated animals, by contrast, have only been conducted in Ghana (one study on henipaviruses in pigs, goats, sheep, dogs, and cats [78] and Gabon (two studies on ebolaviruses, one in pigs [163] and one in dogs [183]). Our current lack of knowledge about the potential of domesticated animals to host and transmit filoviruses is particularly striking given the ubiquity of large mammal livestock (see Figures 3.4-E and 3.4-F), dogs, and cats across the continent. There is limited evidence of susceptibility of pigs, sheep and goats, dogs, and cats to some ebolaviruses. Pigs are, in particular, a documented risk for RESTV, with observed viral circulation among pigs and indirect evidence of transmission to their handlers in the Philippines [140]. Experimentally-infected pigs are also able to transmit EBOV [162], the ebolavirus that has caused the most human mortality [134, 192], and the associated risk has not been adequately evaluated.

Both RESTV spillover in the Philippines and the major Malaysian NiV outbreak occurred in the context of highly intensive, high-throughput swine production [72]. The less intensive livestock production systems in Africa may, for now, reduce the risk of such amplification events [141]. The potential for amplification, however, is likely to rise along with economic development and global trends of agricultural intensification [144, 146, 147], and too little is known about the risk posed by either dogs—despite their possible role as asymptomatic hosts—or livestock held in smallholdings.

3.4 Discussion

We have summarized the current state of knowledge about domesticated animals as hosts of henipaviruses and filoviruses. These findings have highlighted gaps in the research effort, particularly the near-complete lack of studies of domesticated animals as hosts of filoviruses in Africa (see section 3.3.4). South Asia represents a major geographic gap; direct bat-to-human transmission is a major spillover route in Bangladesh, but given that both studies we identified described evidence of a role of domesticated animals in NiV spillover [171, 157], further studies are warranted. The dearth of published studies on filoviruses in Oceania or Asia is also notable given the known pig-mediated spillover of RESTV in the Philippines [140]. We note that we detected only one study on pigs in China—and none on any other domesticated animal—despite the detection of RESTV in pigs there [148], the proximity to known outbreaks of pig-mediated NiV outbreaks (e.g., in Malaysia), and China's housing of an estimated 65% of the world's domesticated pigs, mostly in intensive production settings. It is possible that additional studies in any of the above regions have been published in non-English language journals.

The potential role of cats and dogs as intermediate hosts of zoonotic viruses also merits further study. Without isolation of virus or observed clinical signs, observed high seroprevalences in dogs of antibodies to NiV in Malaysia and the Philippines and to EBOV in Gabon do not necessarily indicate any direct risk to human health. Nonetheless, further evaluation of that risk and of the possibility that dogs act as EBOV carriers is warranted, particularly given frequent close contact between people and dogs and the use of dogs to hunt wildlife susceptible to EVD outbreaks, such as duikers [183, 142]. High viral loads and the presence of infectious secretions in HeV-infected dogs pose a potential zoonotic transmission risk. Further study of the pathology and epidemiology of both henipaviruses and filoviruses in these widespread species is justified.

Clarifying the role of domesticated animals as hosts of henipaviruses and filoviruses (as well as other zoonoses not described here) may help implement proactive strategies to protect against outbreaks of these viruses, such as sentinel surveillance programs. Whether domesticated animals act as amplifying or dead-end hosts of a virus, detection of infection could warn of increased transmission risk to people before any active human infections occur. In many regions, domesticated animal deaths are rarely investigated for emerging or novel pathogens [193]. Due to the relative rarity of private veterinarians in much of Central and West Africa [194, 195], where filovirus spillover risk appears particularly high, partnerships with government agriculture and veterinary departments and non-governmental organizations may help disseminate advice to farmers and other animal owners. Initiatives such as the PREDICT project of the Emerging Pandemic Threats program or the Dynamic Drivers of

Disease in Africa (DDDAC) project could help establish surveillance capacity [196–198]. In addition to acting as early warning systems, such programs can build human capacity and generate data for additional research into these pathogens.

Few of the studies returned in this search examined domesticated animals as part of a wider ecosystem, although some studies outside the search's scope (due to lack of specificity to a virus) have looked at behaviors of people [199] or domesticated animals [200] that potentially promote contact with bats or bridging species. Guided by a One Health approach, cross-scale studies assessing domesticated animals in the context of their potential interactions with bats, humans, wildlife, and their environment represent another neglected area of research and could help interpret the evidence described in this review.

Henipaviruses and filoviruses are among the better-studied zoonotic bat-borne viruses, yet we have identified gaps in our knowledge of the past and potential roles of domesticated animals as hosts of these important pathogens. Due to our focus on formally published results, restrictions on the publication types and language included in our search, and a tendency, particularly of multidisciplinary outbreak investigations, to omit negative results, it is likely that we have underestimated the research effort expended on domesticated animal infections with henipaviruses and filoviruses. Nonetheless, the number of open questions remaining in this field is striking and underscores the need for continued emphasis on a One Health approach.

Chapter 4

The frequency of spillover

4.1 Background

The last five years have seen an unprecedented number of cases of Ebola virus disease, which has taken an enormous toll in terms of mortality, economic damage, disruption to other public health programs and infrastructure, and public fear and mistrust [201–203].[1] Months of delay and dozens of cases may occur before an outbreak is reported, as in the 2013–2016 West African outbreak during its first few months in Guinea [205, 206]. This delay raises questions about how often and how early and often EVD outbreaks are detected, particularly those that lead to fewer cases.

Most EVD spillover events are likely to be "dead ends" that do not transmit further, and most of these likely remain undetected. Spillover events from wildlife to people face myriad barriers to transmission and establishment—including host susceptibility, mobility, and onward contact with other susceptible individuals—[207, 208]. All diseases face the possibility of stochastic extinction upon introduction, and this is especially likely for a disease such as EVD that results in highly heterogeneous secondary transmission events [207, 209]. Given a sufficiently skewed distribution of secondary infections, even a disease with a basic reproduction number (R_0) greater than 1 is more likely than not to die out after a single index case [210]. However, few single-generation spillover events of EVD have been documented [154].

Authorship note: As noted in the Declaration of this document, some of the text below is excerpted or adapted from a previously published article [5]. All text is in my own words. All uses of the pronoun "I" refer to methods I carried out independently, while uses of the pronoun "we" indicate contributions of the co-authors on the relevant papers.

[1] Mistrust in the context of Ebola is also a very loaded word, one often used to shame people into compliance, and one I wish I had not used here [204].

It is difficult to assess the efficiency of current health systems in detecting, treating, and preventing onward transmission of EVD, as the number unobserved outbreaks is by definition unknown. Here we use three distinct data sets from the 2013–2016 outbreak in West Africa, using the properties of person-to-person EVD transmission to estimate the likely true distribution of EVD outbreak sizes. I did this by simulating the early stages of outbreaks and using maximum likelihood estimation of size-dependent detection rates to link them to the reported distribution of outbreak sizes. I thereby provide estimates for 1) the probability of observing an EVD outbreak of a given size and 2) the number of small outbreaks and spillover events that are likely to have gone undetected since EVD was first reported in 1976.

4.2 Materials and methods

4.2.1 Data

Because published estimates of the true secondary case distribution of EVD vary widely—with estimates of R_0 alone ranging from subcritical (i.e., < 1) to > 3 [211, 212]—I parameterised our simulations with three previously estimated distributions, each based on different assumptions and data from different geographic areas. Each of these previous analyses provided parameter estimates and credible intervals for a negative binomial distribution. Negative binomial distributions are commonly used to represent secondary infections [207] and can be parametrised by the disease's basic reproduction number (R_0) and a dispersion parameter k measuring heterogeneity in secondary case numbers, with probability distribution $f(x) = \frac{\Gamma(x+k)}{\Gamma(k)x!}(\frac{k}{k+R_0})^k(1-\frac{k}{k+R_0})^x$. One set of estimates was obtained from all reported exposures from over 19,000 cases from Guinea, Liberia, and Sierra Leone (henceforth referred to as the full outbreak dataset) [213]. The second estimates were derived from cases in a single district of Sierra Leone, Western Area [214]. The final set of estimates was based on chains of transmission from 152 cases in early 2014 in Conakry, Guinea [209, 215].

All three sets of secondary infection distribution estimates were based on data from the large EVD outbreak in West Africa in 2013-2016, although they accounted for different data types, time periods, locations, and assumptions about transmission.

The full outbreak data is based on the largest dataset of the three: approximately 33% of the more than 19,000 cases who reported exposures during the course of outbreak response [213]. The authors of the study reconstructed transmission networks from these reported exposures; they estimated the offspring distribution from fit models of the outdegree distribution of the network under varying assumptions of the relationship of the sampled network to the full outbreak. They produced two estimates of R_0 and k under more

and less conservative assumptions about that relationship, and we used the parameters of these two estimates as the endpoints for sampling. Advantages of this dataset for our analysis include the amount of directly applicable exposure data, a large and diverse geographic area that may be more representative of data from urban areas alone, and the thorough analysis of the underlying exposure network. The primary disadvantage of this dataset is that it uses data from up through May 2015, by which time the outbreak had been ongoing for over a year and extensive control measures and behavioral modifications were in place.

The other two sets of offspring distribution estimates—from Western Area, Sierra Leone [214], and Conakry, Guinea [209, 215]—may more closely approximate the transmission processes associated with spillover/index cases. The Guinea data represents very early stages of the outbreak (up to August 2014), but it consists of cases in a large urban center, in a country with a lower-than-average R_0 [216], and its estimation methods are quite simple. The analysis applied to the Sierra Leone data analyzes changes in the offspring distribution across stages of the outbreak and across age classes, thereby offering insights into the process of superspreading at early stages of outbreaks; however, much of this data also originated in an urban center (Freetown), in a country with a high estimate of R_0 compared to most of the same outbreak [216], and it includes only data from safe burials although unsafe burials have been estimated to transmit to as many as 6.1 additional cases per death [217]. For these reasons, we believe the Sierra Leone dataset represents a conservative estimate of the amount of superspreading, while the Guinea dataset provides a less conservative estimate; parameter estimates from the full outbreak dataset span a wide range, but their median values fall in between those from Sierra Leone and Guinea.

For all datasets, I assumed independence of R_0 and the dispersion parameter. This assumption may have produced a slightly wider range of possible distributions than in the original papers. Table 4.2 shows results from all three sets of parameters.

I excluded from our distribution of reported outbreak sizes instances of laboratory infection and outbreaks of Reston virus, which follow extremely different spillover and transmission dynamics than African ebolaviruses. Table 4.1 shows the full list of included outbreaks.

4.2.2 Analysis

A diagram of the full analysis is shown in Figure 4.1. For each dataset, I sampled 500 values each of R_0 and the dispersion parameter k to approximate bounds supplied in the original papers. From each parameter set, I simulated the early stages of each of 10^4 outbreaks as stochastic branching processes for up to 50 generations or 57 cases (whichever limit was reached first). As expected, most outbreaks died out within a few generations, representing the stuttering chains of interest. To allow simulated outbreaks to be linked to observed ones,

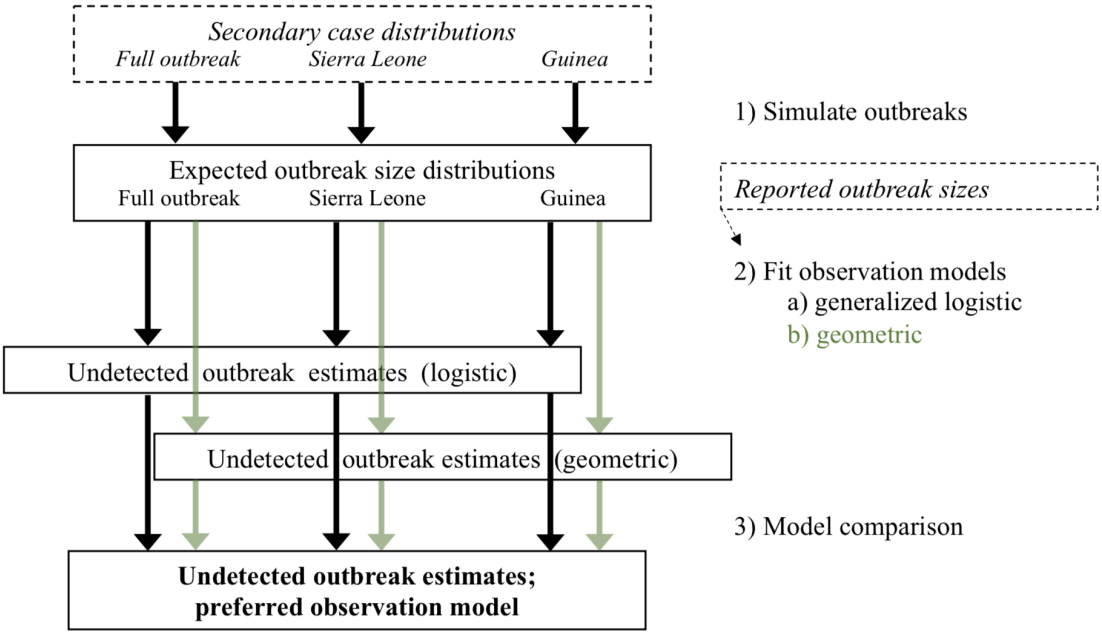

Fig. 4.1 Diagram of stages of analysis (solid lines and numbered steps at right) and data inputs at each stage (italics and dashed lines). Parallel analyses were conducted for data from the full outbreak across West Africa, in Sierra Leone only (Western Area), and in Guinea only (Conakry).

Year of origin	Country of origin	Other countries affected	Cases
1977	Democratic Republic of the Congo		1
2011	Uganda		1
2012	Uganda		6
2017	Democratic Republic of the Congo		8
2012	Uganda		11
2005	Republic of the Congo		12
2004	Sudan		17
2008	Democratic Republic of the Congo		32
1979	Sudan		34
2003	Republic of the Congo		35
2012	Democratic Republic of the Congo		36
1996	Gabon		37
1994	Gabon		52
1996	Gabon	South Africa	62
2014	Democratic Republic of the Congo		66
2001	Gabon and Republic of the Congo		124
2007	Uganda		131
2002	Republic of the Congo		143
2007	Democratic Republic of the Congo		264
1976	Sudan		284
1995	Democratic Republic of the Congo		315
1976	Democratic Republic of the Congo		318
2000	Uganda		425
2013	Guinea	Liberia, Sierra Leone, Italy, Mali, Nigeria, Senegal, Spain, United States	28645

Table 4.1 Reported outbreaks included in analysis, sorted by size. Outbreaks reported by multiple countries but originating from the same spillover event (e.g., in the case of the 2013–2016 West African outbreak) are pooled. Outbreaks occurring outside of Africa, in laboratory settings, or of Reston virus are excluded. A 1994 single-case spillover of Taï Forest virus disease in a researcher infected in Côte d'Ivoire but treated in Switzerland was also excluded. All outbreak information is used as provided by the Centers for Disease Control and Prevention [154].

I set a cutoff value based on two assumptions: 1) outbreaks larger than this cutoff are always observed, and 2) outbreaks smaller than this cutoff die out for primarily stochastic reasons, while larger outbreaks may die out for other reasons (such as interventions). Under the latter assumption, I fit observation models according to the likelihood of any outbreak reaching a certain size rather than the (infinitesimally small) likelihood of large outbreaks dying out for purely stochastic reasons. After close inspection of the data, I set the initial cutoff to 57 cases to include the 1994 Gabon outbreak (52 cases; Table 4.1), which was misidentified as a yellow fever outbreak while ongoing, and to exclude the 1996 Gabon outbreak (62 cases), which was subject to nosocomial control measures [218]. All results are robust to the choice of cutoff value in a sensitivity analysis (Figure 4.6).

I then modelled the probability of detecting an outbreak of size i ($Pr(i)$) using two possible linking functions:

1. the cumulative distribution function of the geometric distribution based on the probability of detecting a single case (p), where $Pr(i) = 1-(1-p)^i$ (see e.g., [219]), and

2. a generalized logistic linking function (where $Pr(i) = (1+e^{(}(\beta - i)))^{(} - \alpha))$.

The observation function derived from the geometric distribution models assumes that the probability of detecting an outbreak is the cumulative probability of detecting at least one case, where each case has an equal and independent probability of being detected. The generalized logistic observation function allows that individual probability of detection to vary in with outbreak size in a flexible way; i.e., the chance of detecting any one case in a cluster of size i is $1 - \sqrt[i]{1-(1+e^{\beta - i})^{-\alpha}}$.

The likelihood for either linking function was:

$$\mathscr{L}(N|\theta) = T_a! \prod_{i=1,2,\ldots 57,58+} \frac{f_i^{T_i}}{T_i!} \prod_{i=1}^{57} \binom{T_i}{N_i} Pr(i)^{N_i}(1-Pr(i))^{T_i - N_i}$$

Where θ is either p or $\{\alpha, \beta\}$, N_i and T_i are the observed and expected numbers of outbreaks of size i, respectively (with T_{58+} as the number of all outbreaks larger than the cutoff), T_a is the total number of observed and unobserved outbreaks, and f_i is the density of outbreaks of size i from 10^4 outbreak simulations (with densities of zero set to the minimum nonzero density). The two components of the likelihood function represent:

1. $T_a! \prod_{i=1,2,\ldots 57,58+} \frac{f_i^{T_i}}{T_i!}$: the likelihood of T_i outbreaks of size i being drawn from T_a outbreaks given the outbreak size distribution generated in simulation and

2. $\prod_{i=1}^{57} \binom{T_i}{N_i} Pr(i)^{N_i}(1-Pr(i))^{T_i - N_i}$: the likelihood of observing N_i outbreaks of size i given T_i true outbreaks of size i and some probability of observing an outbreak of size i ($Pr(i)$).

Because $T = \{T_1, T_2, \ldots T_{57}, T_{58+}\}$ is unobserved, I maximized this likelihood following a gradient descent algorithm similar to expectation maximization (EM). At each of 1000 iterations (or until a tolerance in the difference in likelihood was reached), I maximized the likelihood as follows:

1. Setting a starting estimate for the true number of outbreaks (T_a) as round($\frac{T_{58+}}{f_{58+}}$);

2. Setting a starting estimate for T as the medians of the binomial distributions of size T_a and probabilities f;

3. Setting minimum values of each value of T_i as the observed number of outbreaks of size i and a minimum value of T_a as the observed number of all outbreaks;

4. **'Expectation' step.** Finding an estimate of T ($\hat{T}$) that maximizes the likelihood given a fixed estimate of Θ;

   (a) Calculating the changes to the likelihood function of all single-outbreak increases or decreases in any member of $\hat{T}$ that satisfy the minima set in step 3;

   (b) For each possible single-outbreak increase or decrease in $\hat{T}$, performing the increment or decrement that most maximizes the likelihood, then updating $\hat{T}_a$ accordingly;

   (c) Repeating steps a and b until a local likelihood maximum is reached;

   (d) To prevent returning local maxima, perturbing $\hat{T}$ 2000 times at each of 10 perturbation strengths.

   (e) Updating $\hat{T}$ and returning to step a if the likelihood of any perturbed $\hat{T}$ is higher than the current maximum likelihood estimate.

5. **'Maximization' step.** Maximizing the likelihood over θ given $\hat{T}$, using the Nelder-Mead algorithm for the logistic observation function or Brent optimization for the geometric observation function.

6. Returning to step 4 and iterating until no changes improve the (negative log) likelihood more than the tolerance threshold of 10-10 or 1000 iterations have occurred.

Finally, to test the globality of these maximum likelihood estimates, I performed additional perturbations for a random subset of 150 the final 1500 estimates. I perturbed these estimates of $\hat{T}$ for an additional 4000 perturbations at each of 500 strengths. None of these perturbations resulted in higher likelihood estimates.

I assessed goodness of fit by simulating outbreaks and the observation process 10^4 times. To confirm the goodness of fit of the final models, I simulated the outbreak observation process 10^4 times. For each of these simulations, I:

1. Sampled a distribution of outbreak sizes from simulation, based on the full outbreak dataset parameters,

2. Sampled an outbreak size (i) with weights from the simulated distribution,

3. Randomly assigned each outbreak to be reported or unreported, according to the corresponding estimate of $Pr(i)$ from the fit (logistic) observation model, and

4. Repeated steps 2 and 3 until a total of 13 outbreaks smaller than the cutoff value were observed (as per the data).

Finally, I performed several sensitivity analyses, including variations in the cutoff value used to define outbreaks subject to stochastic extinction. A key assumption of this work is that index cases infected directly from zoonotic spillover are equally likely to transmit to other people as cases in naïve outbreak scenarios. Evidence for or against this assumption in the case of EVD is limited, although some zoonoses may be less likely to transmit from index cases, e.g., due to host barriers the pathogen must evolve to overcome or due to a lack of control efforts. I therefore also tested the consequences of this assumption by:

1. expanding the range of allowed R_0 values for early-stage epidemics to include both slightly subcritical infection (R_0 =0.5 or 0.75) and greater infectivity than estimated for the West African outbreak (R_0 up to 3),

2. expanding the range of dispersion parameters considered to include lower amounts of superspreading (k up to 2.1), and

3. simulating the effects of control interventions and behavior change by producing sets of outbreak size simulations with R_{eff} decay of 10, 20, or 30% per generation. I simulated 10^4 outbreaks each with values of R_0 from 0.5 to 3 at intervals of 0.25, values of k from 0.1 to 2.1 at intervals of 0.25, and values of R_{eff} decay of 0 to 30% per generation, at intervals of 10%.

4.3 Results

Parameter estimates for the generalized logistic observation function suggest a sigmoidal effect of cluster size upon an individual's probability of being detected as an EVD case, starting at a median of 2.4% and approaching a median of about 50% at clusters of size 15 and higher (Figure 4.2). Parameter estimates for the geometric observation function suggest a median individual probability of EVD detection of 8.4% (Figure 4.2). The generalized logistic model consistently outperformed the geometric model according to AICc (Figure 4.3); all results below are from the generalized logistic model. Simulations of the fit models resulted in estimates in agreement with the data (Figure 4.4).

For the full outbreak, Sierra Leona, and Guinea datasets, respectively, I estimated that medians of 67 (range 35–283; Figure 4.5-C), 26 (range 15–37; Figure 4.5-D), and 118.5

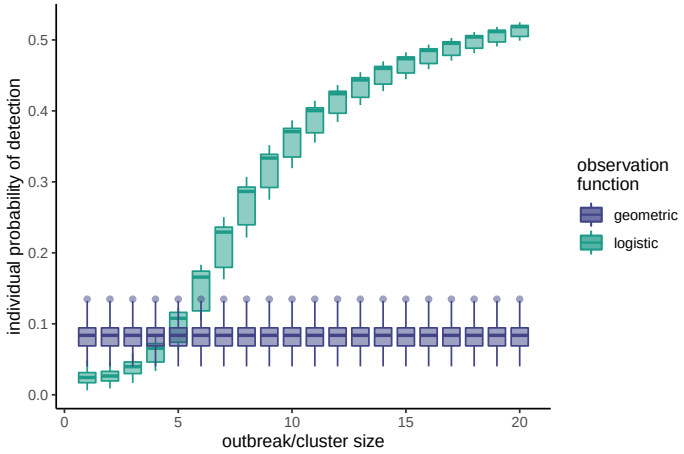

Fig. 4.2 Estimated individual probabilities of detection, by cluster size and observation function. Both observation functions model the probability of cluster detection as the cumulative probability of at least one individual being detected; these individual probabilities are constant for the geometric function and cluster size-dependent for the logistic function.

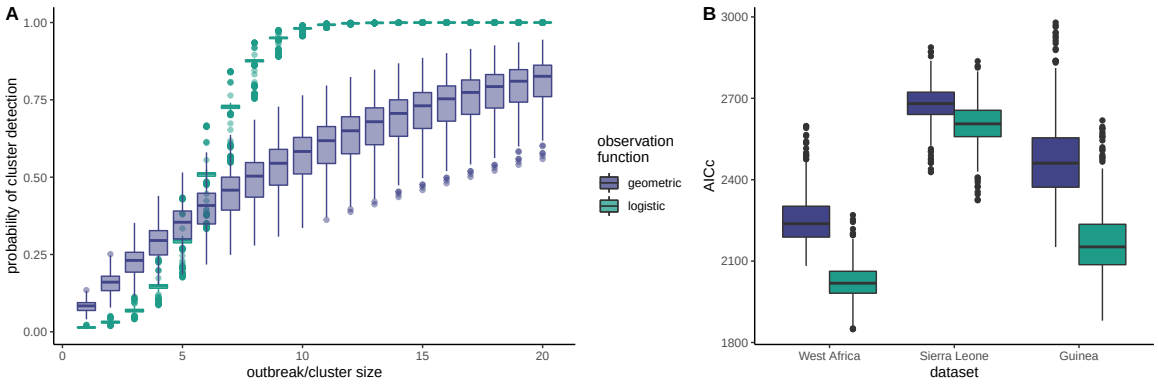

Fig. 4.3 Comparison of observation functions. A. Estimated probabilities of cluster detection, by cluster size and observation function. The geometric observation function (violet) is based on the cumulative distribution function of a geometric distribution (with a single parameter), while the logistic function (green) is a generalized logistic function with two parameters. B. Ranges, 95% quantiles, interquartile ranges, and medians of AICc values for observation models applied to each dataset, by linking function used.

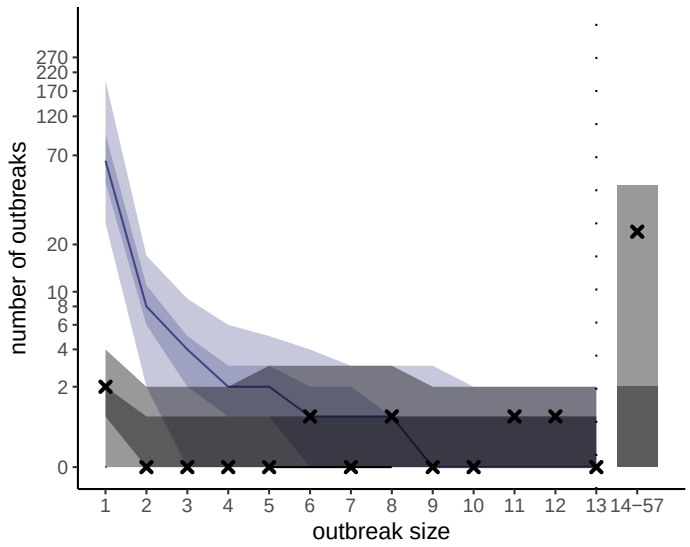

Fig. 4.4 Simulated outbreak observations. Predicted numbers of total outbreaks (violet) and observed outbreaks (black) of each size from 104 simulations of the models fit to the full outbreak data. Lighter regions and darker regions represent the 95% CI and IQR of simulations, respectively. Points marked with X represent real reported outbreaks.

(range 75–192; Figure 4.5-E) spillover events and small outbreaks have gone undetected since EVD was first reported. These represent overall detection probabilities of 26.4% (range 7.8–40.7%), 48.0% (range 39.3–61.5%), and 16.8% (range 11.1–24.2%), respectively. Most of these undetected outbreaks are dead-end zoonotic spillovers causing a single human case. I estimated medians of 56 such undetected spillovers from the full outbreak data (range 28–263, corresponding to detection probabilities of 0.1–6.7%), 22 from the Sierra Leone data (range 14–31, corresponding to detection probabilities of 6.0–12.5%), and 101.5 from the Guinea data (range 64–161, corresponding to detection probabilities of 1.2–3.0%). Simulations of outbreak sizes and the observation process produce predicted observation counts concordant with the data (see Figure S2).

These results were consistent across several sensitivity analyses. Varying the cutoff value from outbreaks of 5 cases to outbreaks of 55 cases (for the full outbreak data) only resulted in a total difference of about 8% of the minimum value (from 24.2% probability of detection at a cutoff of 5 cases to 26.2% probability at 50 or 55 cases; see Figure 4.6). Repeating the analysis for the full outbreak data across a wider range of dispersion parameters and R_0 values than previous estimates likewise results in detection probabilities in a similar range; between all combinations of R_0 values between 0.5 and 3 and dispersion parameters between 0.1 and 2.1 (both by intervals of 0.25), the range of median estimates for proportion of small outbreaks and spillover events is 2% to 92% (Figure 4.7). The range within common

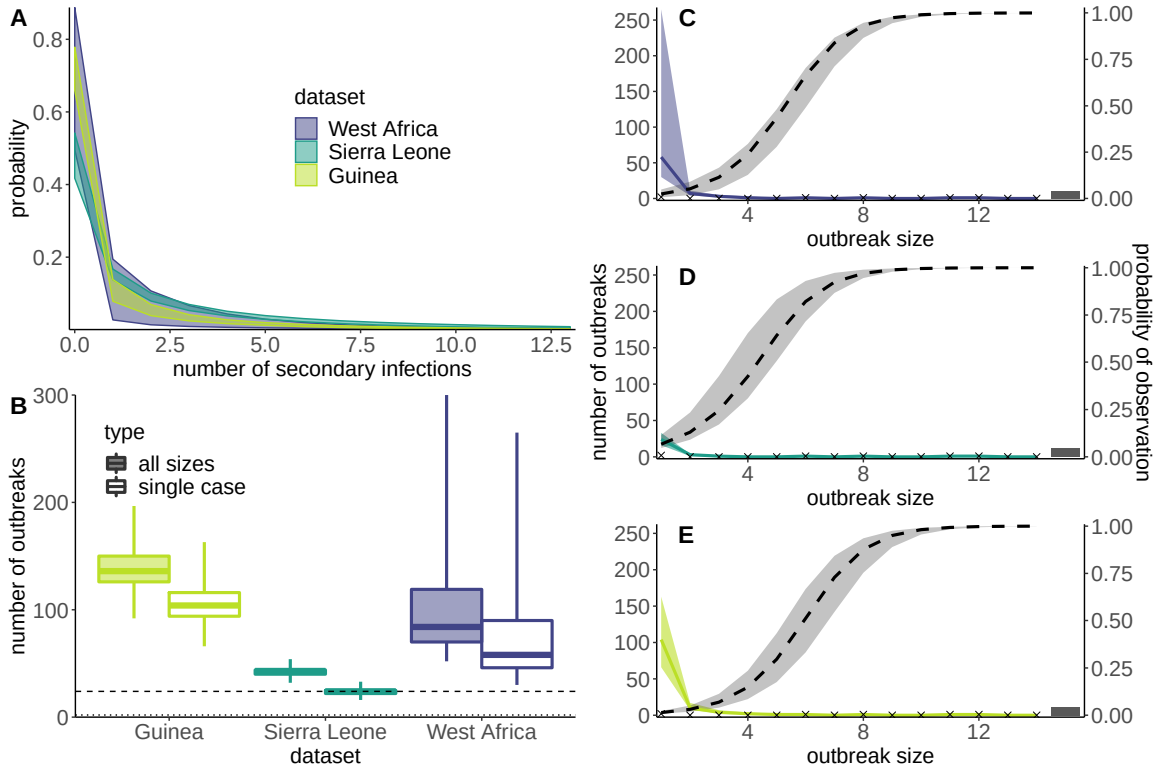

Fig. 4.5 A. Ranges of secondary infection distributions of all three datasets. B. Estimated numbers of all small outbreaks and spillover events (solid) and single-case spillover events (white) for each dataset. The dashed line indicates all observed EVD outbreaks and the dotted line indicates all observed single-case spillover events. C-E. Medians and ranges of estimated true (observed and unobserved) small EVD outbreaks by outbreak size for the full West African outbreak (C), Western Area, Sierra Leone only (D), and Conakry, Guinea only (E). The colored areas indicate ranges of from all 500 parameter sets. The dashed lines and grey areas indicate estimated probabilities of observing an outbreak of each size (median and full ranges from 500 parameter sets). Points marked with "X" indicate the number of observed outbreaks of each size. Outbreaks of 15 cases or larger are pooled.

	Full outbreak	Sierra Leone	Guinea
R_0	$\sim$ unif$(1, 1.5)$	$\sim$ logNorm$(\ln(2.39), 0.09)$	$\sim$ logNorm$(\ln(0.95), 0.09)$
Dispersion (k)	$\sim$ unif$(0.03, 0.52)$	$\sim$ norm$(0.37, 0.025)$	$\sim$ norm$(0.18, 0.025)$
Median number of undetected outbreaks since 1976 (range)	67 (35–283)	26 (15–37)	118.5 (75–192)
Median number of undetected "dead-end" spillovers since 1976 (range)	56 (28–263)	22 (14–31)	101.5 (64–161)
Median outbreak detection probability (range)	26.4% (7.8–40.7%)	48.0% (39.3–61.5%)	16.8% (11.1–24.2%)
Median "dead-end" spillover detection probability (range)	3.4% (0.1–6.7%)	8.3% (6.0–12.5%)	1.9% (1.2–3.0%)

Table 4.2 Parameters and estimates by data source. Estimates from analysis based on published secondary infection distributions based on data from across West Africa [213], from Western Area, Sierra Leone [214], and from Conakry, Guinea [209, 215].

existing estimates of R_0 (1–1.5, inclusive) and k (0.1–0.6, inclusive) for EVD is 13%–45%. Finally, I tested the effect on our results of allowing outbreaks to become slightly less infectious (e.g., due to successful attempts to control the outbreak, behavioural modifications, or pathogen evolution to become less virulent) by having R_{eff} decay 10, 20, or 30% per generation (Figure 4.7B). At very high values of the dispersion parameter (i.e., with minimal superspreading), the addition of this decay decreases the median proportion of detections. Within the same parameter ranges of common estimates (R_0 1–1.5; k 0.1–0.6, inclusive), median estimates for the detected proportion of small outbreaks and spillover events with R_{eff} decay of 0.3 range from 8% to 34%.

Estimates across this wide range of scenarios result in some variation, but the conclusion that the majority of EVD outbreaks are undetected remains except when $R_0 > 2$ and $k > 1$. Addition of a decay constant in general results in lower estimates of observation probabilities. This suggests that our estimates of undetected outbreaks are more likely biased toward underestimation than overestimation by not accounting for control efforts or susceptible depletion.

4.4 Discussion

Median estimates from all three datasets suggest at least half of all EVD spillover events (and possibly as many as 83%) have gone undetected. Although most of these spillover events have been "dead-ends" or very small outbreaks, these models suggest this could represent

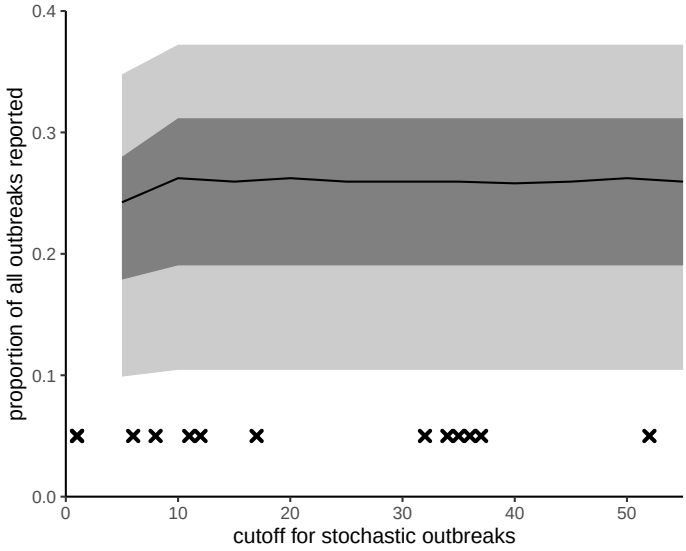

Fig. 4.6 Effects of outbreak cutoff size on detection estimates. Medians, 95% confidence intervals, and interquartile ranges for estimated proportions of all EVD outbreaks to have been detected vs. the cutoff value for stochastic outbreaks chosen for this analysis (based on the full outbreak data). Points marked with X along the bottom axis indicate the sizes of real reported outbreaks.

well over 100 cases (from a minimum of 16 from the Sierra Leone data to a maximum of 317 from the full outbreak data). While the specific estimates of these missed small outbreaks are highly sensitive to assumptions about the underlying secondary case distribution, the central prediction is robust to different datasets, methodological choices such as the cutoff value for stochastic outbreaks, and a wide range of plausible R_0 values and dispersion parameters.

Consistently lower AICc values for the logistic observation model, which predicts a dependence of individual detection probability on cluster size, suggest that outbreak surveillance is not adequately modelled as the combination of independent individual detection probabilities. This analysis instead suggests that individual cases are more likely to be correctly detected when part of a cluster of cases; identifying EVD cases that do not exist within clusters (or have not yet caused clusters) may be even more difficult than previously assumed.

Even using data with very different estimates of the underlying offspring distribution (e.g., values of R_0 from subcritical for the Guinea data to 2.4 for the Sierra Leone data), our analysis consistently predicts that most EVD spillover events and small outbreaks are not detected. That all three analyses from which we have drawn our estimates generate such different parameters highlights the difficulty of estimating them in a naïve, uncontrolled scenario when relevant data is collected in outbreak settings. However, the importance of

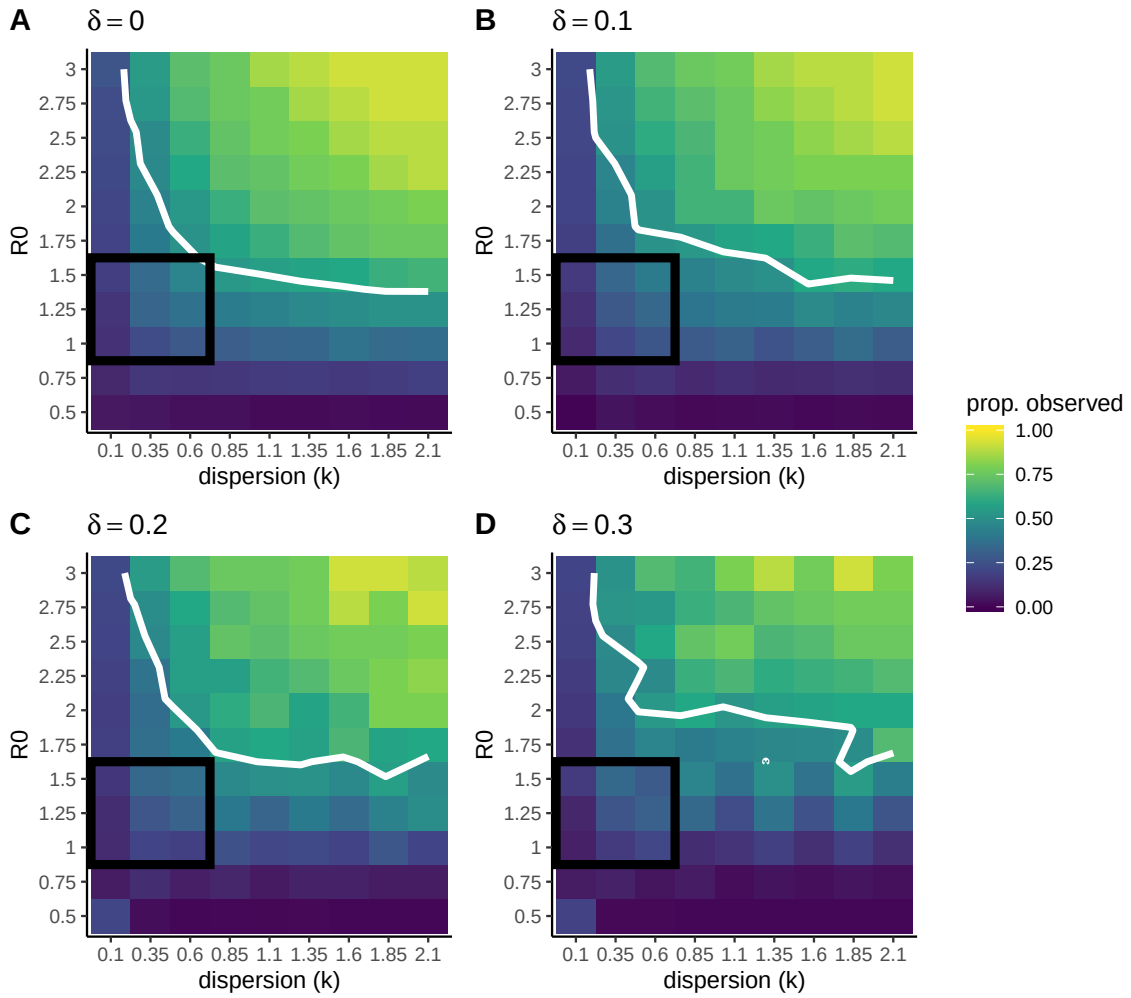

Fig. 4.7 Effects of R_0 value, dispersion parameter, and R_{eff} decay on detection estimates. Estimated proportion of all EVD outbreaks observed as a function of R0 and dispersion parameter k, where higher values of k indicate greater heterogeneity in secondary infections. Each subplot was generated with a different decay constant δ that reduces the effective reproductive number R_{eff} by 0, 10, 20, or 30% per generation. All estimations were performed with a cutoff of 57 cases. The area indicated by the black box represents parameter values included in the main analysis.

superspreading is a consistent result of models applied to EVD, even at very early stages of outbreaks [220]; our sensitivity analysis (Figure 4.7) shows that we predict at least 40% of spillover events are undetected as long as moderate superspreading occurs ($k < 1$) and $R_0 < 2$.

The true value of R_0 for a typical spillover case is most likely lower than those used here, due to the unusual epidemiology of the West African outbreak [221]; the very low human population densities at which spillover events often occur [222, 223]; and potential asymptomatic cases and uncharacteristic low-transmitting cases, which may not be sufficiently accounted for in existing R_0 estimates [224]. Additionally, although asymptomatic infections are uncommon among contacts of human EVD cases [225], they may be a more common outcome of direct zoonotic spillover, e.g., with an ebolavirus strain that is poorly adapted to human hosts; this appears to be the case with Reston virus [60, 226]. Accounting for outbreaks that become less infectious over time (due to, e.g., control interventions, susceptible depletion, or host behavioural modification)[2] causes our estimated outbreak detection rates to drop; accounting for this decay by combining this type of analysis with a dynamic model of EVD and its control is likely to produce lower estimated detection rates than we present here. It is possible that all these factors render our results underestimations, potentially explaining high seroprevalence of Ebola virus antibodies in some populations [227].

Due to these and other assumptions with less clear consequences, this analysis not intended to be a precise quantification of rates of EVD detection, but rather a demonstration of the high probability that many spillovers go undetected and that many large outbreaks are not detected early. The regions from which our data come may be unrepresentative in ways we have not considered; no EVD spillovers have been reported in Sierra Leone, so the generalizability of the Sierra Leone dataset to the typical spillover case is unknown. Finally, we assume that each documented outbreak has a single index case from spillover. While we know of no outbreaks with multiple index cases, the origins of some have not been fully traced, and outbreaks originating from a multiple-spillover event are less likely to die out stochastically [228].

There is a clear need to improve outbreak detection and rapid response, and investment in these areas is among the most efficient ways of reducing EVD mortality [229].[3] Paving the way, Uganda instated a viral haemorrhagic fever surveillance programme in 2010 that has increased the number of outbreaks detected while reducing their mean size and mean time to confirmation [230]. We note that Uganda is one of only two countries to have detected

[2] In other words, due to effective political action, an overall improvement in health and well-being, immunity (ideally from vaccines rather than infections), and improved public health and social support systems.

[3] Whether efficient investment is what we should be looking for is another question entirely (and one I discuss more in coming chapters).

spillovers resulting in a single case (Table 4.1), which we expect to be the true most common outbreak size, and it quickly mobilised to successfully contain the spread of EVD cases across the border with the Democratic Republic of the Congo in 2018 [231]. This potential success does, however, highlight the lack of spatial resolution as a limitation of our study.[4] The small number of total observed EVD spillover events means this analysis is uninformative on a country-by-country basis, obscuring potential differences in detection between countries. Additional work could consider more systematically spatial variation in contexts likely to lead to spillover and onward transmission, as well as barriers to treatment and reporting.

These estimates suggest that most spillover events and small outbreaks of EVD are not reported to international bodies but rather are handled locally, likely as fevers of unknown origin or mischaracterised as more common causes of fever (e.g., malaria) [232]. Supporting core public health and sanitation infrastructure in the areas where spillover is likely to occur may prove vital to preventing the onward transmission of these unseen index cases. Furthermore, promoting the safe management of fever and enhancing local diagnostic capacity has the potential to improve facility-based national surveillance systems and ultimately increase the chance of early detection of EVD outbreaks, both large and small.

[4]Demographic information would also be useful to understand how the social vulnerability of index cases affects outbreak risk.

Chapter 5

Outbreak detection and syndromic detectability

5.1 Background

Outbreaks of Ebola virus disease (EVD) and other emerging zoonotic diseases are most easily contained during the first few transmission cycles, when cases are localised and small in number [233]. Numbers of case contacts—and corresponding difficulties and costs of containment—grow exponentially in an epidemic's earliest stages and may quickly overwhelm healthcare capacity, especially in unequal and resource-limited settings [234–236]. Since the first reported outbreaks in 1976, EVD response has therefore often required international epidemiological responses, including two recent multi-year Public Health Emergencies of International Concern [237]. Although early outbreak detection and reporting is especially critical in such models of global health security, EVD has rarely been reported to international health organizations soon enough, often involving costly months of delay [205]. We recently estimated that less than half of past EVD outbreaks have been detected, confirmed, and reported [5]. Many other emerging diseases, including other viral haemorrhagic fevers (VHFs), have received less epidemiological attention than EVD, and detection rates are likely to be even lower in the early stages of an epidemic [238].

Authorship note: As noted in the Declaration of this document, some of the text below is excerpted or adapted from an article currently available as a preprint [10]. All text is in my own words except where explicitly noted in footnotes. All uses of the pronoun "I" refer to methods I carried out independently, while uses of the pronoun "we" indicate contributions of the co-authors on the relevant paper.

Prompt detection of emerging viruses is limited by access to health care, local diagnostic capacity, and reporting efficiency. Rural clinics in West Africa, for example, generally lack local access to laboratory methods for definitive confirmatory testing for pathogens such as yellow fever and dengue viruses, and are even less likely to have tests for Ebola virus and similarly rare pathogens [232, 239]. In this context, early detection of VHF outbreaks requires that clinicians differentially diagnose often-nonspecific febrile syndromes against a background of widespread febrile illness, a particularly challenging process in places with limited health and public health infrastructure [239–241]. Even in the relatively well-financed international responses to Ebola outbreaks, triaging patients for Ebola risk based on clinical presentation is a difficult task [242–245]. Furthermore, practitioners' knowledge of clinical profiles of rare or emerging diseases may be inaccurate or inappropriate for many settings, especially for vector-borne diseases caused by a variety of strains and for which mild cases are often unobserved [246, 247].

In addition to infrastructure for detection, the endemic context in which spillover occurs contributes to the detectability of diseases with similar presentations. In resource-limited clinical settings, treating as many patients as possible is often a higher priority than diagnosing any specific disease or performing particular surveillance functions. Diagnosis is often performed through trial and error with treatment rather than through the use of laboratory testing [232]. In parts of sub-Saharan Africa, for example, febrile illnesses are often misdiagnosed as common diseases such as malaria, even in the presence of unusual clinical features or negative malaria test results [248]. Furthermore, these settings face compounding challenges caused by limited training and infrastructure. Healthcare workers are not well positioned to be able to quickly and thoroughly interpret relatively rare and/or subjective clinical features such as hiccups or fatigue—and under-resourced places with limited diagnostic capacity are also likely to face more endemic "noise" from other poorly controlled diseases [232, 249].

Until diagnostic capacity and public health infrastructure improve in many low- and middle-income countries, syndromic surveillance is likely to remain the primary method of detecting emerging outbreaks. New methods are therefore needed to both understand the consequences of endemic disease on emerging outbreak detection and improve the efficacy of syndromic approaches to outbreak detection and response. To model the current state of syndromic surveillance and understand opportunities for improvement, we develop a Bayesian algorithm for aetiological identification of outbreaks based on case clinical features. I test this algorithm against data from 87 outbreaks of dengue, meningococcal disease, malaria, and typhoid fever. I then simulate outbreaks of 21 different syndromes to estimate the detectability of each (i.e., the estimated probability of a cluster of cases being correctly

identified by a syndromic surveillance regime, based on its clinical features) as a function of the number of cases. I examine spatial heterogeneity in syndrome detectability across sub-Saharan Africa by incorporating estimates of malaria, dengue, yellow fever, and diarrheal disease incidence at high spatial resolution, as well as the ecological risk distributions of Crimean-Congo haemorrhagic fever and Ebola virus disease. By estimating detectability across this spatially variant endemic context, I identify potential "hidden hotspots" where VHFs are especially likely to spill over and transmit among people, representing places notonly at risk of spillover, but at potentially compounding (i.e., syndemic) risk of emergence.

5.2 Materials and methods

5.2.1 Core model

The aetiological estimation model at the core of these analyses is a simple Bayesian algorithm to update the prior probabilities of a range of potentially overlapping syndromes (in this case, 22 potentially haemorrhagic febrile syndromes) based on new syndromic information (x) and a literature-derived database of clinical feature probability distributions (i.e., syndromic profiles consisting of expected probability $p_{k,n}$ and variance $v_{k,n}$ of a case of syndrome n presenting with clinical feature k). For each syndrome, we calculated relative posterior probabilities ($\hat{P}_n$) of each syndrome n given the set of clinical observations x from c cases by combining syndromic priors (i.e., relative incidences and adjusted spillover rates) with estimated likelihoods of the clinical observation data given the syndromic profile database we collected (described in full in Text B.1 in Appendix B, along with other model details), then normalising across all probability estimates. Where I_n is the incidence of syndrome n, these values can be estimated starting with the raw posterior probability (P_n) of syndrome n given observed data x:

$$P_n = P(n|x) = \frac{I_n}{\sum_{m=1}^{M} I_m} \frac{P(x|n)}{P(x)}$$

Taking $P(x|n)$ as the joint probability of each value of x as a binomial draw from underlying beta-distributed clinical profiles, we can substitute the probability mass function for the beta-binomial distribution:

$$\begin{pmatrix} P_n P(x) = \frac{I_n}{\sum_{m=1}^{M} I_m} \prod_{k=1}^{K} c \\ x_{k,n} \frac{B(x_{k,n}+v_k p_{k,n}, c-x_{k,n}+1-v_k p_{k,n})}{B(v_k p_{k,n}, 1-v_k p_{k,n})} \end{pmatrix}$$

We then normalise by all 22 values of $P_n P(x)$ to estimate the relative posterior probability of syndrome n, $\hat{P}_n$; normalising in this way eliminates the need to estimate $P(x)$, the naïve probability of data x, while retaining all information about the relative probabilities of each syndrome:

$$\hat{P}_n = \frac{P_n P(x)}{\sum_{m=1}^{M} P_m P(x)}$$

When x is simulated directly from our clinical features database (i.e., when a syndrome presents exactly as expected, $x_{k,n} = X \sim \text{Bin}(c, p \sim \text{ Beta}(v_{k,n}p_{k,n}, v_{k,n}(1-p_{k,n}))))$, we can refer to the quantity $\hat{P}_n$ as the 'detectability' of syndrome n at cluster size c. Detectability represents the theoretical maximum sensitivity of syndromic surveillance of syndrome clusters based on their expected clinical presentations (considering only the $K = 18$ clinical features for which we collected data). The expected detectable size of a syndrome n within its local disease context is the minimum cluster size c for which $\hat{P}_n > 0.5$. Unless otherwise stated, we used the medians (and appropriate quantiles for 95% confidence intervals and interquartile ranges) of 100 Monte Carlo simulations as detectability estimates.

5.2.2 Data collection

To inform our model, we collected clinical profiles and incidence data on 22 potentially haemorrhagic febrile syndromes (see Text B.1 for full inclusion and exclusion criteria). These VHFs span a range of ecological and epidemiological characteristics, including mammalian zoonoses (e.g., EVD, Marburg virus disease) and vector-borne diseases (e.g., epidemic typhus and Crimean-Congo haemorrhagic fever). We also generated profiles for the more common febrile syndromes that comprise the endemic context of selected VHFs (e.g., dengue, dengue haemorrhagic fever, uncomplicated malaria). Based on an extensive search of the clinical literature, including case and outbreak reports, we estimated the probability distributions (i.e., expected probability $p_{k,n}$ and variance $v_{k,n}$ of a range of signs and symptoms (i.e., clinical features) for each syndrome. To use as priors in our aetiological probability model, we also gathered estimates of the incidence of each disease by country from the Global Burden of Disease Survey (GBD 2017 [250]); where these were not available for a disease (in all cases zoonotic), we estimated spillover rates from the literature to approximate prior probabilities of zoonotic outbreaks. We incorporated and performed a sensitivity analysis on the effects of a "spillover scalar" to weight the prior probabilities of these rarer diseases in the algorithm (Text B.3).

5.2.3 Analysis

We first calibrated the spillover scalar and collinearity parameters using a grid search (Text B.3 in Appendix B). To understand model performance on real data, we then applied the aetiological identification algorithm to a published dataset of clinical feature data from 87 outbreaks of malaria, dengue, meningococcal disease, and typhoid fever in South Asia (Text B.3). As the outbreaks in the dataset varied in terms of the number of clinical feature probabilities reported, we estimated both the probability of correct aetiological identification of the outbreak and the expected detectability of the outbreak given the clinical features reported.

We then estimated the detectability over the course of an outbreak (up to 20 cases) under different syndromic surveillance regimes (i.e., considering all symptoms, typical symptoms, or minimal VHF symptoms; Text B.1). Finally, to estimate geospatial variability in the difficulty of detecting Ebola virus outbreaks, we estimated mean detectability of 5 simulated 10-case EVD clusters across sub-Saharan Africa using high-spatial resolution incidence estimates for malaria [251, 252], yellow fever [253], dengue [254], Crimean-Congo haemorrhagic fever [47], diarrhoeal diseases, typhoid, and invasive non-typhoidal Salmonella [255–257] (Text B.4).

5.3 Results

Algorithm performance on historical outbreaks

On the test set of 87 malaria, dengue, meningococcal septicaemia, and typhoid fever outbreaks from South Asia, the calibrated algorithm correctly identified the true outbreak cause in almost all cases, its accuracy increasing with the number of clinical features available and the size of the outbreak/symptom cluster (Figure 5.1). In a few cases (i.e., two outbreaks of meningococcal disease and one outbreak each of dengue and malaria), probability of the true aetiology peaked at approximately ten cases and then declined, indicating relatively poor correspondence between the symptoms reported in the real-world outbreaks and the syndromic fingerprints in our database. Posterior probabilities of the true outbreak aetiologies, across all outbreaks and cluster sizes, were higher than the respective incidence-based prior probabilities in 94% of cases (Figure B.7A). To account for variability in data quality—e.g., I expected poor algorithm performance when applied to those outbreaks for which only one or two clinical features were reported—I also estimated a performance ratio for each outbreak. According to this ratio, malaria detection probabilities were consistently higher than expected, while dengue and meningococcal detection probabilities were consistent with expectations (Figure B.7B). Algorithm performance on typhoid outbreaks was the least

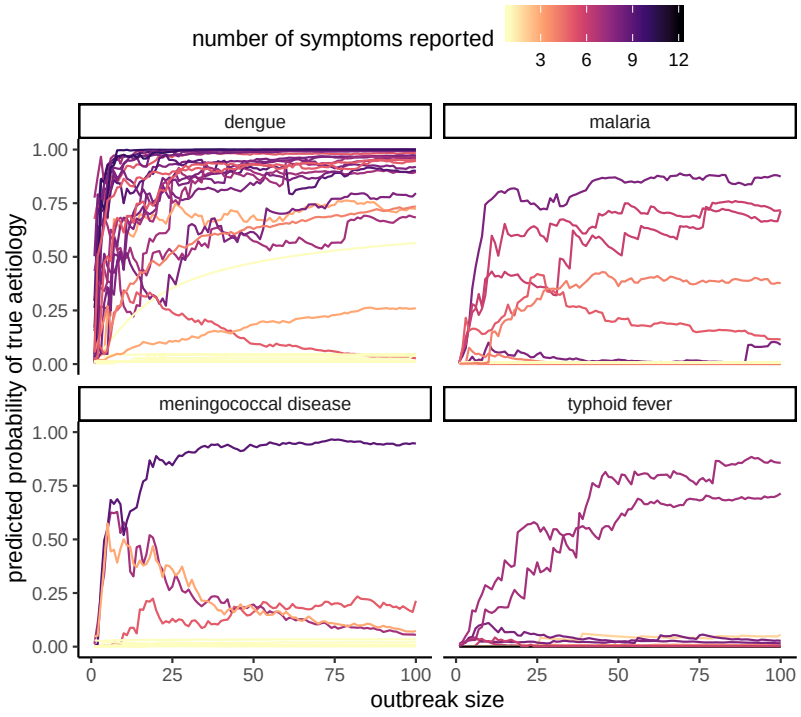

Fig. 5.1 Posterior probabilities of correct algorithmic identification of dengue, malaria, meningococcal disease, and typhoid fever outbreaks in South Asia, as a function of the size of the simulated outbreak and the number of relevant clinical features reported for the outbreak. Each line corresponds to one real-world disease outbreak in South Asia, with a different set of reported clinical features available for each outbreak.

accurate, with seven of ten outbreaks predicted to have less than 10% of their expected probability (Figure B.7B). Typhoid outbreaks with several clinical features reported tended to be misidentified as diarrhoeal diseases with a higher-than-expected probability, and those with few symptoms reported (in several instances, only a low probability of death and/or haemorrhage) tended to be misidentified as lower or upper respiratory infections with a higher-than-expected probability (Figure B.7C).

5.3.1 Estimated detectability of febrile outbreaks

By applying an aetiological identification algorithm to simulated outbreaks of all 21 syndromes, I estimate the detectable sizes of each syndrome as well as likely misidentifications between syndromes (Figure 5.2). We estimate, for example, that Ebola virus disease and Marburg virus disease (MVD) are most likely to be misidentified as dengue haemorrhagic fever, yellow fever, or typhoid fever. The clinical features caused by EVD and MVD outbreaks are more likely to be caused by other diseases until at least 6 and 7 cases occur, respectively. Before this detectability threshold, the balance of probabilities suggests a few cases of more common aetiologies are presenting with rare clinical features; after this threshold, the presentation of cases is unusual enough to suggest a common presentation of extremely rare aetiologies (i.e., filoviral disease). Figure 5.3 summarises the estimated detectabilities—i.e., probabilities of correct aetiological identification—for each syndrome as a function of both cluster size and clinical features considered.

Other rare VHFs and zoonotic diseases have greater syndromic overlap with malaria, including Rift Valley fever and epidemic typhus (Figure 5.2); these two syndromes are not 50% detectable until clusters of 12 and 15 cases, respectively (Figure 5.3). Lassa fever overlaps most with malaria at small cluster sizes (approx. 1–5 cases) and dengue haemorrhagic fever at larger sizes (approx. 5+ cases) and is not 50% detectable until a cluster size of 25 cases. Considering all 18 clinical features included in the database, most other syndromes reach 50% detectability within the first 5 cases; this includes moderately rare syndromes such as leptospirosis, yellow fever, and typhoid fever. Reducing the range of clinical features considered dramatically reduces identifiability of most syndromes (Figure 5.3). Considering only minimal VHF features (i.e., fever, haemorrhage/bleeding, death, hiccups, and jaundice) renders most syndromes undetectable by 20 cases, suggesting that e.g., case definitions for EVD or MVD are insufficient to detect them within the first 20 cases. However, the addition of nonstandard symptoms improves the detectability of filoviral diseases and other VHFs substantially.

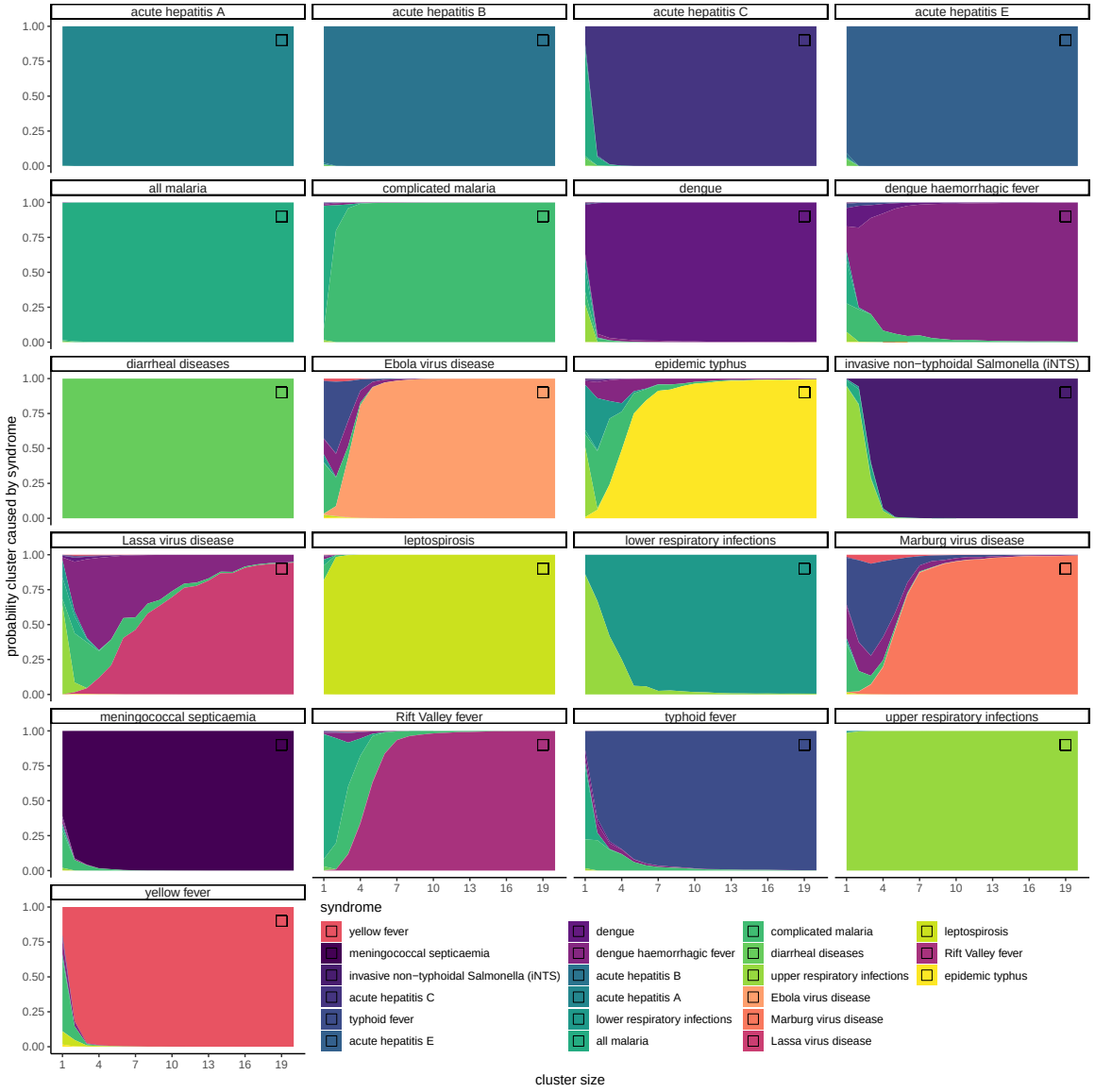

Fig. 5.2 Aetiological posterior probabilities assigned to clinical feature clusters of between 1 and 20 cases, based on application of the aetiological identification algorithm to 100 simulated clusters of each syndrome, including all 18 clinical features. Squares in the upper right corner of each plot indicate the colour of the "true" syndrome, i.e., the syndrome used to simulate clinical feature clusters.

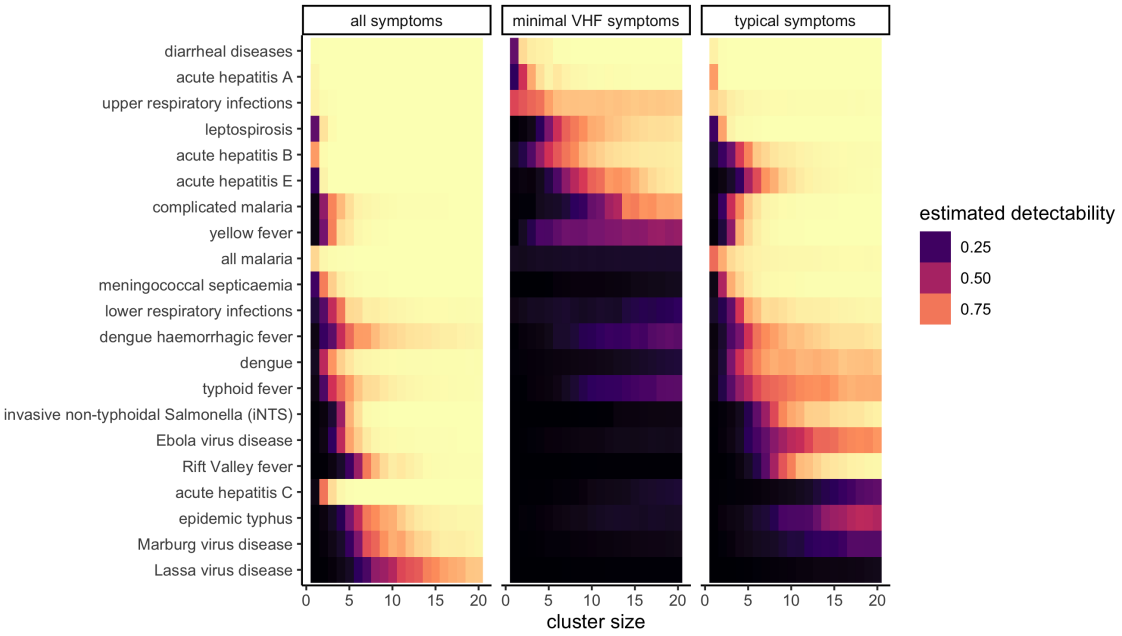

Fig. 5.3 Detectability of selected infectious syndromes in sub-Saharan Africa when considering different sets of clinical features. Left: all clinical features included in the database (i.e., fever, diarrhoea, death, fatigue or weakness, anorexia, nausea and/or vomiting, abdominal pain, any haemorrhage or bleeding, sore throat, cough, hiccups, headache, and jaundice). Centre: minimal viral haemorrhagic fever signs and symptoms (i.e., fever, death, hiccups, jaundice, and haemorrhage/bleeding). Right: only symptoms typical of a syndrome (i.e., those more common for a syndrome than for the incidence-weighted mean of all included syndromes).

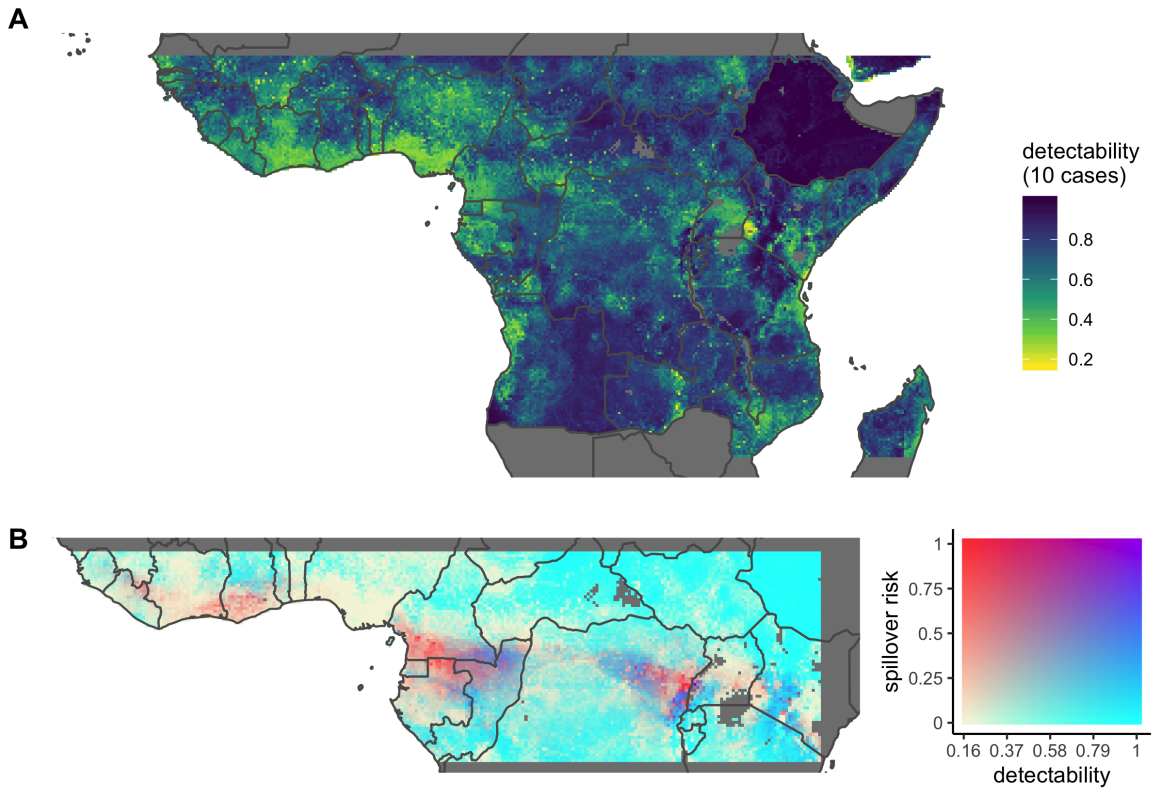

Fig. 5.4 A. Estimated detectability of a cluster of ten cases of Ebola virus disease, based on full reporting of clinical features and incorporating geospatial estimates of per capita malaria, dengue, yellow fever, typhoid, invasive non-typhoidal Salmonella, Crimean-Congo-haemorrhagic fever, and diarrheal disease incidences. B. Estimated detectability of ten cases of EVD (blue) vs. expected spillover risk (red) [258].

5.3.2 Spatial variation in detectability of Ebola virus disease outbreaks

Considering endemic context at a higher spatial resolution reveals heterogeneity in detectability and regions where EVD is most able to spread undetected due to syndemic overlap with other febrile syndromes (Figure 5.4A). Whereas existing risk maps for EVD consider the ecological niche of Ebola virus in reservoir hosts and/or human population density and movement, we add an entirely new layer to the EVD map representing variation in syndromic detectability. Considering detectability of EVD clusters in the context of existing geospatial estimates of spillover risk demonstrates potential "hidden hotspots" where EVD is both most able to spread undetected by syndromic surveillance and most likely to spill over from wildlife into people (Figure 5.4B). These potential hidden hotspots include central coastal West Africa, northern provinces of the Democratic Republic of the Congo, and the region joining Equatorial Guinea, Gabon, and Cameroon (Figure 5.4B).

5.4 Discussion

Detection of case clusters is critical to breaking the chain of events that leads from a single zoonotic spillover event to a large-scale epidemic. Although the epidemiological process underlying this chain of events has received growing attention [92], the process of clinical detection has rarely been studied directly due to the inherent difficulties of measuring cases and outbreaks that were never recorded. Here we have attempted to address this gap by quantifying how the endemic context in which a disease occurs obscures syndromic signals. This compounding co-obfuscation represents a theoretical pathway to embodiment of syndemic vulnerabilities as emerging infectious disease risk [259, 260]. We have developed tools, models, and theoretical inferences about this pathway, as well as more broadly about the interactions between endemic disease, syndemicity, and core public health capacity (in particular the ability to quickly and accurately detect outbreaks at a local level).

I have introduced new measures of syndromic distance and a new model of syndromic surveillance and tested this model against a range of outbreaks with varying data quality, demonstrating its strong utility in identifying outbreak aetiologies. I have used these new methods to estimate the sensitivity of syndromic surveillance to a range of potentially haemorrhagic fevers. I have also quantified how syndromic overlap between febrile syndromes in sub-Saharan Africa affects the expected number of cases required to detect outbreaks across the region. Finally, by incorporating geospatial estimates of the incidences of common febrile syndromes, this analysis provides evidence for "hidden hotspots" where Ebola virus is both likely to spill over and especially difficult to detect, creating spaces suitable for unchecked transmission before detection and intervention is possible [233].

5.4.1 Algorithmic outbreak identification and syndromic detectability

This syndromic surveillance model, which combines the prior incidences and clinical profiles of a range of diseases to predict the causes of clinical feature clusters, presents a more mechanistic approach than other models intended for outbreak attribution [261]. Among the primary limitations of expanding this approach is the time- and labour-intensive nature of parameterisation based on literature. Testing the aetiological identification algorithm against 87 real outbreaks highlights both the strengths of this approach and these data limitations; while the algorithm was frequently able to predict the true aetiology from limited dengue and malaria outbreak data, performance was less accurate for typhoid fever. Given more outbreak data—in terms of quantity, syndromes represented, and consistency of clinical feature reporting—we expect to be able to improve the sensitivity, specificity, and accuracy of the algorithm for categorising real outbreak data. As is, however, this mechanistic approach

still enables strong insights into the relationships among outbreak detection, case definitions and the values of clinical features for disease identification, and local endemic context.

A central challenge to developing this approach has been the lack of standardised clinical data, especially given the high dimensionality of the model. For example, we have been unable to gather comparable data on non-communicable diseases or toxic aetiologies. Although haemorrhagic and febrile syndromes are unlikely to be misdiagnosed as non-infectious syndromes [232], the paucity of data on such syndromes may prevent such an approach from being used on, for example, syndromes presenting with jaundice or neurological symptoms. Particularly scant data is also available for many uncommon or seemingly insignificant clinical features, such as hiccups or headache. Although these features are mild, this analysis has nonetheless shown that they are important for both the sensitivity and specificity of syndromic surveillance approaches. Additionally, few studies describing the presentation of syndromes describe heterogeneity in their presentation. I accounted for this heterogeneity by introducing wider clinical feature distributions for those syndromes which represent pooled aetiological agents (e.g., ascribing high heterogeneity to "diarrhoeal diseases," which includes a range of pathogens, and moderate heterogeneity to most clinical features of EVD, which may be caused by several distinct filovirus species). However, more consistent and comprehensive reporting of clinical feature prevalence across strains and settings would enable stronger accounting for heterogeneity in disease presentation.

More broadly, using literature-derived clinical feature probabilities makes this model extremely high-dimensional, making thorough validation of and sensitivity analysis on all parameters prohibitively complex without standardised clinical datasets. However, all clinical feature occurrence parameters are clinically interpretable and approximate existing processes of expert clinical diagnosis. Our literature-derived parameter set can therefore be easily interpreted and refined, e.g., by expert clinicians, Bayesian or machine learning methods, or incorporation of standardised clinical data.

This parameter set therefore represents an important starting point to harnessing complex clinical information to identify outbreaks and undetected disease more quickly and accurately than current approaches. These methods have the additional strengths of being scalable, clinically interpretable, tolerant of missing data, and useful in the presence of different clinical feature combinations. This flexibility renders these methods more practical for disease detection at a population level than, for example, the decision tree-based or machine learning methods commonly used by individual-level aetiological prediction models [262–264]. Furthermore, an advantage of this approach is its ability to exploit—rather than work against—the uncertainty inherent in syndromic data from diseases with heterogeneous presentations. Critically, this allows detection of diseases at population levels even before

any individual-level diagnosis occurs (e.g., before the development of tests for rare/novel pathogens or in settings with insufficient diagnostic capacity).

This approach has the potential to clarify aspects of disease emergence far beyond those presented here for viral haemorrhagic fevers. For example, upon expanding the range of signs/symptoms, diseases, and spatial data, it may be possible to estimate the properties of diseases least likely to be detectable by current surveillance infrastructure. The inclusion of more pathognomonic signs and symptoms in particular could improve ability to distinguish between diseases. It would also be possible to estimate observation probabilities and predicted spillover locations of other poorly observed emerging diseases and to develop geographically specific case definitions. For example, application of similar methods to respiratory syndromic profiles could illuminate the factors affecting detection of SARS coronavirus 2 disease (COVID-19) outbreaks and rapidly adapt syndromic screening protocols to local contexts (although any such decision-making is inherently political and must involve conscientious engagement, as I will discuss in the next chapter) [265].

5.4.2 Spatial detectability of Ebola virus disease

This work demonstrates that filoviral diseases, along with yellow fever, represent a distinct and distinguishable group of syndromes based on their estimated syndromic distances from other febrile syndromes in sub-Saharan Africa. However, filoviral haemorrhagic fevers remain difficult to detect based on symptoms alone due to their relative rarity. A cluster of haemorrhagic fever with a high risk of mortality, for example, even with a low proportion of jaundice, is more likely to be caused by yellow fever than either Marburg virus disease or Ebola virus disease until well more than 20 cases have occurred. Consideration of every clinical feature in the dataset—the collection of which would require extensive health system coordination, universal health access, and deep clinical expertise—still only allows for attribution of EVD or MVD by the sixth and seventh case, respectively. In an area unaccustomed to such diseases or without adequate resources, months of transmission could occur "silently" to public health systems, such as during the two largest Ebola outbreaks to date [133, 202, 205, 206, 266, 267].

This analysis suggests that common clinical case definitions for filovirus diseases are insufficient for detection of viral haemorrhagic fever outbreaks, including EVD outbreaks, in many parts of West and Central Africa. Clusters of clinical features caused by an EVD outbreak, even if they are identified as related, are too commonly attributable to other febrile symptoms. Correctly identifying EVD cases based on case definitions alone is a known challenge even for Ebola treatment centres (ETCs) during ongoing outbreaks; addition of more specific clinical features including conjunctivitis and diarrhoea has been shown to

improve the accuracy of ETC triage protocols 11. Correctly identifying the first cases of an outbreak—i.e., when filoviral disease is unlikely to be a common diagnostic consideration—requires even greater sensitivity and specificity to Ebola's clinical manifestations than ETC triage. Furthermore, predicted variation in the detectability of EVD clusters across West and Central Africa indicates that appropriate case definitions for routine surveillance might require tailoring to local or regional endemic context.

Although a strength of this approach is the use of endemic disease data to understand rare and poorly observed diseases, it is still limited by the availability of appropriate ecological and epidemiological data. The relatively high predicted detectability of EVD outbreaks in Ethiopia, for example, may be an artefact of underestimated incidences of dengue, malaria, and yellow fever in the country (Figure B.8). More broadly, niche maps for filoviral and other zoonotic diseases with wildlife origins rely on incompletely observed human/primate outbreak data for validation [268]. The Ebola virus spillover map used to generate Figure 5.4-B, for example, was fit to known instances of spillover in people (either directly from the putative reservoir or via intermediate hosts such as apes and duikers) [258]. While cross-validated on subsets of known spillovers and built on independent, underlying ecological data (i.e., fruit bat and non-molossid microbat diversity, bat demographic patterns, and human population density), such models still face fundamental challenges related to potential spatially heterogeneous observation biases. More consistent ecological data collection, especially related to bat abundance estimates and migratory patterns, could help overcome these limitations and identify regions of high ecological spillover risk. Furthermore, it may be possible to understand these hidden hotspots more deeply by integrating ecological and observational uncertainties into a single spillover modelling framework.

While niche maps for vector-borne diseases are somewhat more reliable, especially given careful surveillance and mapping of the *Aedes aegypti* mosquito [269], rarer and newer diseases are still less understood. The global dengue virus map has been refined over several years with an evidence-based, consensus-building process [254, 270, 271] and approximates risk well, even though the four circulating serotypes create a complex underlying pattern of immunity that complicates predictions of infection risk and outbreak severity [272]. The yellow fever virus map for Africa is comparatively newer, and model uncertainty is still high in East and Central Africa, where occurrence data is comparatively sparse [253]. Minor differences in niche model parameterization can produce major downstream differences in model-based inference [268, 273]; future work can capture this uncertainty by combining risk maps from several sources. Similarly, future work may benefit from using models that are spatially tailored to the area of interest [268], or incorporate other dimensions of spatiotemporal heterogeneity like seasonal spillover risk. These dimensions might be especially

informative for ruling out arboviral diseases [274, 275], but could also be informative for filoviruses as spillover drivers become clearer [222].

Syndemic interactions among diseases further complicate the detection process. Ecological risk factors are likely to be clustered within populations, especially for the handful of diseases that share zoonotic reservoirs (EVD and MVD) or mosquito vectors (dengue, yellow fever, and nearly a dozen other emerging viruses). Corresponding social risk factors—like food insecurity and water storage, or limited access to primary healthcare—are also highly spatially correlated, further increasing the odds that these diseases cluster together at fine spatial scales. These factors compound any potential biological associations between diseases [276], and resulting co-morbidities can alter clinical presentations, complicating both diagnosis and treatment. This makes outbreak dynamics more complex, and potentially more severe, than each disease would normally cause in isolation [249]. This is a particular problem for emerging viruses, which may have poorly characterized clinical presentations and case definitions for several years after emergence [277]; failure to characterise new syndromes in full can delay a national or global response by weeks or months, with strong consequences for the rate of epidemic spread [233]. For example, recent work suggests that the majority of Zika cases in the Americas were likely misidentified as chikungunya and dengue, long before the outbreak was formally reported [278]. Recent work also suggests that official case definitions for Zika by the World Health Organization miss a majority of paediatric Zika cases because the case definitions target the disease's adult manifestation, which is substantially different than its appearance in children [247]. Similar risks are apparent for EVD and MVD, especially in the hotspots we identify.

While some of the predicted hidden hotspots overlap with recently estimated hotspots for EVD epidemic risk, we introduce several new predicted areas of risk based on the difficulty of detection. For example, both southeastern Guinea and northeastern Democratic Republic of Congo emerged as hidden hotspots in our model, were identified as hotspots in recent epidemic risk models [279, 280], and have served as the geographic origins of the two largest recorded Ebola epidemics. We also, however, predict EVD detection to be especially difficult in coastal West Africa—especially southern Ghana and Cote d'Ivoire—and in Equatorial Guinea, eastern Cameroon, and northern Gabon/Republic of Congo.

These regions may represent locations of historically unobserved outbreaks [5]. These hidden hotspots represent only those places where Ebola virus disease is most likely to be undetectable by syndromic surveillance; they do not indicate anything else about the state of infrastructure for surveillance, public health coordination, or diagnosis. However, these predictions are supported by their correspondence with serosurveys and a lack of reported outbreaks despite high ecological suitability [281–283]. Moderately high seroprevalence

of filovirus antibodies has been observed in wildlife and/or human populations in these regions [281, 283, 142, 284, 143, 285, 286, 227, 287], but human outbreaks have rarely been reported [154]. Reanalysis of historical outbreaks in these regions, especially those with ambiguous syndromic presentations, could provide further evidence about the nature of local ecology and surveillance.

5.4.3 Implications for syndromic surveillance

In addition to understanding the broader ecology and epidemiology of emerging haemorrhagic fevers, these results suggest several opportunities for improving syndromic surveillance as currently practiced. Similar analyses could, for example, lead to the establishment of geographically adaptable case definitions that are maximally sensitive and specific to their local endemic contexts. Case definitions for emerging diseases are often variable over space and time even in well-observed outbreaks [288] 60, and this methodology offers a starting point for consistent and quantitative validation of case definitions' sensitivity and specificity in different contexts. Furthermore, although it seems unlikely that a healthcare worker would initiate the testing for diseases as rare as EVD or MVD outside the context of an on-going outbreak, the findings from this study do suggest a diagnostic testing algorithm of sorts. For instance, having all samples from suspected yellow fever cases that have tested negative for yellow fever automatically tested for EVD and MVD, could improve detection capacity even given diagnostic constraints at the healthcare facility-level. The data limitations encountered in this study highlight the need for standardised clinical data collection, especially for signs and symptoms rarely associated with the syndromes under consideration. Beyond improving syndromic models, such standardisation—and rapid sharing of data where appropriate [289]—could enable algorithmic detection of outbreaks of misdiagnosed diseases based on key clinical metrics. This method could enhance and complement existing genomic [290–293] and statistical [294–296] approaches to outbreak detection.

These results suggest that the best way to find filovirus outbreaks early is to build systems for controlling the endemic diseases that obscure them. Just as under-resourcing health systems creates multiple interacting effects that allow disease to thrive, improving basic public health infrastructure can have far-reaching effects. This analysis demonstrates the benefits of diagnostic and surveillance infrastructure for improving detection of emerging haemorrhagic fevers, but also that supporting population health—including universal health coverage [297, 298], water and sanitation infrastructure [299, 300], and strategies to address the socio-political determinants of health [301, 302]—has compounding benefits in terms of disease detection. By reducing endemic burdens, for example, progress in these areas can make rare epidemics easier to detect (an indirect effect analogous to that of vaccination

and sanitation for reducing antibiotic overprescription and antimicrobial resistance [303]). Furthermore, the presence of well-equipped healthcare facilities and local public health officials are likely to enable reporting and control measures, reducing the risk of outbreaks spreading once started. Additional research within the framework introduced here could quantify these potential effects. Such holistic, system-wide approaches are likely to be vital against the interconnected challenges of emerging infectious diseases.

Chapter 6

Discussion

6.1 Scientific contributions

With this thesis, I have sought to understand more deeply how viruses circulating among bats "spill over," cause disease, and become epidemic in people. I have done this by applying and developing a range of quantitative ecological and epidemiological methodologies and models, focusing in particular on bat-origin viruses across multiple ecological scales. By making quantitative inferences about the dynamic process of zoonotic infectious disease emergence—of bat henipaviruses and filoviruses, but likely to generalise to some extent across other types of emerging infections—I have provided new evidence that risks of spillover from a wildlife reservoir are higher than typically accounted for, particularly in places where public health infrastructure is limited. For example, Chapter 2 demonstrates the complexity of henipaviral dynamics in bat hosts, which defy easy explanation by conventional disease ecological models; even for this well-funded and well-observed system, in a long-term study of a closed population, the dynamics of viral circulation in this reservoir host remain uncertain and unpredictable. In Chapter 3, I used a quantitative review to directly demonstrate gaps in current scientific knowledge about the ecological mechanisms of bat-origin viral spillover to people; for example, the risks to human health posed by amplification of Nipah virus in pigs remain inestimable, and even less empirical data is available about the potential risks posed by spillover of other henipa- and filoviruses via other common domesticated animals. In Chapter 4 I demonstrate that currently reported data on Ebola outbreaks is most consistent with the estimate that at least half of Ebola spillover events—including many small outbreaks, like those in the first several months of typical Ebola epidemics—have gone undetected by public health systems. In Chapter 5, I show that a simple explanation for this apparent surveillance failure is the far more widespread burden of preventable endemic fevers (in combination with underfunded health systems limited to syndromic surveillance).

Furthermore, using models of observation biases (Chapters 4 and 5) and systematic study of the literature itself (Chapter 3), I demonstrate some of the fundamental biases and limitations that shape data created by and used in the study of emerging infectious diseases. Many of these biases are straightforwardly self-perpetuating: i.e., we know about what we study, and we study what we know about. Our understanding of the problem of infectious disease emergence is strongly determined by what viruses have already spilled over, as well as by which of those zoonoses are then detected by public health systems—introducing, as discussed in Chapter 5, a strong bias limiting the detection of novel or rare diseases in settings with limited health infrastructure or high incidence of other infectious diseases. A skewed subset of viruses with zoonotic potential thus become the viruses we associate with epidemic risk, generating increased research and surveillance attention (and in turn, we are able to detect such outbreaks more easily). The animals we study to contextualise the zoonotic potential of these viruses (Chapter 3) are determined in a similar way. Even our understandings of reservoir ecology are limited by anthropocentric biases, which have left host-pathogen dynamics in bats inexplicable with leading epidemiological frameworks (Chapter 2); many of the fundamental questions of bat immunology and ecology remain unanswered (not to mention all the other reservoir hosts we don't yet know about). The resulting gaps in scientific knowledge of global zoonotic potential almost certainly leave everyone—but especially the most marginalised people globally—exposed to zoonoses about which we know very little and have not begun to prepare.

A critical property of these gaps is that they are not evenly or equitably distributed; on the contrary, the processes that lead to knowledge and data gaps when it comes to zoonotic emergence are likely to overlap and compound one another. This is true, as discussed above, when it comes to the selection and sampling of study diseases and hosts, but may be even more consequential when it comes to the compounding of structural violence and social inequalities. As discussed in Chapter 5, for example, rare and emerging diseases are more difficult to detect both where access to confirmatory diagnostics is limited (i.e., in underfunded health systems and those without universal access to care) and where baseline health and well-being is low (i.e., where preventable and endemic fevers are common). Both of these problems are distributed among and within populations according to intersecting gradients of wealth and power [304, 305], which have become concentrated in fewer and fewer hands globally through centuries of racial capitalism (according to a rich body of theory and empirical scholarship, e.g., Robinson [306]). We cannot, therefore, expect structural barriers to disease detection and prevention to be distributed independently; rather we can expect them to be syndemic at the level of populations, i.e., co-occurring and compounding [307], in regions subject to widespread violence and neglect or with extreme internal inequality. In this way,

the social forces that create and maintain unjust distributions of health and disease also maintain structural, self-perpetuating scientific ignorance thereof. These self-reproducing biases reflect the epistemic bubble of a field dominated by the narrow priorities, questions, and methodologies of U.S. American and British "health security" programmes at the expense of holistic and historicised study of the causes of disease and its maldistribution.

Taken together, the work developed in this thesis demonstrates that spillover of bat-origin zoonotic viruses is likely to be more common than typically accounted for, that major gaps remain in the ability of ecological methods to categorise or evaluate the risks posed by zoonotic spillover and emergence, and that many of these gaps originate with and compound the material constraints of underresourced public health systems. While I have tried to develop models capable of accounting for and correcting these gaps, I believe this work also highlights the inherent limitations of quantitative or scientific work to understand a problem generated in large part by social and political forces—let alone to address the urgent problems of accelerating zoonotic emergence in the twenty-first century.

6.2 Assumptions and limitations

All of the work in this thesis rests on theoretical and methodological assumptions that affect its inferences and conclusions to varying degrees. Here, I will briefly summarise these assumptions for each chapter individual as well as the work—and the conclusions I have drawn above—as a whole.

In Chapter 2, I tried to circumvent the strongest assumptions of an SIR model (i.e., the existence of lifelong immunity and immediately contagious infection) by generalising to a framework of interrelated compartmental models. By generalising to this extent, I avoid any particular set of assumptions about the duration of immunity or the existence of an infected but non-infectious state (E, and its relationship to the infectious infected state, I). However, the modelling framework still contains many inherent assumptions, including that the population is well-mixed (i.e., there is no persistent social structure in the captive colony that creates differential transmission risk), that there is minimal heterogeneity in response to infection, and that "true" dynamics of the host-pathogen system can be well-described by (at least) one of the submodels contained within the four-state modelling framework. While these assumptions are common among studies of infectious disease dynamics and reasonably unlikely to affect the core results, they could be inappropriate in certain cases, such as if a subset of bats have an unusual response to infection and if this group is critical to viral persistence in the population. Furthermore, my interpretation of the results assumes a correspondence between my chosen metric for statistical likelihood (i.e., the joint

likelihood of individual-level seroconversion and seroreversion times, as well as population-level seroprevalences at each time point) and the "ground truth" of the system. Again this assumption is reasonable to a point. Likelihood metrics like the one used in Chapter 2 (or in full detail in Appendix A) describe the correspondence between data and model, and to what extent the latter is likely to have produced the former. The relatively low likelihood of all fit models under the R+ assumption (as well as the extreme parameter values requires to achieve even this poor fit) does strongly suggest that seropositivity for henipaviruses in *E. helvum* is unlikely to indicate immunity in all cases. However, the interpretation of multiple similarly high likelihoods—such as multiple fit models under the EIR+ assumption—is more complicated, particularly as the data-driven likelihood measure I used fails to account for the biological reasonableness of the underlying model structure. In summary, this model comparison has possibly proved more useful as a way to rule possibilities out than to establish any single hypothesis about the nature of henipaviral circulation and *E. helvum*. We can nonetheless learn from this analysis that this host-pathogen system is complex, and its explanation requires some extension or modification of the standard assumptions covered by models such as SIR, SIRS, and SILI.

Without a dynamic modelling framework, Chapter 3 is the least constrained by methodological assumptions. However, the methodology of a quantitative literature review itself rests on certain assumptions about the underlying literature base, including that important/relevant studies have all been published (and in English and in accessible journals, at that). A consistent problem revealed by meta-scientific studies is the underreporting of negative and inconclusive results, about which publication is poorly incentivised [308]. I have assumed that negative results—e.g., that a specific species is *not* a suitable host of henipaviruses or filoviruses, or has been tested for infection in settings with high risk of transmission with only negative results—are all included in scientific literature and otherwise not widely disseminated or known. This assumption seems unavoidable from the perspective of a post-publication analysis, but is not likely to be correct given the evidence of widespread publication bias favouring positive results (across scientific disciplines) [308, 309]. Furthermore, I have relied on formally published literature in the English language, which, although a standard assumption of systematic reviews, represents a stringent Anglocentric conception of ecological knowledge. A more thorough assessment of the risk associated with domesticated animals would involve the synthesis of knowledge from multiple realms; as it is, the assumptions made in this chapter mean that it best describes the extent of knowledge associated with specific formal systems of (largely biomedical) knowledge generation.

In Chapter 4, I used models of early-stage Ebola emergence and size-dependent outbreak detection to estimate probable distributions of "missing" Ebola spillovers and outbreaks (i.e.,

those that were not identified as Ebola and/or reported to international health authorities). This produces an inherently fuzzy estimate, producing wide bounds spanning hundreds of outbreaks that nonetheless indicate the high probability of many small outbreaks and spillover events going undetected. However, even these wide bounds may fail to include the ground truth if the model is poorly specified or if the data is particularly unrepresentative (other than in the outbreak sizes included). By using all available historical outbreak data, I aimed to maximise representativeness of the data; however, doing so required fairly extreme spatiotemporal homogenisation. I have assumed that over a large geographic area (stretching from West Africa to Sudan and Uganda), over a long period of time (1976–2017), the same fundamental observation function applies on average. There is undoubtedly important variation in detection capacity across this region and in the time since 1976; detection is not a function of outbreak size alone, but also of time, space, public health infrastructure, and (as discussed in Chapter 5) the presence of other diseases. The core assumption I made in Chapter 4, however, is that despite this variation the relationship between outbreak detection probability and outbreak size can be well described *in aggregate* by a geometric or generalised logistic function. I think this is a reasonable assumption on the basis that there is an evident and epidemiologically intuitive relationship between outbreak size and detection probability; this was reinforced for me by the results of the analysis presented in the chapter. However, there remains a strong possibility of spatial bias in the locations represented by the data, which represent those places where Ebola has (in most cases) successfully spread. This analysis is therefore best thought of as covering the narrow geography of those places where Ebola has been detected, rather than any wider region. I remain interested in how the spatial and temporal resolution of these estimates and other measures of Ebola risk may be improved despite the limitations of existing spillover data.

In Chapter 5 I developed a simplified model of syndromic surveillance and outbreak identification. As quantitative descriptions of a clinical process, the models in this chapter rest on a number of simplifying assumptions, including that the selected disease syndromes are (on average) static and consistent across diverse populations, that all cases within a typical outbreak are sufficiently clustered in space and time to be epidemiologically linked by aetiology, and that the data used to parameterise the work (i.e., manually synthesised syndromic information, the Global Burden of Disease survey, and ecological niche maps representing approximate spillover risk for a range of zoonoses) are sufficiently accurate. Due to the complexity of the model and its data inputs, the consequences of these assumptions are difficult to disentangle in a systematic way; for this reason I used the outbreak presentation data from South Asia to test the parameterisation of the model as a whole (although the use of this data adds the additional assumption that syndromic presentations are similar in South

Asia and in Africa). Despite such attempts to cross-check the model against independent data, it is likely that some of the results of this chapter—particularly related to high resolution geospatial estimates or diseases with few known human infections (e.g., Marburg virus disease or CCHF)—would change with more complete or more accurate data.

Many of the assumptions and limitations I have highlighted throughout this thesis are the consequence of a lack of data (or data that is open access and consistently reported). The total lack of available data on important or well-researched questions often took me by surprise. I did not anticipate, for example, just how difficult it would be to gather and reconcile data on the clinical features of various well-known fevers; because knowledge of such features are so crucial for clinical practice, I assumed this information would be widely available. The lack of standardised data formats or access protocols was a central barrier to the work presented in Chapter 5, and the limitations of the data used in Chapters 2–4 became core challenges of those chapters' respective analyses. Some of these data limitations are unavoidable constraints of the topic; as discussed throughout this document, data about emerging infectious diseases is often sparse and incomplete, and such data is inherently constrained and biased by the history of a disease's emergence to date. That basic syndromic data is inconsistently available for more well-known diseases, such as dengue or yellow fever—despite the evident importance of such data to clinical and public health practice—is more difficult to explain but likely reflects the misalignment of incentives for open data synthesis and curation in the health sciences. The centrality of these data limitations highlights that the effective study of emerging infections requires open and transparent science, multisectoral and interdisciplinary collaboration, careful contextualisation of data within the processes that create it, and active work to challenge the biases created by social forces upon those processes. Historical patterns of disease surveillance and reporting are inadequate to support an accurate understanding or equitable prioritisation of zoonotic emergence risks.

6.3 Beyond epidemiology

Instead of conclusively demonstrating the ways bat-origin viruses spill over and become epidemic, I have consistently illuminated just how much we do *not* yet know about this process. Missing outbreaks (Chapter 4), complex puzzles (Chapter 2), research questions unasked and unanswered (Chapter 3), and compounding system failures (Chapter 5) characterise the quantitative data available on henipavirus and ebolavirus spillover and emergence. I hope the analyses presented here provide some insights and useful tools that move us toward a more comprehensive understanding of bat-origin viral spillover and emergence, including a better understanding of the data already available about historical outbreaks. Beyond

this, I hope that the methods development, synthesised data sets, and code tools I have developed prove useful to other disease ecologists and epidemiologists seeking to continue that process. In sum, however, a central lesson from this work is that much more needs to be done before knowledge of spillover's determinants and mechanisms is widely actionable across disease systems. The same cannot necessarily be said for zoonotic emergence, which as an epidemiological process among people is subject to the social forces that structure all human disease [259, 305].

While I have repeatedly demonstrated uncertainty surrounding the drivers of Ebola spillover, the drivers of Ebola emergence can be well understood through synthesis of epidemiological analysis and the wider sociopolitical contexts within which outbreaks have occurred. For example, Benton and Yi Dionne [310] used a political economy approach to trace the root cause of the West African Ebola epidemic of 2013–2016 to slavery, colonialism, civil war, neoliberal economic policies such as Structural Adjustment Programs [311], and the distribution of foreign aid that created a decentralised health system of foreign-led NGOs [310]. Such long-term political dynamics rendered West African governments dependent on the same international "benevolence" (via tightly controlled foreign aid and philanthropy) that undermined the creation of sustainable and resilient health systems [310, 312]. The ecological or behavioural circumstances of the original spillover in Guinea did not determine the way the spillover became an epidemic; in the most primary way, the dynamics of Ebola emergence in 2014 were driven by these political manifestations of racial capitalism (i.e., the political economic system in which wealth accumulation for some depends on the "propagat[ion of] fatalities, and the forms and patterns that coalesce into premature death" among systematically dehumanised people [313, 306]).

Other actors and structures of racial capitalism have enabled and amplified smaller Ebola outbreaks, including the very first recorded epidemic in Nzara in 1976. British colonial "resettlement" of Azande people in Nzara had disrupted both local ecosystems and human lives and livelihoods several decades earlier; the purpose of the so-called Zande scheme was to disrupt agricultural livelihoods and replace them with waged labour in the cotton industry [314–316]. The first few documented *Sudan ebolavirus* infections are directly connected to a cotton factory built during this scheme, including several people who worked there as waged labourers [314, 317]. The continued dominance of the globalised cotton industry in Nzara in 1976 reflects the persistence of ecological, sociopolitical, and economic disruption in Sudan in the wake of colonisation; with native ecosystems and indigenous livelihoods no longer available, Azande dispossession has persisted long after the end of direct British rule. The existence of the Nzara cotton factory as a probable origin and transmission site reflects the (colonial) creation of the conditions that kept people working

in globalised waged labour in 1976, and its role in the history of Ebola is therefore directly attributable to British imperialism in its colonial and neocolonial forms.

In the following decades, Ebola has frequently co-occurred with conditions of war, poverty, inequality, and other preventable infectious diseases. The Democratic Republic of the Congo (DRC, known as Zaire until 1997), for example, remains especially vulnerable to Ebola outbreaks due to complex histories of colonial and neocolonial exploitation, armed conflict reshaped in the wake of the 1994 Rwandan genocide, and other forms of widespread physical and economic violence [204, 318–324]. In North Kivu (one of the provinces involved in the second largest Ebola outbreak to date) in 2009, violence caused a reported 40% of all deaths in some health zones [325]. Furthermore, displacement, theft, trauma, and other consequences of this persistent, long-term insecurity are pervasive [325–327]. These structural forces have produced deep, complex vulnerabilities to the consequences of Ebola, including direct and indirect morbidity and mortality as well as the breakdown of critical public health infrastructure and disruption of public health activities [328, 329]. Rather than redressing the historical and ongoing ecological, social, and economic injustices in the DRC, however, global political powers seem to have (whether actively or tacitly) selected a nihilistic model of outbreak response fundamentally incapable of addressing the nation's root vulnerabilities to disease [330, 331, 204, 332, 333]. Indeed, much of the "global health" response to Ebola in both the DRC and West Africa has reproduced colonial heirarchies and reinforced systems of dehumanisation and extraction, further entrenching the extreme health risks long imposed in these regions in part for the benefit of globalised supply chains [204, 334–336].

Ebola outbreaks in many ways require only "textbook" epidemiology, preventable by basic public health and infection control tools that have been cheap and widely available for decades [337, 202]. That Ebola continues to cause so much preventable harm reveals the contradictions in a project of "global health" that relies on "containing and managing 'crises' rather than addressing the structural problems that give rise to these events in the first place." [335, 205, 338] Stopping Ebola emergence does not simply require more investment in international response teams or improved vaccines, although such investments can represent life-saving harm reduction measures. Stopping Ebola emergence sustainably requires changing the conditions that allow Ebola to spread uncontrolled, i.e., supporting the development of equitable systems of care and empowering people and communities to protect themselves—in part through dismantling the extractive and coercive political and economic insitutions that block these solutions [332, 339, 340, 334]. The work presented in this thesis corroborates this point; rapid Ebola response and containment requires the kind of early, local detection of spillover events currently (Chapter 5) and historically (Chapter 4) impeded

by unjust global distributions of more easily prevented diseases and of health resources (such as diagnostics) in general.

The true frequency of Ebola outbreaks, the vast challenges posed by preventable endemic fevers, the potentially irreducible complexity of the ecological origins of spillover, and the compounding effects of social vulnerabilities on disease all challenge dominant technocratic "health security" narratives about infectious disease emergence. The United States is one of the world's largest funders of global health security; approximately 17% of recent global health security funding tracked by the Georgetown Infectious Disease Atlas (GIDA) comes from a handful of US American state agencies including the US Agency for International Development (USAID), the Centers for Disease Control and Prevention (CDC) and other branches of the Department of Health and Human Services (HHS), and the Bureau of International Security and Nonproliferation [341]. Such funding often goes to projects such as pandemic response surge capacity, wildlife surveillance and virome prediction, and disease forecasting centers which promise technological solutions to the deep-rooted social problems of disease [341–346]. The inherent limitations and contradictions of such initiatives have been further laid bare by the COVID-19 pandemic in the United States, where such narrowly scoped projects could do little to prevent more than half a million deaths [23] in a nation where the maintenance of mass insecurity is a capitalist prerogative—evidenced by the lack of universal access to treatment, as well as the disproportionate disease and mortality burdens faced by groups like the working class and racialised minorities [347–352]. Indeed, even globally-minded funding bodies based in the United States, such as the Bill and Melinda Gates Foundation, have refused to advocate for the life-saving sharing of intellectual property during this pandemic (via a waiver of the World Trade Organization's TRIPS Agreement), prioritising the profit motive of pharmaceutical companies above the end of the pandemic or the avoidance of global vaccine apartheid [353–355]. The health security agenda, no matter how much money is budgeted for health research, is simply not a suitable replacement for long-term investment in equitable systems of care nor robust, open collaboration in the face of a global health crisis. To pretend that new technologies are the answer to this crisis—or that new research is needed to know how to act—is a distraction that serves to justify inaction.[1]

The recent invisibilisation of Ebola (and in particular the injustice of its distribution) is likewise a process that has served to obscure a violent status quo. The 2013–2016 epidemic galvanised global attention (as well as stigma and fear) in part due to its unprecedented size, with nearly 30,000 suspected cases and more than 11,000 deaths from Ebola directly [202, 335]. The racialisation and spectacle that dominated political discourse around this epidemic, however, laid the groundwork for its subsequent neglect [338, 136]. With priorities for

[1] See Benjamin on the "datafication of injustice" [356].

response set largely by global health security hegemons like the United States government, Ebola vanished from the political agenda after 2016, as fears of racialised contagion arriving from abroad subsided and were replaced by a renewed understanding of Ebola as a "neglected tropical disease" restricted to (systemically dehumanised and devalued) African people [338, 357]. In the few years since 2016, Ebola has therefore transformed in much of public and scientific consciousness from a global emergency into a seemingly naturalised, endemic force [205, 358, 335]. This naturalisation is today especially apparent in the DRC. Although the DRC has experienced a devastating Ebola outbreak every year since the West African epidemic, this complex ecological and social crisis has received little attention outside of Africa [20, 359, 360, 204].

This endemicisation of Ebola sanitises preventable deaths and obscures agency, urgency, and accountability for this process, hiding its violence from those not directly subject to it. Furthermore, the endemicisation and collective forgetting of Ebola since 2015 hides the crucial, widely-shared finding that reliably preventing Ebola outbreaks requires developing and strengthening universal health systems [361, 202]—systems still opposed even domestically by nearly all mainstream politicians in the United States, the only high income country globally without universal health coverage for its citizens [362]. Only by forgetting or obscuring the lessons of Ebola can the United States government continue to "lead" in global health security without offering the most basic health security to its own citizens [346].

When I discuss knowledge gaps in the histories of zoonotic viruses, I am therefore not talking only about neutral ignorance but also about silences created through violence in order to evade accountability for the injustices that shape current distributions of disease. We must not just keep "learning lessons" about disease that never solidify into solutions [363, 364, 361, 344, 206]. These piecemeal lessons, which proliferate around epidemics and pandemics, are an evasion: a way of moving on with the true causes of harm not only unrepaired but unacknowledged.[2]

As many gaps as there may be in the scientific picture of zoonotic spillover, the histories of recent zoonotic emergence events leave little doubt about the fundamental causes of disease in the present day. We stop disease emergence the same way we improve all health: by redistributing the means of good health (i.e., wealth and power) and actively constructing robust and universal systems of care, including health care and other determinants of good

[2]My thinking on this point is strongly influenced by critiques of similarly incremental research on and reform of the prison industrial complex in the United States, in which the project of "reforming reformed reforms" has become an industry unto itself, even as more money and resources flow into the systems being reformed [365, 313]. Although beyond the scope of this work, the parallels between "health security" and the more directly carceral forms of the U.S. American prison industrial complex are deep and influential, and the impact of the nation's brutally carceral logic on human health (via zoonotic disease) is immediately apparent from elevated rates of COVID-19 infections in prisons, jails, and detention centres [366–369].

health, such as peace, housing, food, water, and community social support. There is no alternative—no pandemic response team, no ecological intervention, no amount of economic growth, no cutting edge technology—that can counteract the health consequences of ecological destruction, climate change, the colonial underdevelopment and continued exploitation of much of the Global South, the precaritisation of working people around the world, or destabilisation of entire regions through military interference and the global arms trade. The most efficient vaccine development pipeline will not prevent disease equitably if global vaccine distribution is determined by the profit motive of pharmaceutical corporations. The best diagnostics and treatments will not prevent disease if their distribution is determined by for-profit insurers. Health security has little to offer in the absence of political commitments to health as a universal public good and a human right. Understanding zoonotic viruses will not prevent epidemics if we do not address the maldistribution of resources that needlessly keeps people poor and sick.

Over the coming decades, we will inevitably face more death and suffering from zoonotic infectious diseases unless we reverse the political and economic trends that have created vulnerability among some people for the benefit of others. The zero sum logic of capitalism—that my health not only can but *must* come at the expense of someone else's—is violently untrue when applied to infectious disease. Indeed, pandemics (and much of the work in this thesis) demonstrate the inescapable interdependence of people, not only with bats, pathogens, or our environments, but also with every other person on this planet [370, 371]. Health is not the absence of a list of diseases, but a shared future we must all build together.

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Appendix A

Captive colony serological likelihood function

Likelihoods for the captive colony account for individual, longitudinal data as well as population-level, cross-sectional data. We therefore considered the likelihood that each observed time to seroconversion (e.g., S$\rightarrow$I or E for the EIR+ assumption) and seroreversion (e.g., I or E$\rightarrow$S for the EIR+ assumption, or the expected immune waning time for the R+ assumption), accounting for 1) the probability of an individual following a certain infection pathway and 2) the probability of a given conversion/reversion time given that pathway. The probabilities of any pathway, including for convenience the probabilities of exiting any cycle between states that are both seronegative or both seropositive, are below. These are the adult transition probabilities, but we use them for the likelihood for all age classes, assuming the chances of following any given path to seroconversion/reversion (and the time taken to do so) is in reality the same for an individual of any age.

$$
\begin{aligned}
Pr(R \to S) &= \frac{\omega}{\omega + m} \\
Pr(E \to S) &= \frac{\sigma_1}{\sigma_1 + \sigma_2 + \varepsilon + m} \\
Pr(E \to I) &= \frac{\varepsilon}{\sigma_1 + \sigma_2 + \varepsilon + m} \\
Pr(E \to R) &= \frac{\sigma_2}{\sigma_1 + \sigma_2 + \varepsilon + m} \\
Pr(I \to S) &= \frac{\gamma_1}{\gamma_1 + \gamma_2 + \rho + m} \\
Pr(I \to E) &= \frac{\rho}{\gamma_1 + \gamma_2 + \rho + m} \\
Pr(I \to R) &= \frac{\gamma_2}{\gamma_1 + \gamma_2 + \rho + m} \\
Pr(R \to S) &= \frac{\omega}{\omega + m} \\
Pr(\text{exit I-E}) &= 1 - (\frac{\varepsilon}{\sigma_1 + \sigma_2 + \varepsilon + m})(\frac{\rho}{\gamma_1 + \gamma_2 + \rho + m}) \\
Pr(\text{exit E-I}) &= Pr(\text{exit I-E}) \\
Pr(\text{exit I-S}) &= 1 - (\frac{\gamma_1}{\gamma_1 + \gamma_2 + \rho + m})(\frac{\beta_2 I^*}{\beta_2 I* + \beta_1 I^* + m}) \\
Pr(\text{exit S-I}) &= Pr(\text{exit I-S}) \\
Pr(\text{exit E-S}) &= 1 - (\frac{\sigma_1}{\sigma_1 + \sigma_2 + \varepsilon + m})(\frac{\beta_1 I^*}{\beta_2 I* + \beta_1 I^* + m}) \\
Pr(\text{exit S-E}) &= Pr(\text{exit E-S})
\end{aligned}
$$

Our likelihood function differs based on the serological assumption used (i.e., only immune individuals are seropositive, R+, or all non-susceptible individuals are seropositive, EIR+). Some expected seroconversion/reversion times are the combination of many individual state transition times (e.g., under the R+ assumption, an individual may undergo many cycles of acute and latent infection before seroconverting). The full likelihood function for such times is the convolution of the relevant probability density functions. However, due to computational constraints we made the simplifying assumption of merging these individual state transitions into a single, exponentially-distributed transition with the same expected time.

Assumption: only R seropositive (R+)

Seroreversion probabilities are simple under the assumption that R is the only seropositive compartment. Where t is a single seroreversion time:

$$\text{with } \theta = \{\sigma_1, \sigma_2, \varepsilon, \rho, \gamma_1, \gamma_2, \omega, m\}$$
$$\mathscr{L}(\theta|t) = Pr(R \to S)\omega e^{-\omega t}$$

Seroreversion probabilities under this assumption are somewhat more complicated, because an individual can undergo infinite pathways through the three seronegative states (S, E, and I) by undertaking any number of three different possible cycles (between the S and E states, between S and I, and between I and E). Due to the complexity of this function, we consider only the discrete number of cycles $i \in (0, M)$ for S-E or S-I cycles and $j \in (0, Q)$ for E-I cycles. $M = \text{round}(\frac{\beta_1 I^* \sigma_1}{m(\beta_1 I^* + \sigma_1)})$ in models with S-E cycles and $M = \text{round}(\frac{\beta_2 I^* \gamma_1}{m(\beta_2 I^* + \gamma_1)})$ in models with S-I cycles. No models have both S-E and S-I cycles due to the specification of either β_1 or β_2; $Q = \text{round}(\frac{\rho\varepsilon}{m(\rho+\varepsilon)})$.

If S-E cycles are possible (i.e., if β_1 is specified), the probability of any seroconversion time t, where $r(\text{path})$ is the expected time to complete a pathway inclusive of any cycles within seronegative states, is:

$$\text{with } \theta = \{\sigma_1, \sigma_2, \varepsilon, \rho, \gamma_1, \gamma_2, \omega, m\}$$
$$\begin{aligned}
\mathscr{L}(\theta|t) &= Pr(S \to E)Pr(E \to R)\frac{\beta_1 I^* \sigma_2}{\beta_1 I^* + \sigma_2} e^{\frac{\beta_1 I^* \sigma_2}{\beta_1 I^* + \sigma_2} t} \\
&\quad + \sum_{i=1}^{Q} \sum_{j=0}^{M} (1 - Pr(\text{exit S-E}))^i (1 - Pr(\text{exit E-I}))^j L_{ij} \\
&\quad + \sum_{j=1}^{M} (1 - Pr(\text{exit E-I}))^j L_j \\
L_i j &= Pr(S \to E)Pr(E \to I)Pr(I \to R)r(S \to E \to I \to R)e^{-r(S \to E \to I \to R)t} \\
L_j &= Pr(S \to E)Pr(E \to I)Pr(I \to R)r(S \to E \to I \to R)e^{-r(S \to E \to I \to R)t} \\
&\quad + Pr(S \to E)Pr(E \to R)r(S \to E \to R)e^{-r(S \to E \to R)t}
\end{aligned}$$

where, given i S-E cycles and j E-I cycles

$$r(S \to E \to I \to R) = \frac{1}{j(\frac{1}{\varepsilon} + \frac{1}{\rho}) + i(\frac{1}{\sigma_1} + \frac{1}{\beta_1 I^*}) + \frac{1}{\varepsilon} + \frac{1}{\gamma_2} + \frac{1}{\beta_1 I^*}}$$
$$r(S \to E \to R) = \frac{1}{j(\frac{1}{\varepsilon} + \frac{1}{\rho}) + \frac{1}{\sigma_2} + \frac{1}{\beta_1 I^*}}$$

If instead β_2 is specified, the probability of any seroconversion time t is:

$$\begin{aligned}
&\text{with } \theta = \{\sigma_1, \sigma_2, \varepsilon, \rho, \gamma_1, \gamma_2, \omega, m\} \\
\mathscr{L}(\theta|t) &= Pr(S \to I)Pr(I \to R)\frac{\beta_2 I^* \gamma_2}{\beta_2 I^* + \gamma_2} e^{\frac{\beta_2 I^* \gamma_2}{\beta_2 I^* + \gamma_2} t} \\
&\quad + \sum_{i=1}^{Q}\sum_{j=0}^{M}(1 - Pr(\text{exit S-I}))^i (1 - Pr(\text{exit I-E}))^j L_{ij} \\
&\quad + \sum_{j=1}^{M}(1 - Pr(\text{exit I-E}))^j L_j \\
L_i j &= Pr(S \to I)Pr(I \to E)Pr(E \to R)r(S \to I \to E \to R)e^{-r(S \to I \to E \to R)t} \\
L_j &= Pr(S \to I)Pr(I \to E)Pr(E \to R)r(S \to I \to E \to R)e^{-r(S \to I \to E \to R)t} \\
&\quad + Pr(S \to I)Pr(I \to R)r(S \to I \to R)e^{-r(S \to I \to R)t} \\
&\quad \text{where, given i S-I cycles and j I-E cycles} \\
r(S \to I \to E \to R) &= \frac{1}{j(\frac{1}{\varepsilon} + \frac{1}{\rho}) + i(\frac{1}{\gamma_1} + \frac{1}{\beta_2 I^*}) + \frac{1}{\rho} + \frac{1}{\sigma_2} + \frac{1}{\beta_2 I^*}} \\
r(S \to I \to R) &= \frac{1}{j(\frac{1}{\varepsilon} + \frac{1}{\rho}) + \frac{1}{\gamma_2} + \frac{1}{\beta_2 I^*}}
\end{aligned}$$

Assumption: E and R seropositive (ER+)

Seroreversion under the ER+ assumption includes both R to S transitions and E to I or S transitions. The probability of any seroreversion time t given either specification of β is:

$$\begin{aligned}
&\text{with } \theta = \{\sigma_1, \sigma_2, \varepsilon, \rho, \gamma_1, \gamma_2, \omega, m\} \\
\mathscr{L}(\theta|t) &= \frac{Pr(S \to E)S^* + Pr(I \to E)I^*}{Pr(S \to E)S^* + Pr(I \to E)I^* + Pr(I \to R)I^*}(\\
&\quad Pr(E \to R)Pr(R \to S)(\frac{\sigma_2 \omega}{\sigma_2 + \omega})e^{-\frac{\sigma_2 \omega}{\sigma_2 + \omega} t} \\
&\quad + Pr(E \to I)\varepsilon e^{-\varepsilon t} \\
&\quad + Pr(E \to S)\gamma_1 e^{-\gamma_1 t}) \\
&\quad + \frac{Pr(I \to R)I^*}{Pr(S \to E)S^* + Pr(I \to E)I^* + Pr(I \to R)I^*} Pr(R \to S)\omega e^{-\omega t}
\end{aligned}$$

Seroconversion under the ER+ assumption includes both S to E transitions and I to E or R transitions and may include cycles between the seronegative states S and I:

$$\text{with } \theta = \{\sigma_1, \sigma_2, \varepsilon, \rho, \gamma_1, \gamma_2, \omega, m\}$$

$$\mathscr{L}(\theta|t) = \frac{Pr(R \to S)R^* + Pr(E \to S)E^*}{Pr(R \to S)R^* + Pr(E \to S)E^* + Pr(E \to I)E^*}($$
$$Pr(S \to I)Pr(I \to R)(\frac{\beta_2 I^* \gamma_2}{\beta_2 I^* + \gamma_2})e^{-\frac{\beta_2 I^* \gamma_2}{\beta_2 I^* + \gamma_2}t}$$
$$+ Pr(S \to E)\beta_1 I^* e^{-\beta_1 I^* t}$$
$$+ Pr(S \to I)Pr(I \to E)(\frac{\beta_2 I^* \rho}{\beta_2 I^* + \rho})e^{-\frac{\beta_2 I^* \rho}{\beta_2 I^* + \rho}t}$$
$$+ \sum_{i=1}^{M}(1 - Pr(\text{exit I-S}))^i L_i))$$
$$+ \frac{Pr(E \to I)E^*}{Pr(R \to S)R^* + Pr(E \to S)E^* + Pr(E \to I)E^*}($$
$$Pr(I \to R)\gamma_2 e^{-\gamma_2 t}$$
$$+ Pr(I \to E)\rho e^{-\rho t}$$
$$+ \sum_{j=1}^{Q}(1 - Pr(\text{exit I-S}))^j L_j)$$

$$L_i = Pr(S \to I)Pr(I \to E)r(S \to I \to E)e^{-r(S \to I \to E)t}$$

where, given i cycles

$$r(S \to I \to E) = \frac{\gamma_1(\beta_2 I^*)^2 \rho}{\gamma_1(\beta_2 I^*) + \gamma_1 \beta_2 I^* \rho + \beta_2 I^* \rho i(\gamma_1 + \beta_2 I^*)}$$

$$L_j = Pr(I \to E)r(I \to E)e^{-r(I \to E)t}$$

where, given j I-E cycles

$$r(I \to E) = \frac{\gamma_1 \beta_2 I^* \rho}{\rho j(\gamma_1 + \beta_2 I^*) + \gamma_1 \beta_2 I^*}$$

Assumption: E, I, and R seropositive (EIR+)

In a model with transmission from S to E, the likelihood of a seroreversion time t is:

$$
\begin{aligned}
\text{with } \theta &= \{\sigma_1, \sigma_2, \varepsilon, \rho, \gamma_1, \gamma_2, \omega, m\} \\
\mathscr{L}(\theta|t) &= Pr(E \to S)\sigma_1 e^{-\sigma_1 t} \\
&\quad + Pr(E \to R)Pr(R \to S)\left(\frac{\sigma_2\omega}{\sigma_2+\omega}\right)e^{-\frac{\sigma_2\omega}{\sigma_2+\omega}t} \\
&\quad + Pr(E \to I)Pr(I \to S)\left(\frac{\varepsilon\gamma_1}{\varepsilon+\gamma_1}\right)e^{-\frac{\varepsilon\gamma_1}{\varepsilon+\gamma_1}t} \\
&\quad + Pr(E \to I)Pr(I \to R)Pr(R \to S)\left(\frac{\varepsilon\gamma_2\omega}{\varepsilon\omega+\varepsilon\gamma_2+\gamma_2\omega}\right)e^{-\frac{\varepsilon\gamma_2\omega}{\varepsilon\omega+\varepsilon\gamma_2+\gamma_2\omega}t} \\
&\quad + \sum_{i=1}^{M}(1-Pr(\text{exit}))^i L_i \\
L_i &= Pr(E \to S)r(E \to S)e^{-r(E\to S)t} \\
&\quad + Pr(E \to R)Pr(R \to S)r(E \to R \to S)e^{-r(E\to R\to S)t} \\
&\quad + Pr(E \to I)Pr(I \to R)Pr(R \to S)r(E \to I \to R \to S)e^{-r(E\to I\to R\to S)t}
\end{aligned}
$$

where, given i cycles

$$
\begin{aligned}
r(E \to S) &= \frac{\varepsilon\rho\sigma_1}{\sigma_1 i(\varepsilon+\rho)+\rho\varepsilon} \\
r(E \to R \to S) &= \frac{\sigma_2\omega\rho\varepsilon}{\varepsilon\rho\omega+\varepsilon\rho\sigma_2+\sigma_2\omega i(\varepsilon+\rho)} \\
r(E \to I \to R \to S) &= \frac{\rho\varepsilon\gamma_2\omega}{\omega\gamma_2 i(\rho+\varepsilon)+\gamma_2\omega\rho+\varepsilon\omega\rho+\gamma_2\rho\varepsilon}
\end{aligned}
$$

In a model with transmission from S to I, the likelihood of a seroreversion time t is:

$$
\begin{aligned}
\mathscr{L}(\theta|t) &= Pr(I \to S)\gamma_1 e^{-\gamma_1 t} \\
&\quad + Pr(I \to R)Pr(R \to S)(\frac{\gamma_2\omega}{\gamma_2+\omega})e^{-\frac{\gamma_2\omega}{\gamma_2+\omega}t} \\
&\quad + Pr(I \to E)Pr(E \to S)(\frac{\rho\sigma_1}{\rho+\sigma_1})e^{-\frac{\rho\sigma_1}{\rho+\sigma_1}t} \\
&\quad + Pr(I \to E)Pr(E \to R)Pr(R \to S)(\frac{\rho\sigma_2\omega}{\rho\omega+\rho\sigma_2+\sigma_2\omega})e^{-\frac{\rho\sigma_2\omega}{\rho\omega+\rho\sigma_2+\sigma_2\omega}t} \\
&\quad + \sum_{i=1}^{M}(1-Pr(\text{exit I-E}))^i L_i \\
L_i &= Pr(I \to S)r(I \to S)e^{-r(I\to S)t} \\
&\quad + Pr(I \to R)Pr(R \to S)r(I \to R \to S)e^{-r(I\to R\to S)t} \\
&\quad + Pr(I \to E)Pr(E \to S)r(I \to E \to S)e^{-r(I\to E\to S)t} \\
&\quad + Pr(I \to E)Pr(E \to R)Pr(R \to S)r(I \to E \to R \to S)e^{-r(I\to E\to R\to S)t}
\end{aligned}
$$

where, given i cycles

$$
\begin{aligned}
r(I \to S) &= \frac{\varepsilon\rho\gamma_1}{\gamma_1 i(\varepsilon+\rho)+\rho\varepsilon} \\
r(I \to R \to S) &= \frac{\gamma_2\omega\rho\varepsilon}{\varepsilon\rho\omega+\varepsilon\rho\gamma_2+\gamma_2\omega i(\varepsilon+\rho)} \\
r(I \to E \to S) &= \frac{\rho\varepsilon\sigma_1}{\sigma_1 i(\rho+\varepsilon)+\sigma_1\varepsilon+\rho\varepsilon} \\
r(I \to E \to R \to S) &= \frac{\rho\varepsilon\sigma_2\omega}{\omega\sigma_2 i(\rho+\varepsilon)+\sigma_2\omega\rho+\varepsilon\omega\rho+\sigma_2\rho\varepsilon}
\end{aligned}
$$

For both models with S to E and S to I transmission, the likelihood associated with a seroconversion time t is simply the expected transmission time. However because measurements of captive colony serology were collected at inconsistent intervals, on two occasions more than a year apart, we assigned each seroconversion time and seroreversion time a minimum and maximum value (based on the earliest and latest times in the preceding and following sampling periods) and assumed a uniform distribution between the two. The true likelihood of a seroconversion/seroreversion time t with a maximum time t_{max} and minimum time t_{min}, if the calculated seroconversion/seroreversion rate is r, is actually

$$
re^{-rt} = e^{-rt_{min}} - e^{-rt_{max}}(\frac{1}{t_{max}-t_{min}})
$$

. For example, the full likelihood of a seroconversion time under the EIR+ assumption is:

$$\mathscr{L}(\theta|t) = \frac{\beta\bar{I}}{\beta\bar{I}+m}\beta\bar{I}e^{-\beta\bar{I}t}$$

where $\bar{I}$ is the mean number of infecteds over the past period t

$$\mathscr{L}(\theta|T \sim U(t_{min}, t_{max})) = \int_{t_{min}}^{t_{max}} Pr(t \sim T)\frac{\beta\bar{I}}{\beta\bar{I}+m}\beta\bar{I}e^{-\beta\bar{I}t}dt$$

$$\mathscr{L}(\theta|T \sim U(t_{min}, t_{max})) = \frac{\beta\bar{I}}{\beta\bar{I}+m}(e^{-\beta\bar{I}t_{min}} - e^{-\beta\bar{I}t_{max}})$$

Finally, the likelihood function includes a term for measured seroprevalences over time. This is the same as the seroprevalence likelihood for the cross-sectional data on wild-caught bats, but for multiple time points at one location and with all age classes pooled due to incomplete age information for the captive bats. Where P_x is the simulated seroprevalence at sampling timepoint x; n_x and p_x are the observed numbers of all bats and seropositive bats at time x, respectively; and $\bar{T}_R$ and $\bar{T}_C$ are the sets of all observed seroreversion times and seroconversion times, respectively, the final function is:

$$\mathscr{L}(\theta|\bar{T}_R, \bar{T}_C, n, p) = \mathscr{L}(\theta|\bar{T}_R)) * \mathscr{L}(\theta|\bar{T}_C)) * \prod_{x=1}^{22} \binom{n_x}{p_x} P_x^{p_x}(1-P_x)^{n_x-p_x}$$

Appendix B

Syndromic data collection and validation

B.1 Parameterisation

B.1.1 Syndrome selection

We selected those co-occurring endemic diseases which, according to the Global Burden of Disease Survey (GBD) 2017 [250], had an incidence of at least one case per year in a reference country (Uganda) and did not meet either of two exclusion criteria. These diseases were excluded if 1) their case definitions (according to either the World Health Organization or the U.S. Centers for Disease Control and Prevention) depend upon the presence of a specific clinical feature not known to be associated with either EVD or MVD (e.g., we excluded tetanus due to the lack of spasms), and/or 2) they present with highly localised symptoms. Of diseases we considered for inclusion, we excluded eight syndromes for symptom specificity: tetanus (jaw stiffness and/or spasm), meningococcal and other causes of meningitis (neck stiffness; we included meningococcal septicaemia), measles (maculopapular rash), varicella and herpes zoster (papular rash), whooping cough (paroxysm, inspiratory whoop, or post-tussive vomiting), and syphilis (chancre). We also excluded five syndromes due to localisation: genital herpes, viral skin diseases, gonococcal infection, chlamydial infection, and scabies.

We split diseases according to their clinically distinct syndromes (e.g., dengue vs. severe dengue 2). We included the following syndromes in analysis: Ebola virus disease, Marburg virus disease, Lassa fever, leptospirosis, Rift Valley fever, epidemic typhus, Crimean-Congo haemorrhagic fever, acute hepatitis A, acute hepatitis B, acute hepatitis C, acute hepatitis E, upper and lower respiratory infections, invasive non-typhoidal Salmonella, typhoid fever, other diarrhoeal diseases, yellow fever, dengue (uncomplicated or severe), and malaria (complicated or uncomplicated).

B.1.2 Clinical feature selection and parameterisation

We included symptoms which 1) were commonly reported present in rare VHF outbreak reports, and 2) were included in case definitions for other diseases under consideration (e.g., jaundice for yellow fever). The signs and symptoms we considered were: fever, diarrhoea, death, fatigue or weakness, anorexia, nausea and/or vomiting, abdominal pain, any haemorrhage or bleeding, sore throat, cough, hiccups, headache, jaundice, conjunctivitis, myalgia and/or arthralgia, rash, hepato- and/or splenomegaly, and any severe neurological manifestation (e.g., seizure, encephalitis).

For each disease-feature pair, we estimated expected clinical feature occurrence probabilities $p_{c,n}$ and their variances $v_{c,n}$ (such that each clinical feature follows the distribution $\text{Beta}(pv,(1-p)v))$ based on a literature search. We gathered clinical feature data from outbreak reports, medical and epidemiological textbooks, and peer-reviewed articles. In many cases, clinical feature probabilities were only described in qualitative terms (e.g., "presenting with fever, often accompanied by jaundice"), and the presentation of quantitative data was inconsistent (e.g., in terms of clinical features presented, setting, sample size, generalisability). Furthermore, data was inconsistently available across syndromes, with relatively large and consistent samples available for Ebola virus disease and little recent data on acute manifestations of hepatitis B and C, despite the relative rarity of EVD. Based on the collected literature (Table B.1), we assigned clinical feature probabilities and variances (Figure B.1) using expert opinion, accounting for: 1) number of studies available; 2) study sample sizes; 3) how representative studies are of sub-Saharan Africa in terms of location, outbreak size, cohort, etc.; 4) reliability of estimates (e.g., probabilities from meta-analyses or "common knowledge" descriptions from medical textbooks); and 5) whether variation in estimates appeared more likely to be caused by observational error (e.g., differences in case definitions between studies) or genuine difference in clinical presentation.

Specifically, we approximated variances in clinical feature probabilities by first designating high and low variance features (e.g., specific and relatively objective signs such as jaundice and conjunctivitis are low variance features, while headache, fatigue, and anorexia are high variance features due to the subjectivity of their assessment); we adjusted these baseline estimates towards a higher variance for those syndrome-feature pairs where the literature (or lack thereof) suggested high variation and/or ambiguity (e.g., for poorly documented syndromes such as Crimean-Congo haemorrhagic fever and those such as diarrheal diseases and lower respiratory diseases that encompass multiple possible aetiological agents.)

Syndrome	Clinical feature sources	Incidence sources	Notes
yellow fever	[372–381]	[250, 253]	
meningococcal septicaemia	[382–385]	[250]	estimated 35% of meningococcal disease [385]
invasive non-typhoidal Salmonella (iNTS)	[386–390]	[250, 255]	
acute hepatitis C	[391–399]	[250]	
typhoid fever	[400–410]	[250, 255]	
acute hepatitis E	[411–422]	[250]	
dengue	[423–435]	[250, 254]	
dengue haemorrhagic fever	[423–435]	[250, 254]	estimated 23% of all dengue cases [434]
acute hepatitis B	[436–440]	[250]	
acute hepatitis A	[441–445]	[250]	
lower respiratory infections	[446–453]	[250]	
all malaria	[454–457]	[250, 252, 251]	
complicated malaria	[454–459]	[250, 252, 251]	4% of all malaria cases [456]
diarrheal diseases	[255, 460–462, 257, 463, 464]	[250, 255]	
upper respiratory infections	[465–469]	[250]	
Ebola virus disease	[470–479]	[258, 154]	Base spillover rate: 1 $year^{-1}$
Marburg virus disease	[480–482]	[155, 483]	Base spillover rate: 0.5 $year^{-1}$
epidemic typhus	[484–490]	[491, 490]	Base spillover rate: 100 $year^{-1}$
Lassa virus disease	[492–496]	[497]	Base spillover rate: 5 $year^{-1}$
leptospirosis	[498, 499]	3	Base spillover rate: 500 $year^{-1}$
Rift Valley fever	[500–506]	[505]	Base spillover rate: 5 $year^{-1}$
Crimean-Congo hamorrhagic fever	[507–510]	[510]	Base spillover rate: 1 $year^{-1}$

Table B.1 Key sources of clinical feature parameters and incidence estimates for all syndromes, including base spillover rates (i.e., relative rates of spillover of zoonotic syndromes over all sub-Saharan Africa).

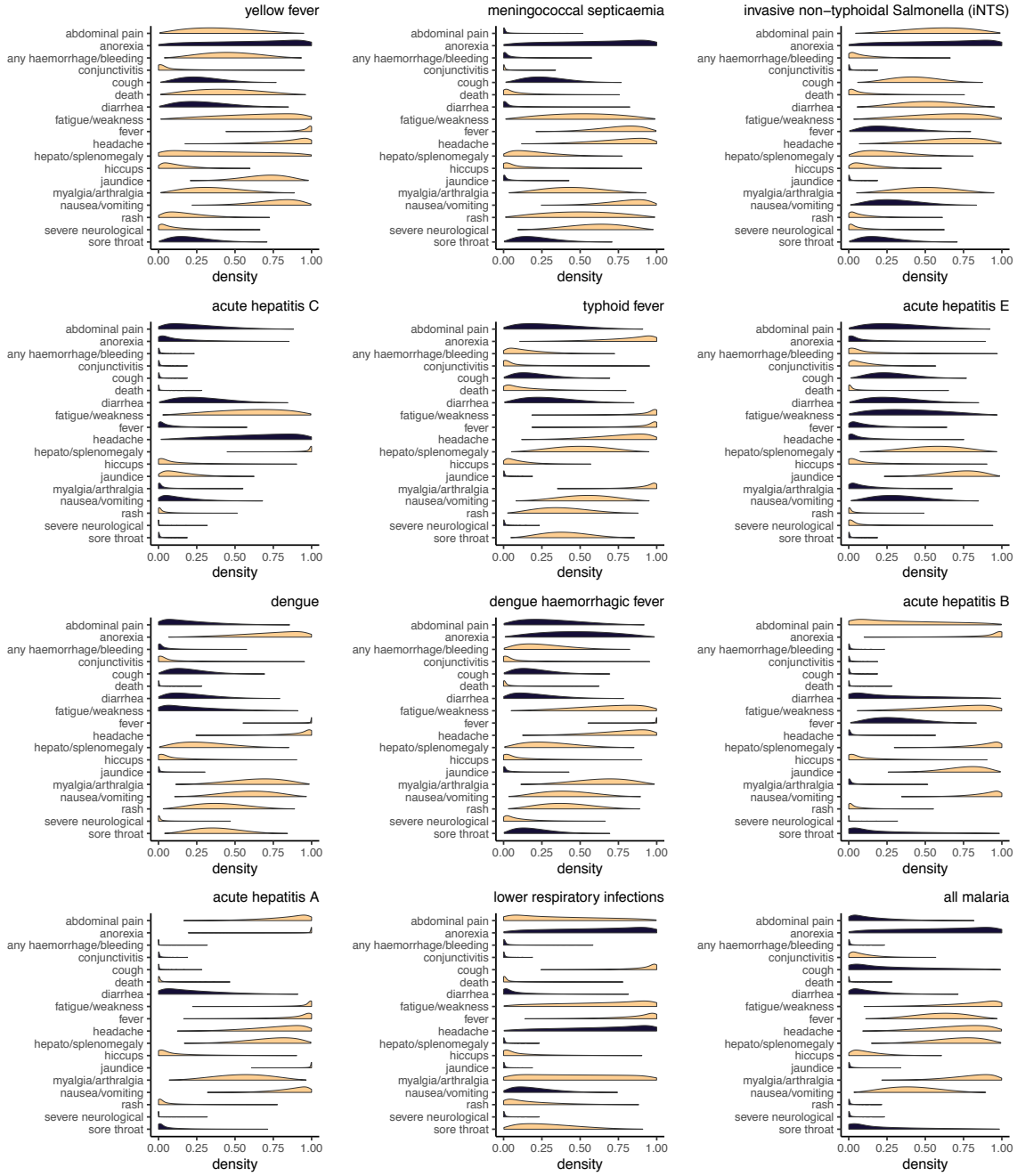

Fig. B.1 Clinical feature occurrence probabilities for all syndromes as estimated for sub-Saharan Africa overall. Typical symptoms—i.e., those more common for a syndrome than for all syndromes, weighted by incidence—are shown in orange.

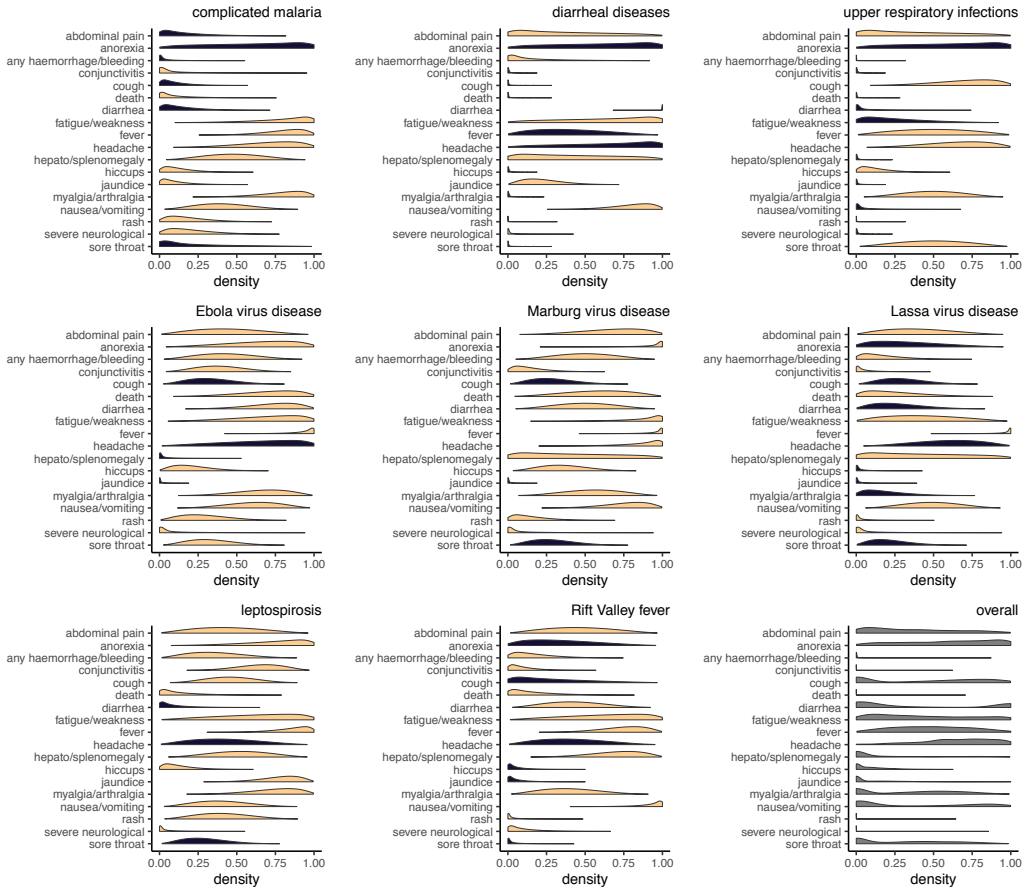

Fig. B.2 (Continued) clinical feature occurrence probabilities for all syndromes as estimated for sub-Saharan Africa overall. Typical symptoms—i.e., those more common for a syndrome than for all syndromes, weighted by incidence—are shown in orange.

B.1.3 Additional data collection and stratification

We gathered incidences from the GBD survey, where available, pooled across age and sex. For the disease syndromes not included in the GBD, we estimated regional spillover rates based on historical outbreak data (Table B.1) and a variable scalar accounting for observational uncertainty. As estimated detection probabilities of these rarer diseases are often poor [511, 491, 5], we performed a sensitivity analysis on all reported results incorporating variation in this scalar (Text B.3).

To compare the sensitivity of different methods of syndromic surveillance, we defined three sets of signs and symptoms associated with each syndrome: all eighteen clinical features for which we collected data; "typical features," i.e., those clinical features with expected occurrence probabilities for the true syndrome greater than the incidence-weighted occurrence probability for all syndromes (and the orange features in Figure B.1); and minimal features for haemorrhagic fevers (i.e., death, haemorrhage, fever, jaundice, and hiccups).

B.2 Estimating clinical feature collinearity and clustering

To summarise overlap in clinical features among the 21 syndromes, we created a matrix of syndromic distances, with all signs and symptoms normalized by the incidence-weighted probability of clinical feature occurrence among all cases. We defined the syndromic distance between syndromes as the Euclidean distance across each pair of sign/symptom probabilities, weighted by a scalar derived from t-SNE to account for collinearity between symptoms (θ_k).

While some rare haemorrhagic fevers—especially Ebola virus disease, Marburg virus disease, typhoid fever, and yellow fever—are closely syndromically related to one another, they are separated by high (>50%) syndromic distances from most other syndromes (Figure B.3). Others—including Lassa fever, Rift Valley fever, and leptospirosis—have relatively small syndromic distances from a range of more common syndromes, especially those related to dengue virus and malaria.

Without individual-level data, we could not account for fine-scale, within-syndrome sign/symptom clustering; however, we attempted to account for coarse population-level clustering and collinearity of clinical features based on simulations of clinical features across a population. To do so, we first simulated clinical features of 10,000 cases of all syndromes, with syndromes sampled according to average incidence across sub-Saharan Africa (at varying spillover scalars; Text B.3) and clinical features sampled according to the clinical profiles shown in Figure B.1. We assumed clinical features within a syndrome to be independently distributed. Coarse symptom clustering (using agglomerative, complete-linkage hierarchical clustering) identifies clusters of relatively rare and severe clinical features—such as death,

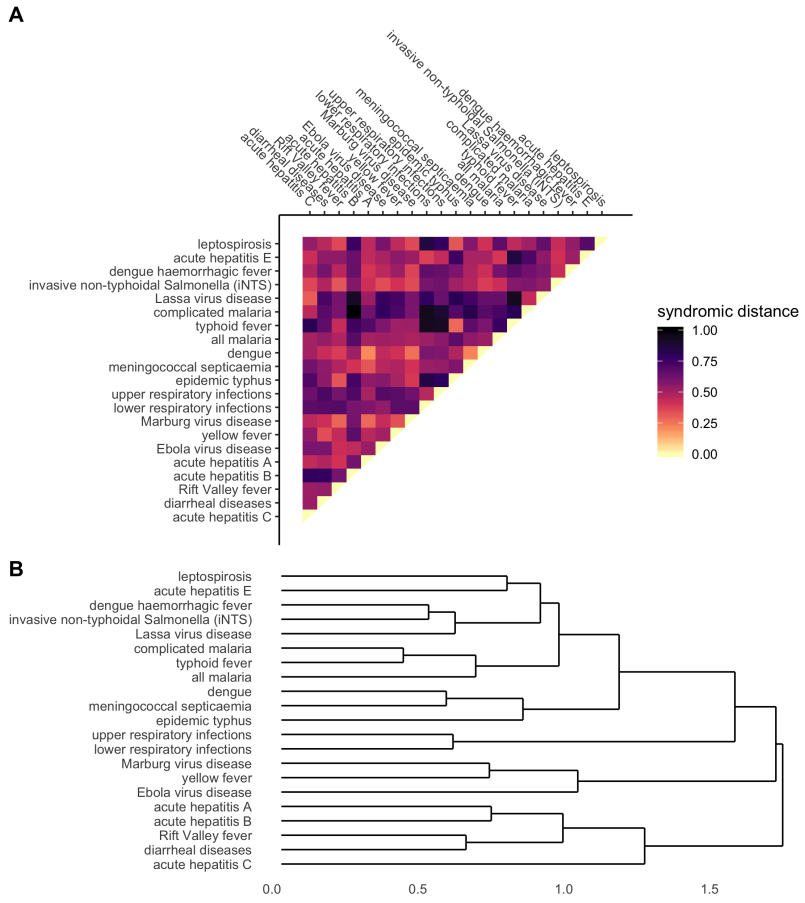

Fig. B.3 Estimated syndromic distances (as a proportion of maximum syndromic distance) of selected infectious disease syndromes, based on average incidence across sub-Saharan Africa. In contrast to a correlation plot, higher distances (darker colours) indicate further separation between the syndromes, and vice versa. B) dendrogram showing syndrome clusters according to their estimated distances and agglomerative hierarchical clustering.

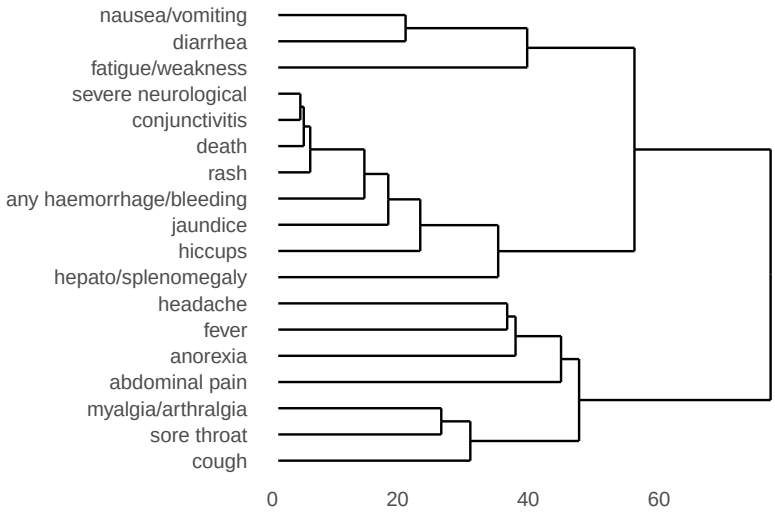

Fig. B.4 Dendrogram representing population-level relationships between various clinical signs and symptoms, based on application of agglomerative hierarchical clustering to a simulated dataset of 10,000 cases of all 21 syndromes, with each syndrome occurring proportional to its incidence.

severe neurological manifestations, conjunctivitis, haemorrhage, and jaundice—as well as of common subjective symptoms—such as headache, anorexia, and abdominal pain (Figure B.4). To account for this clustering within our core algorithm, we used the same simulated linelists to estimate a one-dimensional collinearity scalar (θ) for all clinical features using t-SNE.

B.3 Algorithm calibration and performance

To investigate the effects of the spillover scalar and estimated spillover collinearity constants (θ_k), we estimated the sensitivity and specificity of the aetiological prediction algorithm on 100 simulated cases of each syndrome in sub-Saharan Africa overall for all combinations of spillover scalar in $e^{\{0,1,\ldots 15\}}$ and collinearity weights in $\{0, 0.1, \ldots 1\}$ (Figure B.5). The algorithm was most sensitive to all syndromes with a collinearity weight of zero, without a corresponding loss in specificity (Figure B.6). As expected, the sensitivity of the algorithm to rare zoonotic syndromes increased with the spillover scalar, while sensitivity to endemic diseases decreased at extremely high values. For figures in the main text, we selected a spillover scalar of 10,000 (i.e., assuming these rare syndromes are about 10,000 times as common as observed) to achieve high sensitivity to both sets of syndromes; we also ignored clinical feature collinearity in subsequent analyses. With real-world individual-level data,

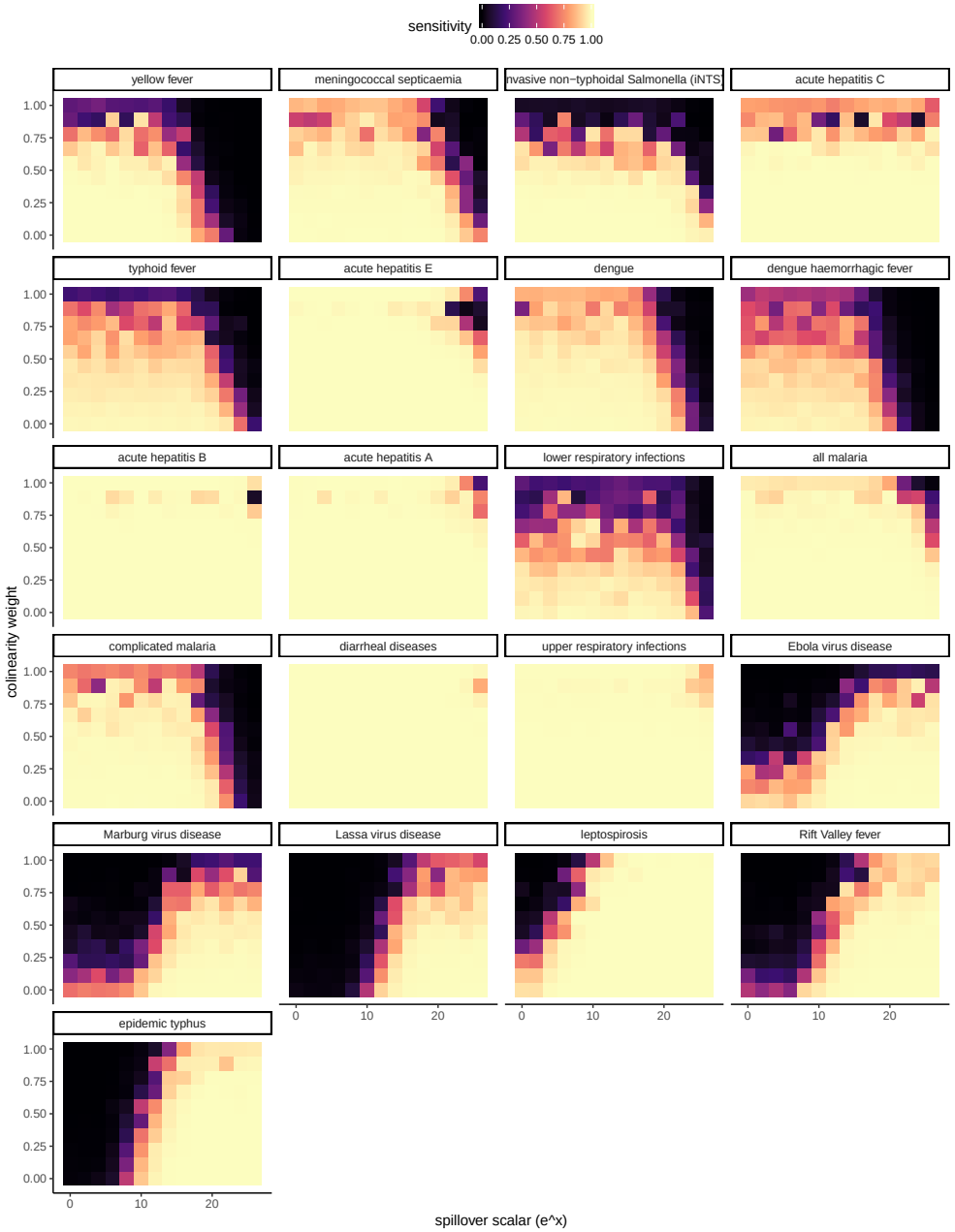

Fig. B.5 Estimated sensitivity of an aetiological identification algorithm to simulated outbreaks of each syndrome, as a function of two tuning parameters: a spillover scalar and a collinearity weight. The spillover scalar increases prior probabilities of rare zoonotic syndromes (i.e., Ebola virus disease, Marburg virus disease, Lassa virus disease, leptospirosis, Rift Valley fever, and epidemic typhus). The collinearity weight mediates the contribution of each clinical sign or symptom to posterior probabilities; a weight of 0 indicates all signs and symptoms are given equal weight, while a weight of 1 indicates the contributions of signs and symptoms are proportional to collinearity factors (θ) calculated from t-SNE.

Fig. B.6 Estimated specificity of an aetiological identification algorithm to simulated outbreaks of each syndrome, as a function of two tuning parameters: a spillover scalar and a collinearity weight. The spillover scalar increases prior probabilities of rare zoonotic syndromes (i.e., Ebola virus disease, Marburg virus disease, Lassa virus disease, leptospirosis, Rift Valley fever, and epidemic typhus). The collinearity weight mediates the contribution of each clinical sign or symptom to posterior probabilities; a weight of 0 indicates all signs and symptoms are given equal weight, while a weight of 1 indicates the contributions of signs and symptoms are proportional to collinearity factors (θ) calculated from t-SNE.

the relationships between clinical features could be better established and used to refine our models.

After calibration our detection algorithm, we tested its ability to identify clusters of clinical features from real outbreak data (Figure B.7). We applied it to a previously-published, publicly available database of febrile outbreaks in South Asia [261]. This dataset included 87 outbreaks of typhoid fever, malaria, dengue, and meningococcal disease in Bangladesh, India, Nepal, Pakistan, and Sri Lanka. As these reports did not include individual-level data, we simulated 10 linelists of up to 100 cases for each, based on reported outbreak-level clinical feature probabilities (assuming independence of each sign/symptom). We assumed no spillover of Ebola virus disease and those syndromes not listed in the GBD (i.e., Marburg virus disease, epidemic typhus, Lassa virus disease, leptospirosis, Rift Valley fever, and Crimean-Congo haemorrhagic fever).

To estimate performance of the algorithm despite highly variable data quality, we define the performance ratio of a prediction as the predicted posterior probability of the true aetiology of an outbreak (i.e., $\hat{P}_{c,n}$ of true aetiology n, where all values of $x_{k,n}$ are drawn from simulated outbreak linelists), divided by the estimated detectability of the true aetiology with the same symptoms reporting (i.e., $\hat{P}_{c,n}$ of a simulated outbreak of aetiology n, where all values of $x_{k,n}$ are drawn from the clinical presentation estimates shown in Figure B.1 and K is restricted to the set of reported symptoms). A performance ratio of 1 therefore indicates the algorithm performed exactly as well as expected to identify the outbreak cause, while a performance ratio of 10 means the predicted posterior probability when applied to real data is 10 times its expected value, accounting for the incidence of the target syndromes and clinical features available in the testing dataset.

B.4 Spatial heterogeneity in Ebola virus disease detectability

To examine spatial heterogeneity in detectability and its implications for syndromic surveillance, we selected Ebola virus disease as a case study, expanding our analysis of EVD by:

1. including country-level data from the GBD survey [250] across sub-Saharan Africa for all syndromes (with the continued exception of rare VHFs not included in the GBD, the incidences of which were estimated based on spillover rates);

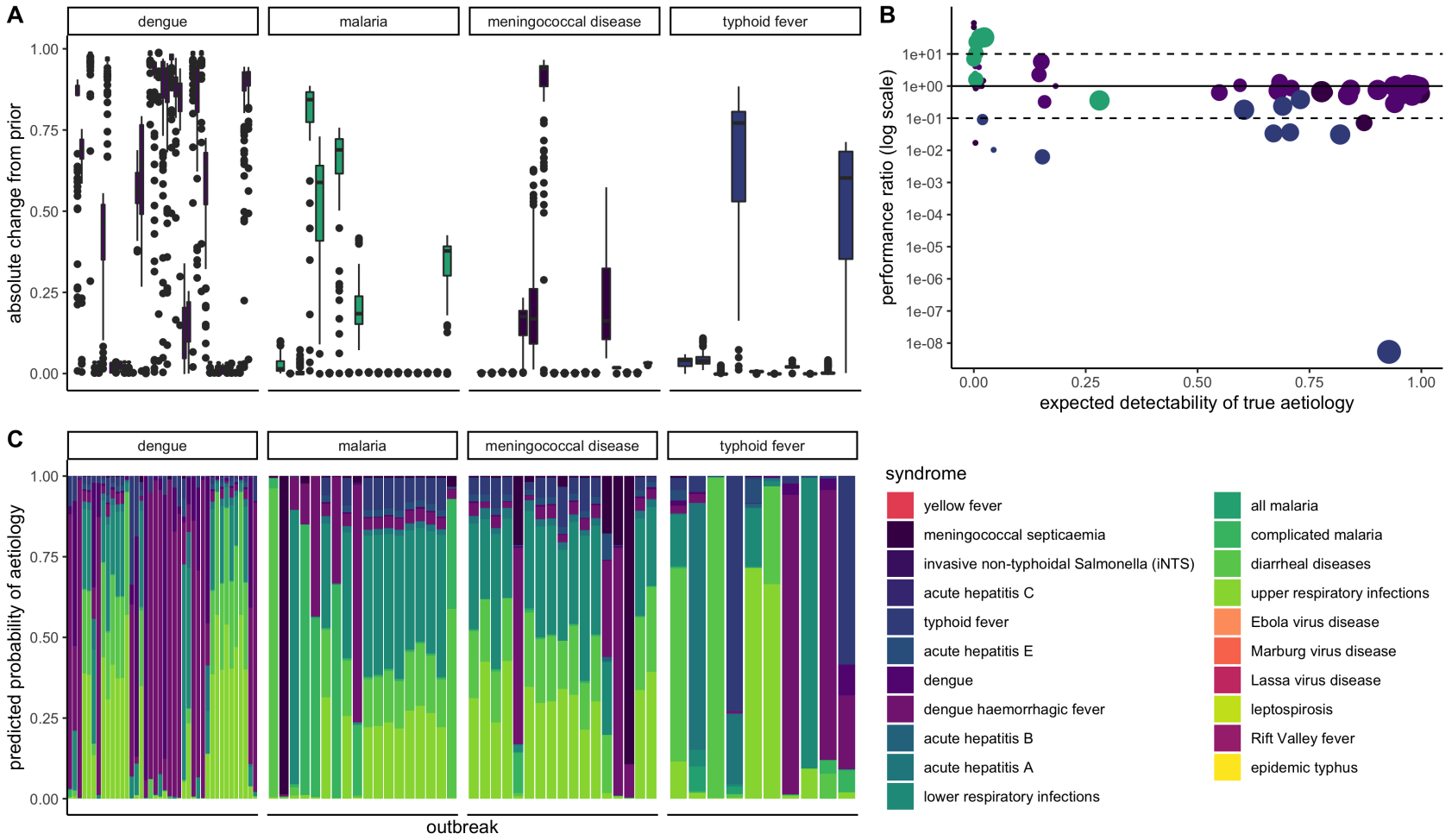

Fig. B.7 Performance of the aetiological identification algorithm applied to 87 outbreaks of dengue, malaria, meningococcal disease, and typhoid fever in South Asia. A) difference between posterior and prior probabilities of current aetiological identification of each outbreak at all cluster sizes between 1 and 100, sorted by outbreak aetiology. B) performance ratio vs. expected detectability at ten cases (i.e., predicted probability of true aetiology when algorithm is applied to real outbreak data over the estimated detectability of ten cases of the same syndrome with the same reported clinical features). Larger points represent more reported symptoms. C) predicted aetiological probabilities of each syndrome for each outbreak, averaged over all cluster sizes between 1 and 100.

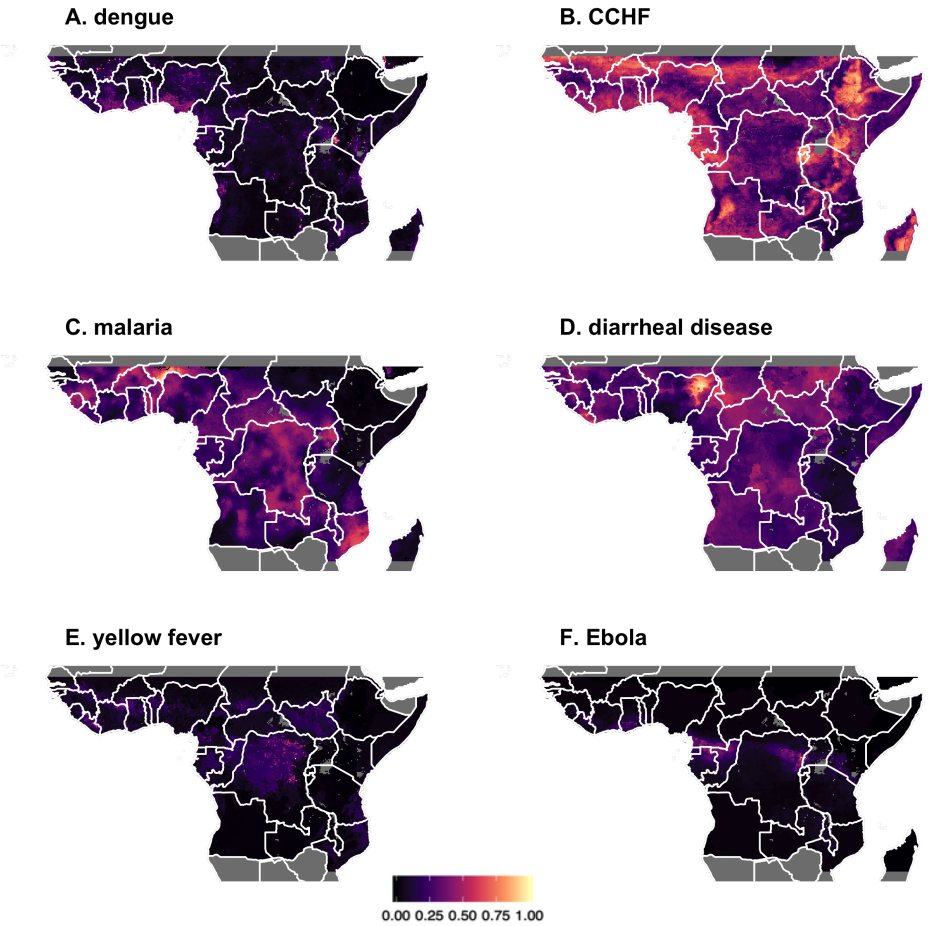

Fig. B.8 Maps showing normalised spatial distributions of estimated dengue, Crimean-Congo-haemorrhagic fever, malaria, diarrhoeal disease, and yellow fever incidence rates per capita (A-E, as used to calculate syndromic prior probabilities in aetiological detection algorithm) and Ebola spillover risk based on an ecological niche model (F).

2. substituting country-level incidence estimates of malaria with those at a higher spatial resolution, using geospatially gridded estimates from the Malaria Atlas, summed across fevers caused by *Plasmodium falciparum* [251] and *Plasmodium vivax* [252];

3. substituting country-level incidence estimates of dengue, yellow fever, Lassa virus disease, and CCHF with geospatially gridded estimates accounting for ecological suitability (Figure B.8). We generated these estimates by normalising ecological niche maps for each grid cell (previously published for dengue [254], yellow fever [253], and CCHF [512]) to sum to country-level incidences; and

4. for each cell, scaling the relevant country mean incidences of typhoid fever, iNTS, and other diarrheal diseases using normalised geospatially gridded estimates of diarrhoeal disease incidence in 2015 [257, 256]. We assume diarrheal disease incidences serve as an adequate proxy for the effects of local water, hygiene, and sanitation risk factors on iNTS and typhoid fever.

For each cell (approximately 29 km^2), we calculated detectability for each syndrome for cluster sizes between 1 and 30 cases. Finally, to identify "hidden hotspots" with both low EVD detectability and high spillover risk, we scaled our EVD detectability estimates by normalised Ebola virus disease spillover probabilities as estimated based on both its ecological niche in wildlife and its human population density [258].