Chapter 8
The Ecology of Pathogen Spillover and Disease Emergence at the Human-Wildlife-Environment Interface

Kathleen A. Alexander, Colin J. Carlson, Bryan L. Lewis, Wayne M. Getz, Madhav V. Marathe, Stephen G. Eubank, Claire E. Sanderson, and Jason K. Blackburn

Abstract Novel diseases are increasingly emerging into human populations through the complex—and often, unseen—stepwise process of spillover from a combination of wildlife, livestock, vectors, and the abiotic environment. Characterizing and modeling the spillover interface are a key part of how eco-epidemiologists respond to the growing global burden of emerging infectious diseases; but the diversity of pathogen life cycles and transmission modes poses a complex challenge for ecologists and clinicians alike. We review our current understanding of the spillover process and present a framework that relates spillover rates and human-to-human transmissibility to the basic reproduction number (R_0). Using pathogens that exemplify important transmission pathways (anthrax, Ebola, influenza, and Zika), we illustrate key aspects of the spillover interface and discuss implications to public health and management of emerging infectious disease.

K. A. Alexander (✉) · C. E. Sanderson
Department of Fish and Wildlife Conservation, Virginia Tech, Blacksburg, VA, USA
e-mail: kathyalx@vt.edu; clairees@vt.edu

C. J. Carlson · W. M. Getz
Department Environmental Science, Policy and Management, UC Berkeley, Berkeley, CA, USA
e-mail: cjcarlson@berkeley.edu; wgetz@berkeley.edu

B. L. Lewis
Department of Population Health Sciences, Department of Computer Science, Biocomplexity Institute, Virginia Tech, Blacksburg, VA, USA
e-mail: blewis@vt.edu

M. V. Marathe · S. G. Eubank
Network Dynamics and Simulation Sciences Laboratory, Biocomplexity Institute, Virginia Tech, Blacksburg, VA, USA
e-mail: mmarathe@vbi.vt.edu; seubank@vbi.vt.edu

J. K. Blackburn
Department of Geography, University of Florida, Gainesville, FL, USA
e-mail: jkblackburn@ufl.edu

8.1 Introduction

The spread of environmental or animal pathogens into human populations is a natural and perpetual process that dates back as far as human records extend. One of the earliest recorded epidemics, the plague of Athens (also called the Thucydides syndrome), took place between 430 and 425 B.C.E. and is believed to have been an outbreak of Ebola virus (Olson et al. 1996) or typhoid fever (Papagrigorakis et al. 2006). Measles emerged in human populations after evolving from rinderpest, a disease of cattle, sometime around the eleventh or twelfth century, and perhaps the most famous disease outbreak in recorded history, the Black Death, was caused by plague (*Yersinia pestis*), a vector-borne zoonosis. In this sense, the emergence of diseases is a natural process, the by-product of pathogen "chatter" between susceptible host populations of different species, with the emergence of diseases into human populations only a small subset of the broader cross talk among mammals, and animals writ large.

This process of spillover is stochastic and, from the perspective of pathogen success, fairly imperfect. The majority of mammalian viruses lack the capacity to even infect humans, and the majority of spillover events that do occur fail to establish circulating infection in the new host. But despite the long and complex history of peoples and plagues, scientific consensus indicates that the rate of infectious disease emergence has been accelerating in more recent history. Differentiating the next pandemic from background noise is a nearly insurmountable challenge and one that is ongoing as new pathogens evolve or are discovered. As participants in clinically relevant research settings, the task of ecologists studying spillover revolves around three key issues:

1. Describing the process of spillover and interactions and state changes between hosts, pathogens, and the environment that lead to disease emergence
2. Developing predictive conceptual and quantitative models that can explain spillover patterns and forecast disease emergence, epidemic behavior, and/or intervention impact
3. Applying ecological and clinical knowledge to develop interventions that mitigate, control, and potentially prevent epidemics and pandemics

Each of these independently poses a substantial challenge. The diversity of pathogens, transmission modes, and eco-epidemiological interfaces further complicates the development of a conceptual framework that will adequately address any one of these challenges, let alone all three.

In this chapter, we review existing research on the spillover interface and the relevant ecological advances that have been made especially in the last two decades. We begin by reviewing the most recent work characterizing the process of pathogen emergence. Building on this, we present a conceptual framework that engages the stages of pathogen emergence as a dynamic continuum rather than a binary, or even linear, set of sequential steps. We use this framework to evaluate a number of pathogens that illustrate key features important to the spillover process. We conclude by discussing how this approach lends itself to a more quantitative and focused

assessment of spillover itself—the key element shaping pathogen emergence potential at the human-animal-environmental interface.

8.2   The Usual Suspects: What Makes an Emerging Zoonosis?

Zoonotic disease emergence arises as a consequence of transmission of a multi-host pathogen from an animal host (direct or indirect transmission) to a human, with or without onward human-to-human transmission and establishment (Antia et al. 2003). We define a **zoonotic reservoir** as one or more epidemiologically connected animal populations and/or environments where a pathogen can be maintained and transmitted to humans (Haydon et al. 2002) and, more broadly, domestic animals as well. Regardless of transmission mode, the process by which a pathogen moves from one host population (or environmental reservoir) to another host population is referred to as **spillover** and arises from complex bidirectional interactions among people, animals, pathogen communities, and environments. This is a key step in zoonotic disease emergence but remains poorly understood and often not explicitly quantified in transmission models (Lloyd-Smith et al. 2009; Iacono et al. 2016), which tend to focus on dynamics within a single population.

Some of the most significant quantitative work at the spillover interface has focused not on predicting rates of zoonotic spillover but on identifying and predicting the common features of spillover diseases and the pathways they tend to exploit. Viruses have been best studied in this context; basic rules of thumb are well established, such that single-stranded RNA viruses are predisposed to become zoonoses, likely due to a predisposition toward evolvability and host switching. Other rules have emerged from studying the networks of viral transmission between different host groups and humans. For example, a study by Johnson et al. (2015) demonstrated a number of key rules, perhaps most importantly that viruses with greater host plasticity in animal reservoirs are more likely to demonstrate human-to-human transmissibility. Some virus families, such as arenaviruses and filoviruses, are predisposed to human-to-human transmission. Correspondingly, some groups of mammals were especially common reservoirs of zoonotic viruses, including rodents (especially for arena- and bunyaviruses), primates (retroviruses), and bats (paramyxoviruses and rhabdoviruses). Pathways of spillover were also noted to differ, with bush meat hunting being a notable source of exposure to nonhuman primate viruses, while proximity of homes to fields was a significant driver for exposure to rodent-borne viruses (Dearing and Dizney 2010). Although sometimes not considered a "pathway of spillover," vectors can also act as a critical component in spillover dynamics with, for example, Johnson et al. showing that virus spillover from bird reservoirs was disproportionately vector borne.

A recent study by Olival et al. (2017) refined and elaborated these findings, confirming that RNA viruses are more commonly zoonotic and that the phylogenetic breadth of viral hosts is the strongest predictor of zoonotic potential (analogous to

Johnson's findings about viral plasticity). Olival et al. also confirmed that bat viruses were disproportionately zoonotic, an unsurprising finding given that many well-known viruses have originated from bat reservoirs [e.g., Ebola and Marburg viruses, Hendra and Nipah viruses, and even severe acute respiratory syndrome (SARS) and, likely, Middle East respiratory syndrome (MERS)]. Olival et al. confirmed that viruses with arthropod vectors have a greater plasticity in their mammalian hosts and showed that viral replication in the cytoplasm also predicts zoonotic potential. Finally, their study shows that human population density in host ranges and the phylogenetic relatedness of wildlife reservoirs to humans were important predictors of zoonotic emergence. These aspects are likely related to the evolutionary processes that occur at the spillover interface, where viruses coevolve with new hosts and incrementally develop greater emergence potential over time (which we discuss below).

Studies like Johnson's and Olival's are a key part of how disease ecologists consolidate information about the emergence of zoonotic diseases and reveal important information about the patterns—and, ideally, processes—that transpire at the spillover interface. Given the recent preponderance of devastating viral outbreaks, such as Ebola and Zika, it is unsurprising that so much attention has been paid to the factors that drive viral emergence. Comparatively less work has been done to consolidate these types of results for other major pathogen groups, like bacteria, protozoans, and fungi. While broad studies like these elucidate general patterns and help develop predictive tools for identifying the zoonotic potential of recently discovered pathogens, these studies do little to explain outbreak process and spillover dynamics for known zoonoses.

8.3   Characterizing Pathogen Spillover

The diversity of existing emerging pathogens can be overwhelming, with over 300 documented emerging infectious diseases occurring between 1940 and 2004 (Jones et al. 2008), and several more, which have since emerged. Greater still, it must be expected, is the diversity of potential zoonotic threats that have not yet emerged into human populations but could do so in the coming years as viruses, hosts, and landscapes experience accelerated change. Frameworks provide an opportunity to generalize patterns across pathogens, supporting model development and interventions that can be especially valuable for diagnosing epidemic profiles and responding during the early days of a pathogen's emergence. Several frameworks have been developed that organize and describe pathogens based on stages of emergence, but the spillover interface is still poorly captured for many diseases, and most frameworks have limited direct applicability to quantitative methods. In this section, we review existing frameworks and, building on this, present our own framework that is explicitly directed at modeling the unique mathematical behavior of pathogen spillover.

8.3.1 Existing Frameworks

In contemporary disease ecology literature, two major frameworks have been proposed that describe the stages of pathogen emergence. The first, and most commonly referenced, was proposed by Wolfe et al. (2007) and divides pathogen emergence into five progressive stages through which a pathogen may pass sequentially:

Wolfe's Stages of Spillover

  I. Agent only in animals
 II. Primary infection in humans
III. Limited outbreak in humans
IV. Long outbreak in humans
 V. Exclusive human agent

In this classification scheme, zoonotic emergence occurs between Stages II and IV. In the most constrained case (Stage II), spillover only ever leads to primary infection in humans with no onward transmission within human populations. Whereas Stage III is characterized by short chains of transmission ("stuttering chains"), Stage IV features human-to-human sustained epidemic transmission. The line between the two is obviously not only subjective but may create difficulties when characterizing expected pathogen behavior. For example, outbreaks of Ebola virus beginning in 1976 were typically small and situated in rural areas where outbreaks could have been classified as Stage III. However, since 2014, Ebola has been considered a Stage IV zoonosis, and modeling work undertaken during the 2014–2015 Ebola epidemic in West Africa showed that "the same epidemiological conditions that were present in 1976 could have generated a large outbreak purely by chance" (Camacho et al. 2014). The line, therefore, between short-chain and epidemic transmission for a pathogen is sometimes unclear.

A second framework, proposed by Lloyd-Smith et al. (2009), refines the Wolfe classification scheme by more formally considering the mathematical definitions of the three intermediate categories:

 II. Spillover into humans (no human-to-human transmission; $R_0 = 0$)
III. Stuttering transmission in humans ($R_0 \leq 1$)
IV. Long outbreak in humans ($R_0 > 1$)

Here, R_0 is defined as the number of secondary infections caused by a typical single infective individual in a wholly susceptible population during its period of infectiousness (Diekmann et al. 1990). Incorporating an explicitly quantitative aspect to the definition of the stages improves the framework in obvious ways and facilitates the more direct integration of epidemiological modeling and zoonosis

research. However, the same data limitations pose a problem for this framework, as a fairly newly emerged zoonosis is unlikely to have enough accompanying surveillance data to characterize its basic R_0, let alone elucidate situational variance due to socioeconomic and ecological factors. Later, we will discuss modeling approaches that can resolve some of these problems.

What do these frameworks contribute to disease ecology? At the most basic level, frameworks for classifying pathogens help us abstract and generalize patterns across hosts, pathogens, and landscapes. Furthermore, developing a more standardized language for describing spillover and disease emergence helps bridge the gap between ecology, infectious disease research, and clinical and public health. With the increasing burden of emerging infectious diseases and the accelerating rate of emergence of novel zoonoses, frameworks for classifying zoonotic disease emergence can help develop and refine prioritization schemes.

8.3.2   Advancing the Spillover Framework

The past few decades of ecological research have shown that pathogen life history is far more flexible and dynamic than any linear set of steps characterizing emergence might capture. A framework oriented on a sequential progression can be useful for conceptualizing the emergence of some pathogens like measles or human immunodeficiency virus (HIV); but the diversity of emerging zoonoses contains many more life histories. Moreover, the development of a framework with an inherent directionality risks "adaptationism," misconstruing the random evolutionary trajectories of pathogens that include humans as a (non-special) part of a broader ecosystem including wildlife, vectors, livestock, and even the soil and water. To improve our understanding of spillover into human populations, we must first better conceptualize the complicated dynamics of interspecies spillover (human or not; Fig. 8.1).

As discussed previously, spillover and emergence of zoonotic pathogens have generally been represented within a framework that focuses on the objects of systems (hosts, pathogens, entities in the environment) (Daszak et al. 2000; Childs et al. 2007) rather than the interacting and cascading systems' processes themselves. It is the active steps of emergence (exposure, contact, invasion, and onward transmission), influenced by host-pathogen evolutionary processes, that ultimately determine the outcome of interactions among entities. In short, spillover and emergence are stochastic processes with outcomes that depend on the probabilities of the occurrence of underlying events. As we will make clear, the variability associated with spillover and emergence is large because the size of groups involved (vis-à-vis number of infected individuals) is small and hence subjects to the vagaries of sampling: it is only after sufficiently many of these events have been observed that we can begin to meaningfully characterize spillover and emergence in terms of expected rates of pathogen transmission. Using our framework, three key processes are delineated that determine (1) the occurrence of pathogen spillover from reservoirs either to an intermediary or directly to a focal host; (2) the occurrence of primary transmission from an intermediary to a focal host, when intermediary hosts
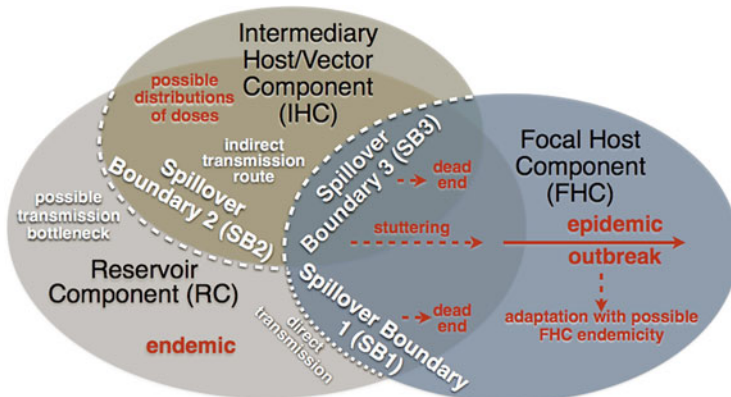
Fig. 8.1 Conceptual model of the process of pathogen spillover and emergence. The ellipses represent three conceptual components: reservoir (RC, either environmental or wildlife populations serving as an ecological system in which the pathogen is endemically maintained), intermediary host/vector (IHC) population that serves to transfer the pathogen from the reservoir to the focal host, and focal host (FHC), generally human or species of special concern (e.g., domestic or highly threatened species). The dotted lines represent three spillover boundaries between RC-FHC (SB1 direct transmission route), RC-IHC (SB2), and IHC-FHC (SB3) (the concatenation of these latter two constitutes the indirect transmission route)

play a role (which is in most cases); and (3) the occurrence of secondary focal host-to-host transmission required for true disease emergence in the focal host. We use the term true emergence to contrast with the observation of multiple focal host cases of an infectious disease arising exclusively from spillover (Antia et al. 2003). Using emerging zoonotic disease examples, we explore this framework and provide recommendations for evaluating zoonotic outbreaks, managing interventions during outbreaks, and planning future research.

8.3.2.1   Structural Elements

The model has three main compartments: a reservoir component (RC, self-sustaining or endemic source of pathogen that may be purely environmental or involve at least one host species as well), an intermediary host/vector component (IHC) where prevalence would drop to zero if the reservoir were removed (if this component is self-sustaining, then it just becomes part of the reservoir), and a focal host component (FHC) where epidemic outbreaks may occur and the potential for endemic establishment of the pathogen exists through evolutionary processes. Each of these compartments in the model is influenced by various factors and interactions (e.g., factors which influence the state of the host, pathogen, and environment and the resultant interactions; see Table 8.1 for examples), as well as the processes of source-host contact, intensity and duration of exposure, pathogen invasion potential for individual hosts (i.e., interactions between pathogens and the immune system), and onward transmission and adaptation within host populations. We find it insightful to

Table 8.1 The disease emergence process is divided into four main steps. Examples of both factors and zoonotic pathogen systems are provided for each emergence step

Process	Example		
	Factor	Disease	Mechanism
Host exposure (spatial overlap between host and pathogen)	Host behavior	Chagas disease	Sedentary lifestyles and rearing of domestic animals in particular, such as the Brazilian guinea pigs (*Cavia aperea*), were important in creating favorable conditions for the domiciliation (successful home invasion) of the vector (Triatominae) (Alexander and McNutt 2010)
	Habitat alteration and fragmentation	*Borrelia burgdorferi*, Lyme disease	Deforestation and habitat fragmentation results in decreasing mammalian species diversity and increasing population densities of the reservoir with concomitant increased human exposure (Allan et al. 2003)
	Agricultural processes	*Cryptosporidium parvum*	Fecal contamination of water sources in agriculture production systems and food processing (Orlandi et al. 2002)
	Commercial resource use	Ebola	Logging of forests and exposure to virus, commercial sale of bush meat
	Climate	*Yersinia pestis*, plague	El Niño Southern Oscillation events increase the number of *Yersinia pestis* flea vectors and rodent host populations and are linked to prairie dog colony extinction events due to this pathogen (Stapp et al. 2004)
	Movement of infected hosts	*Trypanosoma brucei rhodesiense*, sleeping sickness	Movement of infected cattle is linked to an outbreak of human sleeping sickness in a previously unaffected area of Uganda (Fèvre et al. 2005)
	Seasonal dynamics	Lassa virus	Dry season shifts increases in rodent host densities in houses may increase the risk of contact with rodent host and excreta (Fichet-Calvet et al. 2007)
	Host density	Hantavirus	Increases in rodent populations and density are

(continued)

Table 8.1 (continued)

Process	Example		
	Factor	Disease	Mechanism
			associated with increased contact and pathogen spillover to humans (Wells et al. 1997)
	Disruption of reservoir host social structure	*Mycobacterium bovis*, bovine tuberculosis	Culling of badgers to control TB exposure induced badger long-distance movement and dispersal (Donnelly et al. 2003)
Contact (nature of contact with the pathogen will determine if pathogen can invade host)	Predation of infected hosts	Bluetongue virus	Bluetongue virus, a vector-borne pathogen, infects ruminants, shrews, and some rodent species. Ingestion of infected prey allows virus transmission to African predators without vector involvement (Alexander et al. 1994)
	Predation of infected hosts	African horse sickness virus	African horse sickness is a vector-borne disease that principle affects equids. Domestic dog and African predators are thought to be infected from ingestion of infected equid species (Alexander et al. 1995)
	Diet	Ebola	Hosts that eat certain fruits are brought together where transmission of the virus can occur from the bat reservoir through saliva contamination of fruit and ingestion by other species such as gorillas (Dobson 2005)
	Socioeconomic status of human communities	Leptospirosis	Poverty and compromised sanitation infrastructure increase contact with environmental sources of *Leptospira* (Reis et al. 2008)
	Pathogen release and change in immune protection in the human host	Monkeypox virus	Cross-immunity between smallpox and monkeypox virus and cessation of vaccination have allowed host immunologic release and emergence of monkeypox virus in the human host (Rimoin et al. 2010)

Table 8.1 (continued)

Process	Factor	Disease	Mechanism
	Example		
Pathogen invasion and adaptation (pathogen enters and replicates in the susceptible host)	Virus evolution and strain variability	Influenza viruses	Influenza interspecies transmission is influenced by strain variability. New strains can evolve when two different viruses infect individual cells. Segments derived from each of the infecting "parents" may reassort and create a new strain with a changed host invasion potential (Webster et al. 1997)
	Host physiology, coinfection	*Cryptococcus neoformans*	Immunosuppression of the human host with HIV/AIDS can increase pathogen invasion risk (Chuck and Sande 1989)
	Coinfection can decrease macroparasite infestations	Nematode infections	The gastrointestinal nematode *Heligmosomoides polygyrus* decreases infestation of the tick *Ixodes ricinus* in free-living yellow-necked mice, *Apodemus flavicollis* (Ferrari, Cattadori et al. 2009)
	Tissue tropism	Hendra and Nipah virus	Viral transmission and spillover is influenced by the tissue tropism of the virus and access to the exterior of the host (Hooper et al. 2001; Childs 2004
	Human behavior	Sudden acute respiratory syndrome (SARS)	Wet markets allow different hosts and viruses to have concentrated contact with each other and human, supporting viral change and host adaptation (Brown 2004)
	Mutation frequency, genetic diversity	Venezuelan equine encephalitis virus	RNA mutations allow production of amplification-competent (high equine viremia) viral strains, which can then invade the human host through vector-mediated transmission (Anishchenko et al. 2006)
	Virus evolution and strain variability	SARS	Genetic variations in critical genes, such as the *Spike* gene

Table 8.1 (continued)

Process	Example		
	Factor	Disease	Mechanism
			(protein responsible for host cell receptor binding) influence pathogen invasion potential (Song et al. 2005)
	Human sexual behavior	HIV	Persons at an increased risk of transmitting or being infected by the HIV virus were more likely to practice unprotected sex (Halperin 1999)
Sustained onward transmission in new host(s) (secondary cases of human-human transmission)	Culture and human behavior	Ebola virus	Culturally driven practices such as ritual handwashing and sharing of communal meals at funerals of Ebola-infected individuals have been significantly associated with Ebola viral transmission (Griffin et al. 2003)
	Globalized travel and contact	SARS	Air travel and global traffic facilitate the spread of the pathogen (Ali and Keil 2006)
	Within human host adaptive mutation potential	SARS	Non-synonymous changes in the spike gene are found in viruses with sustained human-to-human transmission. These genetic changes are not found in viruses circulating in the reservoir host (palm civets) or spillover viruses that did not successfully move to the host epidemic space where sustained human-to-human transmission occurs (Pepin et al. 2010)

consider pathogen spillover as typically involving four conceptually distinct, transmission processes: spillover from the reservoir component (RC) directly to the focal host component (FHC) (i.e., spillover boundary 1, SB1), spillover from the RC to the intermediary host/vector component (IHC) (i.e., spillover boundary 2, SB2), spillover from the IHC to the FHC (i.e., spillover boundary 3, SB3), and host-to-host transmission within the FHC itself.

Direct transmission across SB1 occurs between focal susceptible individuals and either individuals from reservoir species, the environment, or fomites (e.g., infected intermediary host fecal material or carcasses). Transmission across SB2 often presents an important bottleneck to pathogens ultimately entering FHC. Transmission

across SB3 is generally the focal spillover process, particularly those vectored by mosquitoes and parasites. Transmission across these spillover boundaries may either result in a dead-end infection of a focal host, a stuttering transmission chain in the focal host ($R_0 < 1$ in FHC), or an epidemic outbreak (R_0 necessarily > 1 in FHS). One or more such outbreaks may lead to adaptation and FHC endemicity.

Situations may exist where some focal hosts have been infected across the SB1 or SB3, resulting in mixed transmission. Emergence within the FHC (i.e., a zoonotic outbreak) requires that novel host(s) then transmit the pathogen to other members of the same species, with the degree of onward transmission determining the nature of the epidemic in the FHC. In some cases, pathogens may routinely spillover without resulting in any onward transmission in the FHC. In this case, the novel host is a dead end, and the epidemic is purely driven by spillover events. In humans, we see examples of this with anthrax and rabies. Once a spillover proceeds to include direct focal host-to-host transmission, if $R_0 < 1$, the process ends in a transmission chain that has a geometric distribution with an expected length of ($1 - 1/R_0$) (distribution of chains that arise from several such transmission events is referred to as stuttering chains, Antia et al. 2003). On the other hand, if $R_0 > 1$, then the probability of an epidemic outbreak in FHC rises steeply with the value of R_0 (Antia et al. 2003).

Finally, it is worth stressing that the reservoir (RC) may itself be a vector-host system with another vector acting as the intermediary (i.e., IHC) between RC and the focal host (FHC). This is the case for West Nile virus (WNV) where RC is maintained by a passerine bird and *Culex* mosquitoes host-vector system but where *Aedes* mosquitoes are an intermediary host/vector component (Kilpatrick 2011; Petersen et al. 2013). Thus, when humans get bitten by WNV-infected *Culex* individuals, transmission can be regarded as direct (i.e., occurring across SB1); but when humans get bitten by WNV-infected *Aedes* individuals, transmission can be regarded as indirect with the pathogen needing to cross both SB2 and SB3 to be transferred from RC to FHC. The reason for this discussion relates to how we ultimately use our model to assess probabilities of outbreaks of zoonotic disease in humans and other focal species of interest.

8.3.2.2   IHC Computational Elements

It is important to note that all models are abstractions. Deciding on the appropriate level of detail to include in a model depends on the questions to be addressed and an understanding of the processes needed in the model to adequately address these questions. In our framework, we assume that little is known about the structure and dynamics of the reservoir. Thus, we simply represent the reservoir in terms of a spatiotemporal risk-of-infection function $R(x, t)$, where x is a point in space (typically 2D) and t is a point in time. More ambitiously, we endeavor to represent the intermediary host in terms of both its population density $Y(x, t)$ and the prevalence of infection $IY(x, t)$ over space and time. Calculation of $PY(x, t)$ in terms of $R(x, t)$ and $Y(x, t)$ represents the real challenge, particularly if the impacts of various critical factors, as elaborated in the sections below, are to be incorporated. The primary focus is on the IHC where most of the interesting dynamics take place

prior to an outbreak within the FHC. Once an outbreak begins in the focal host population, then the emphasis switches to the dynamics of infection within the FHC. This will only progress beyond the dead-end or stuttering phases if the pathogen is sufficiently virulent within FHC to have an associated $R_0 > 1$.

As will become clear from our discussion, many different types of zoonotic systems exist, each requiring its own approach to the development of an appropriate model. Here, we focus on general concepts, as well as some novel elements that have not been introduced elsewhere in the literature. The essence of an IHC model is the intermediary population. Without going into detail regarding age, sex, or spatial structure, the dynamics of this population should minimally be described by a model that includes a demographic recruitment process (e.g., births and immigration), a natural mortality process, a pathogen exposure process, a disease class structure (e.g., susceptible S, infected but not yet infectious E, infectious I, recovered with some level of immunity R that may wane over time), a disease-induced mortality process, and a disease progression transfer matrix. The latter may be rather simple when considering transfers from E to I to R and possibly back to S, but the real challenge lies in modeling the transfer of individuals from class S to class E—i.e., the disease transmission process.

Disease transmission can be unpacked as a concatenation of (1) a source/susceptible host contact process that possibly includes notions of the intensity and duration of exposure to a dose of pathogen and (2) the probability of succumbing to infection given the characteristics of the contact. Contact itself requires an understanding of host behavioral and movement ecology, while dose-exposure computations require explicit characterization of the pathogen encounter risk distribution function $R(x, t)$ introduced above. Note that the movement of susceptible individuals in IHC may alter their movement behavior in response to the distribution of $R(x, t)$, as is the case for anthrax. Finally the probability of succumbing to infection given a contact (C) of intensity w and duration τ will depend on the immunological state of the susceptible in IHC. If a susceptible is immunologically naive, then we would expect the probability of succumbing to be given by a function $C(w, \tau)$ that has the following properties: $C(0, \tau) = 0$ for all $\tau \geq 0$ and $C(w, 0) = 0$ for all $w \geq 0$ imply no dose and no transfer; $C(w, \tau) \geq 0$ is an increasing function of w for fixed τ and of τ for fixed w but is constrained to satisfy $C(w, \tau) \leq 1$ for all $w \geq 0$ and $\tau \geq 0$; and, most importantly, $C(w, k)$ is an increasing function of w when $w\tau = k$. The latter implies that for a constant dose k, it is more contagious to be exposed to a higher dose rate (dose per unit time) for a shorter time than a lower dose rate for a longer time. Perhaps the simplest two-parameter function that satisfies these properties is

$$C(w, \tau) = \left(\frac{c_1 w \tau}{1 + c_1 w \tau}\right)\left(\frac{c_2 w}{1 + c_2 w}\right) \tag{8.1}$$

where $c1 > 0$ and $c2 > 0$ are the parameters in question. If a susceptible is not naive, then we can reduce the value of $C(w, \tau)$ accordingly. This function for C is of course a model, and therefore an oversimplification (and should not be taken to suggest that low doses imply negligible exposure), but offers a useful conceptual framework and is a starting point for more complicated epidemiological models.

8.3.2.3   FHC Empirical Elements

Susceptible individuals within FHC have three possible sources of infection: from RC across spillover boundary SB1, from IHC across spillover boundary SB3, and from host-to-host transmission within FHC. With recent advances in RNA and DNA sequencing technology, we now have the ability to trace the lineage of pathogens that have high mutational rates, in particular single-stranded RNA viruses (Duffy et al. 2008) within families such as the Coronaviridae (including SARS-CoV and MERS-CoV), Flaviviridae (e.g., yellow fever, West Nile, dengue, Zika, and hepatitis C viruses), and Filoviridae (Ebola virus and Marburg virus). Monitoring molecular data over time allows an opportunity to assess the spillover rates of viruses across SB1 and SB3. Genetic sequences from pathogens originating in RC and IHC are necessary here but not always available. Contact tracing can also be used in human populations to infer whether transmission is primary (i.e., across SB1 or SB3) or secondary (i.e., human-to-human within FHC). Finally, once secondary transmission has been identified in the FHC, then contact tracing can also be used to construct next-generation distributions where estimates of R_0 can be developed. Only if $R_0 > 1$ can an outbreak occur, and even then if $R_0 > 1$ is close to 1, epidemic fade-out may be more likely than an epidemic outbreak (Parrish et al. 2008; Lloyd-Smith et al. 2005).

The quantity R_0 is often considered the most important element studied in epidemiology, providing critical insight into epidemic behavior (Heesterbeek 2002). The value of R_0 can be reduced by shortening the period of infectiousness, decreasing the rate of new infections, or by increasing pathogen mortality (Hudson et al. 2008). In a full FHC epidemic with eventual fade-out, host factors themselves may drive the process through changes in contact behavior, treatment, and/or other interventions that reduce R_0, leading to fade-out and cessation of the epidemic. For example, interventions such as quarantining infected individuals limited the SARS outbreak in China in 2003 to fewer than 10,000 cases, even though the international travel of infected individuals puts hundreds of millions of individuals at risk (Smith 2006). Alternatively, the pathogen may establish itself in the new host population, sustained by secondary transmission, leading ultimately to endemic infection (e.g., HIV/AIDS; see below) or eventual epidemic fade-out. In the latter case, the pathogen cannot persist in the population as might happen, for example, when the proportion of susceptible individuals has been greatly reduced by the action of the epidemic itself [e.g., 1918 influenza pandemic, "the Spanish flu" (Taubenberger and Morens 2006)]. Ultimately, it is the convergence and interplay of specific factors from the involved compartments and host-pathogen interactions that will determine if pathogen transmission will successfully occur and the nature of the resultant epidemic(s).

8.3.2.4   Factors Influencing the Disease Emergence Process

A unique suite of factors will influence each step of the pathogen invasion process, determining the potential for disease emergence (Table 8.1). As alluded above,

pathogen exposure is the fundamental requirement for pathogen spillover in a new host and is influenced by the spatial overlap and density of infected and susceptible hosts. Here, various factors can influence the outcome of exposure. External forcings such as climate or extreme weather events are able to drive host and pathogen distributions and disease occurrence (Alexander et al. 2012b). For example, El Niño Southern Oscillation events have been linked to increases in the number of *Yersinia pestis* flea vectors and rodent host populations, leading to increased pathogen invasion and mortality in prairie dog (*Cynomys ludovicianus*) colonies and colony extinction events (Stapp et al. 2004). Likewise, human behavior can influence domestic animal pathogen exposure to wildlife. For example, cattle herding behavior of dog owners influenced contact between African wild dogs (*Lycaon pictus*) and domestic dogs, exposing the wild dogs to canine pathogens and causing catastrophic declines in wild dog populations (Alexander and McNutt 2010).

While spatiotemporal overlap between a potential host and a pathogen reservoir may occur, the nature of the contact between host and pathogen must be appropriate to support host invasion (Morris et al. 2016). For example, socioeconomic status can influence human exposure to leptospirosis where poverty and compromised sanitation infrastructure increase contact with environmental sources of *Leptospira* (Reis et al. 2008). Similarly, bluetongue virus was historically thought to infect only ruminants, shrews, and some rodent species with pathogen transmission being vector dependent. Bluetongue virus in African predators, however, appears to be related to the ingestion of virus-infected prey with prevalence levels associated with feeding behavior and organ access (Alexander et al. 1994).

Pathogen spillover and replication in the new host can be influenced by the presence of other pathogens (Rigaud et al. 2010). Cross-immunity between pathogens can influence disease outcomes, as seen with smallpox and monkeypox virus, where cessation of smallpox vaccination allowed host immunologic release and emergence of monkeypox virus in the human host (Rimoin et al. 2010). Evolutionary change can also influence pathogenicity of an infectious disease organism or modify host resistance and pathogen invasion potential (Tack et al. 2012). In this case, coevolutionary selection occurs in response to variation in a myriad of processes acting on both the host and pathogen affecting their interactions across space and time. These effects make it difficult to generalize pathogen invasion behavior and predict host-pathogen interaction outcomes.

Pathogen factors pertaining primarily to evolutionary change [neutral drift, coevolution with the host, or adaptive evolution (Antia et al. 2003)] often become critical in determining the final outcome of the invasion in situations where regular outbreaks of the pathogen lead to a strain endemic to the FHC. This is the case for all human diseases that have clear origins in wildlife populations. For example, non-synonymous changes in the Spike gene were found only in SARS viruses where sustained human-to-human transmission occurred. These genetic changes were not found in viruses circulating in the reservoir host (palm civets; *Paradoxurus hermaphroditus*) or in those spillover viruses that did not successfully move to the FHC where sustained human-to-human transmission occurred (Pepin et al. 2010). A more dramatic case is HIV-AIDS that has two different simian sources, resulting in two distinct groups of HIV pathogens: one from gorillas (*Gorilla gorilla*; HIV-1) and

the other from sooty mangabeys (*Cercocebus atys*; HIV-2) (Lemey et al. 2003; Keele et al. 2006).

8.3.2.5   Zoonotic Disease Emergence and R_0

Many studies of multi-host pathogen systems have mathematically incorporated the process of spillover (McCormack and Allen 2007; Kilpatrick et al. 2006; Dobson 2004), but failure to monitor spillover rates long term has limited our ability to assess the magnitude of spillover as isolated phenomena from within host species transmission. For example, in diseases such as rabies (Zinsstag et al. 2009) and brucellosis (Zinsstag et al. 2005), where R_0 in humans is zero, we often find calculations of R_0 developed for reservoir populations, without any explicit quantitative consideration of the magnitude of spillover into the FHC. This is also seen in a recent paper that explicitly models dog-to-human transmission for rabies (Zinsstag et al. 2009), including the development of clinical disease in both human and dog populations. R_0 is calculated for dog-to-dog transmission in IHC, but no specification of spillover rates across SB3 is made. This tells us that there is sustained transmission in the dog population, prior to any introduction of interventions; but the estimated dog-to-human contact rate is never used to provide an explicit corresponding estimation of the size of the spillover event. In the context of vector-borne diseases, a similarly approached assessment can be found with *Plasmodium knowlesi* transmission from monkeys to humans through *Anopheles leucosphyrus* mosquitoes, an interesting example of spillover (Cox-Singh and Singh 2008). A recent model of this system (Yakob et al. 2010) could be usefully extended to include the elaboration of spillover values: monkeys to humans and humans back to monkeys, in both cases through mosquitoes. Incorporation of such measures would be useful in understanding and characterizing the dynamic process of disease emergence.

8.3.2.6 R_0, H_T, and Spillover

When transmission has a significant density-dependent component, R_0 is related to the establishment threshold H_T (Diekmann et al. 1990) (but see Lloyd-Smith et al. 2005), defined as the minimum density of susceptible hosts necessary for establishment of the pathogen in a new host population. This threshold may disappear when frequency-dependent transmission predominates (Getz and Pickering 1983), as is the case for sexually transmitted diseases. Establishment of the pathogen will only occur if the necessary threshold density of susceptible individuals is identified and is required to ensure that $R_0 \geq 1$; otherwise, failing to have the necessary density of susceptibles, the pathogen will fade out with $R_0 < 1$. Disease control or eradication efforts are then focused on using this threshold principle to manipulate pathogen fadeout in the new host population through the reduction of susceptibles as, for example, with H1N1 and the use of vaccination and school closures to control the outbreak. However, R_0 and H_T do not apply to transmission across spillover boundaries SB1 and SB3 where primary transmission of zoonotic disease occurs. These concepts are,

by definition, only applicable to the transmission within the reservoir or spillover host populations themselves. Further, spillover and onward transmission differ in an important respect: spillover is a series of onetime events, while onward transmission can either lead to stuttering chains, involving small groups of individuals from the animal and human populations interacting in the FHC, or full-blown outbreaks. Consequently, relative to time, the accumulation of spillover events is a linear process coupled to the nonlinear exponential processes of transmission in the reservoir and spillover host populations (Fig. 8.2). To assess the potential for outbreaks in the FHC, we need estimates of both spillover rates across SB1 and SB3, as well as estimates of the R_0 that will ensue once host-to-host transmission is established in the FHC.

By way of illustration, we can examine how public health systems consider zoonotic diseases. Human health objectives are focused on minimizing and preventing human morbidity and mortality associated with zoonotic disease transmission, and control efforts are directed at reducing or even eliminating initial spillover events. This public health perspective highlights the importance of characterizing spillover both qualitatively and quantitatively. Many emerging zoonotic pathogens present as a spillover epidemic only in the human population with $R_0 = 0$ (e.g., anthrax) or a mixed epidemic type where there is spillover with highly inefficient human-to-human transmission ($R_0 < 1$ in the human host, e.g.,
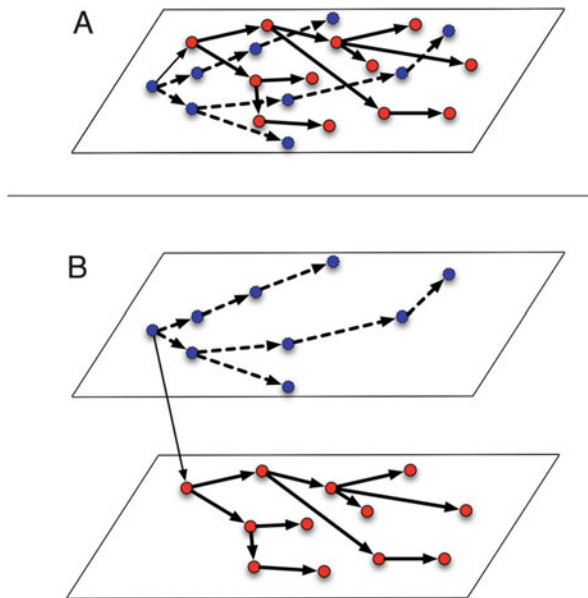

Fig. 8.2 Mixed epidemic dynamics (**a**) shows spillover and onward transmission in a mixed epidemic (spillover epidemic and host epidemic). Blue circles are members of the reservoir population; red, the new host. Edges represent transmission. (**b**) shows exactly the same graph but explicitly separating the two populations. In (**b**), it is obvious that there are two separate processes, linked by a single event. The single spillover event does not lead to a geometrically growing number of spillovers, whereas onward transmission in the new host may. The appropriate interventions and surveillance methods for the two processes are different

monkeypox virus). The immediate focus of control for many emerging zoonoses is not the reduction of infectious animals in the reservoir populations (the reservoir species may not even be known) but minimizing human behaviors and other factors that are thought to contribute to pathogen exposure and invasion risk in humans (e.g., Ebola; see below). In these instances, R_0 in the human or in the reservoir population is not the central factor of interest. Rather, we need to focus on the complex processes of zoonotic pathogen spillover that must occur in the first place. Quantifying spillover rates provides information on the number of cases that can be expected in the FHC over time, a process that is not captured by the traditional R_0 in either the IHC or FHC.

Applying R_0 to our framework suggests that emergence outcomes can therefore be characterized in one of four ways (Lloyd-Smith et al. 2005):

1. The infected host is a dead end—dying and not passing the pathogen on to another human because human-to-human transmission is not possible ($R_0 = 0$ in the FHC).
2. The epidemic stutters along and inevitably fades out because $R_0 \leq 1$ in the FHC.
3. Though $R_0 > 1$ in the FHC, the infected host may or may not pass it on to another human, but the chain of transmission dies out by chance with probability $p_{\text{fadeout}} = 1 - 1/R_0$ (**epidemic fade-out**).
4. $R_0 > 1$ in the FHC, and the transmission chain takes off with probability $p_{\text{breakout}} = 1/R_0$ (**epidemic breakout**).

Fortunately, when $R_0 > 1$ in the FHC, a clear statistical demarcation exists between the epidemic fade-outs (#3) and breakouts (#4), with indicated probabilities. The distribution of sizes of total number of individuals infected is bimodal, with the low-end mode associated with fade-outs and the much larger, upper-end mode with breakouts [cf. simulated distributions of Ebola outbreaks in Getz et al. (2015)]. The emergence of a zoonotic disease thus requires at least a stuttering process in the FHC to occur sufficiently often to ensure an index case for a full epidemic in the FHC.

8.3.3 Applying the Framework

Effective management of emerging disease threats requires that we differentiate among spillover and FHC processes when designing interventions. Our framework lends itself to its own classification scheme for differentiating zoonoses:

Our Framework for Classifying Epidemics

A. Spillover epidemic, either fading or breaking out after initial spillover
B. Mixed epidemic (outbreak in both RC and FHC)
C. Human host epidemic of zoonotic origin (initial spillover, with subsequent adaptation of pathogen to become endemic in the FHC)

D. Animal host epidemic of human origin (as in previous case with roles of human and animal hosts reversed)
E. Human host epidemic with zoonotic genetic source contribution
F. Animal host epidemic with human genetic source contribution

To illustrate these points, we describe four systems of pathogen emergence that represent the epidemic types along the continuum (Table 8.2).

Table 8.2 Epidemic types, examples, and their description

#	Name	Examples	Description
1	Spillover epidemic	Zoonoses—rabies, anthrax (humans) Anthropozoonoses	Only spillover transmission occurs, as the spillover host is a dead-end host for the pathogen, i.e., never enters the host epidemic space. Three kinds of transmission are identified: (a) Zoonoses—animal-to-human pathogen transmission. Also known as obligate zoonotic when referring to pathogens of animal origin (b) Anthropozoonses—human-to-animal pathogen transmission
2	Mixed epidemic	Ebola virus (human) Paramyxoviruses (great apes) Human tuberculosis (elephants; persistent mixed transmission can occur bidirectionally)	Spillover (zoonotic and anthropozoonotic) may be persistent (with varying quiescent periods) but is accompanied by limited secondary human-to-human or animal-to-animal transmission in the host epidemic space
3	Human host epidemic of zoonotic origin	SARS, HIV	A zoonotic pathogen makes a species jump from the zoonotic host departing from the spillover epidemic space, becoming human host adapted with sustained human-to-human transmission
4	Animal host epidemic of human origin	*Mycobacterium bovis*	A human source pathogen makes a species jump from the human host departing from the spillover epidemic space, becoming animal host adapted with sustained animal-to-animal transmission
5	Human host epidemic with zoonotic genetic source contribution	Swine-origin influenza A H1N1	A pathogen co-circulates in human or animal reservoirs, where genetic reassortment and transmission occur
6	Animal host epidemic with human genetic source contribution	Human H1N2 and human-swine reassortant H1N2 and H1N1 influenza A viruses in pigs	

8.3.3.1 Anthrax (Spillover and Epidemic Fade-Out, Obligate Spillover Pathogen: Almost Exclusively RC)

Anthrax is a zoonosis caused by the spore-forming, gram-positive bacterium, *Bacillus anthracis*. This zoonosis affects livestock and wildlife nearly worldwide (Hugh-Jones and Blackburn 2009), with recent reemergence in humans in several agricultural areas (Kracalik et al. 2015). Under certain environmental conditions, spores can persist for long periods of time in the soil and cause subsequent outbreaks (Blackburn et al. 2007; Cherkasskiy 1999; Dragon and Rennie 1995). Across its known geographic distribution, epizootics can range from a few cases (sporadic) to massive outbreaks (Blackburn 2006).

Spillover As a soilborne pathogen, spillover begins at the host-environment interface, and epizootics can persist for weeks to months (Hugh-Jones and Blackburn 2009). Infection may be from either direct ingestion of spores from soil or contaminated vegetation (primarily in grazing herbivores), ingestion of leaves contaminated with blowfly emesis (primarily for browsers) (Blackburn et al. 2010; Braack and De Vos 1990), or direct inoculation from biting flies (Blackburn 2010; Krishna et al. 1958; Blackburn et al. 2014b). Though poorly studied, animal inhalation of spores is not implausible (Turnbull et al. 1998). It has been suggested that during large epizootics, high case numbers of a primary species (e.g., American bison; *Bison bison*) may cause enough environmental contamination that secondary host species (e.g., moose, *Alces alces*, or elk, *Cervus canadensis*) may succumb later in the outbreak (Fig. 8.3a) (Hugh-Jones and Blackburn 2009; Dragon et al. 1999). Specific mechanisms for transmission remain poorly understood and require further research. Human infection is considered secondary and often linked with handling contaminated carcasses or slaughtering infected animals (Woods et al. 2004) and therefore constrained to the spillover. The spatial boundaries of the spillover are limited by the distribution of environmental conditions that support the pathogen; though when livestock control is limited, contaminated meat movement can increase spillover into urban areas (Kracalik et al. 2013, 2015). Limited mechanical transmission may occur within or between herbivorous hosts if tabanid flies do in fact play a role in the transmission cycle (Blackburn et al. 2014a). However, this is likely limited by the seasonality of fly life cycles and conditions that promote pathogen survival. Onward transmission in humans is unlikely. Fade-out results as a consequence of outbreak control interventions [e.g., carcass burning or burial, livestock vaccination campaigns (Kracalik et al. 2014)] or seasonal limits on the pathogen or mechanical vectors, though these conditions are not fully understood.

FHC Limited onward transmission may occur within an ungulate host species if tabanid flies do in fact play a role in the transmission cycle. Onward transmission in humans is highly unlikely. Fade-out results as a consequence of either outbreak control interventions (e.g., carcass burning or burial and sustained preventative vaccination when tenable) or seasonal limits on either the pathogen or mechanical vectors.
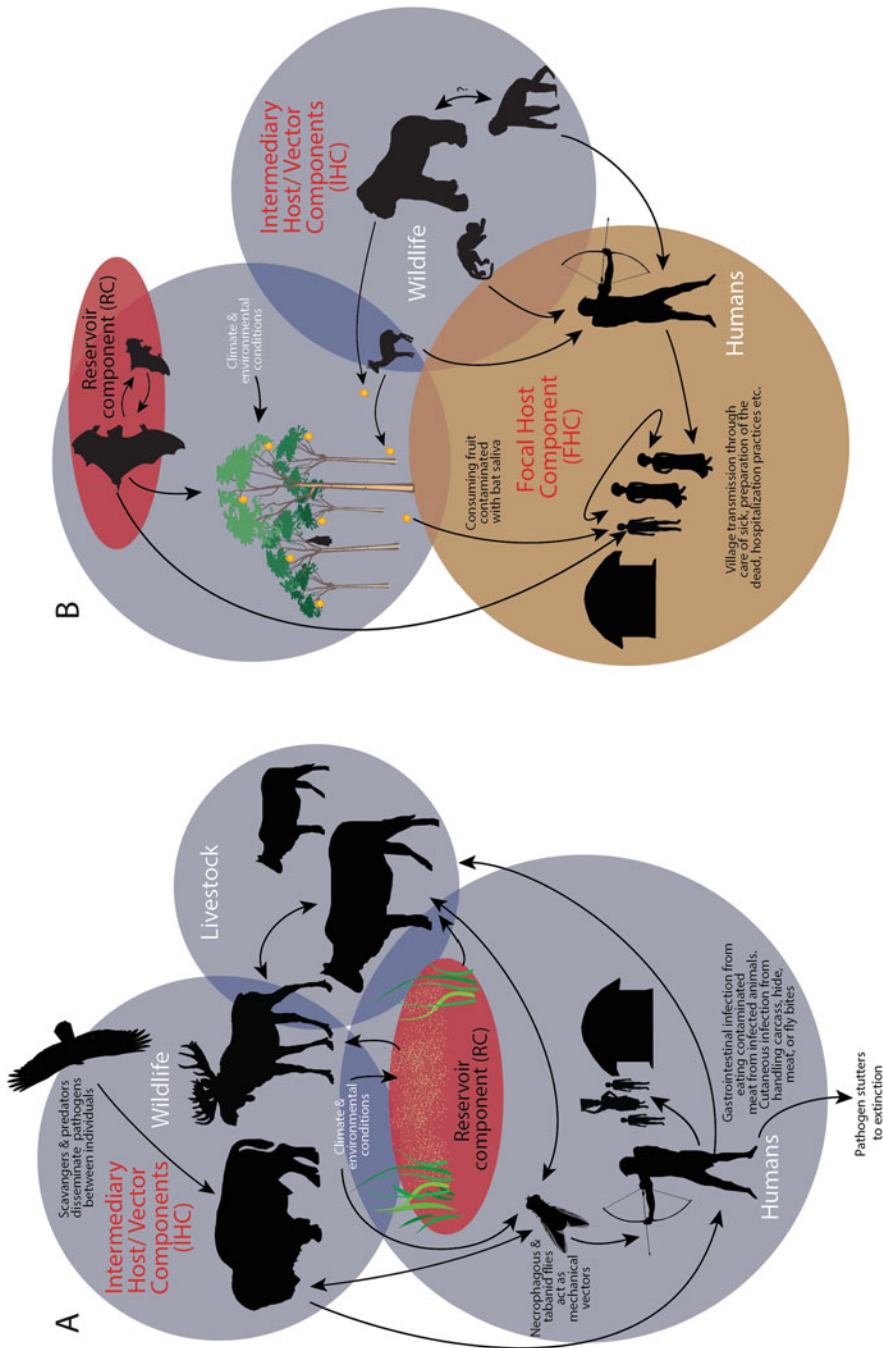
Fig. 8.3 Anthrax disease (**a**) is caused by the spore-forming soil bacterium *Bacillus anthracis* with spillover occurring directly in the environmental reservoir. Host behavior and environmental conditions affect epizootics, with onward transmission limited to nonhuman hosts affected by biting flies. Human cases are

8.3.3.2 Ebola (Mixed Epidemic Type, Mixed Pathogen Type: Spillover Pathogen from RC/IHC and within FHC Transmission)

Ebola hemorrhagic fever is an emerging zoonotic viral disease in West and Central Africa causing severe morbidity and high mortality in humans and wildlife (Alexander et al. 2015). Outbreaks are sporadic with viral quiescent periods upward of 20 years.

Spillover Successful spillover of the pathogen appears to be a complex process involving a number of coupled networks and seasonal drivers (Pinzon et al. 2004), linking the human host-to-virus reservoirs (Fig. 8.3b). Transmission to humans results from direct contact with infected wildlife species through handling and eating of bush meat [duiker; primates, SB3; bats, SB1 (Leroy et al. 2009)] or ingestion of fruit contaminated with Ebola-infected bat saliva [(Alexander et al. 2015), SB1]. Three bat species are considered putative virus reservoirs (Alexander et al. 2015). Spillover epidemics are necessarily limited to the spatial distribution of the reservoir host or distribution network of infected bush meat.

FHC Sustained onward transmission in humans results from close contact with blood, secretions, or tissues of infected individuals. The spatial extent of the host epidemic is then limited to the distribution of human-to-human contacts necessary for successful transmission of the pathogen. Fade-out generally results as a consequence of outbreak control interventions rather than the biology of the pathogen (barrier techniques, quarantine).

8.3.3.3 HIV/AIDS (Human Epidemic of Zoonotic Origin, Human Host Adapted: Initially Spillover, Now Solely FHC Transmission)

HIV-1 and HIV-2 are the causative agents of AIDS in humans.

Spillover Historically, HIV originated from spillover of simian immunodeficiency virus (SIV) pathogens from nonhuman primate species to humans in Africa [SB3 (Heeney et al. 2006)]. On adaptation to the human host, the virus has departed from the spillover.

FHC Successful adaptation of these viruses to sustained human-to-human transmission is a rare event. Of 35 different primate species infected with lentiviruses, only a few viruses from two primate species (chimpanzees, *Pan troglodytes troglodytes*, and sooty mangabeys) successfully invaded and have persisted in the human host population causing global pandemics (Heeney et al. 2006). Here, human-to-human virus transmission dynamics are largely driven by sociocultural factors that influence human behavior (Halperin 1999).

Fig. 8.3 (continued) secondary to animal infections, and onward transmission is unlikely. Ebola (**b**) is an emerging zoonotic disease where spillover dynamics appear to include up to four coupled systems. Population dynamics and seasonal influences appear to be primary drivers of the process of pathogen invasion (Alexander et al. 2012b)

8.3.3.4   Influenza (Epidemic with Reservoir Genetic Source Contribution: Spillover with Potential Bidirectional Transmission Within and Between IHC and FHC)

Spillover Influenza viruses circulate in a wide array of domestic animal and wildlife species with frequent spillover to humans (SB3). Spillback from humans to animals can also occur.

FHC Reassortment of genetic material from these animal reservoirs has been associated with changes in virulence, invasion potential, and adaptation in the human host (Smith et al. 2009; Olsen 2002). Some strains (e.g., H5N1, "bird flu") demonstrate limited human-to-human transmission potential while being highly virulent (Yang et al. 2007). Other strains (e.g., H1N1, "swine flu") are highly adapted to the human host, have relatively low virulence, and cause pandemic disease (Lagace-Wiens et al. 2010).

8.3.4   Evaluating the Framework

Characterization of epidemic types within our framework allows us to more clearly identify direct implications for outbreak control. For example, zoonotic pathogen transmission at SB1 or SB3 will be spatially restricted in occurrence to where the RC or IHC species and humans intersect. In contrast, once a pathogen has evolved and adapted to the human host niche (FHC), the pathogen is freed from this spatial restriction. This moves the outbreak from being described principally by ecological variables such as host range or environment (e.g., Ebola, anthrax) to an outbreak described principally by socioculturally shaped transmission dynamics (e.g., HIV). A caveat here is the movement of infected animal products in the form of bush meat, which can expand the spatial restrictions in spillover also driven by sociocultural influences (Alexander et al. 2012a). The movement of bush meat is a growing concern in the public health and agricultural sectors.

Our framework identifies important gaps in the quantitative evaluation of the zoonotic outbreaks by identifying the need to link together the concatenated stochastic processes of spillover (SB1-3) and onward transmission in the FHC. The real problem, however, of characterizing transmission spillover boundaries is that sample sizes are rather small and observations are only partial: we may have some observations of successful spillovers (e.g., Ebola outbreaks over the past 40 years), but we have no idea how many infected animal-susceptible human contact events actually occurred. Further, during the early stages of a zoonotic outbreak, we do not have data that provides what proportion of transmission events took place across SB1 and SB3 versus that occurring within the FHC. For example, a hunter may be infected with Ebola virus from eating infected gorilla meat (Fig. 8.4). This infected individual may then go on to infect four other people in his family that care for him. Alternatively, five people in this family may handle and eat the meat of an infected gorilla directly and become infected, with no human-to-human transmission occurring. In both cases, five
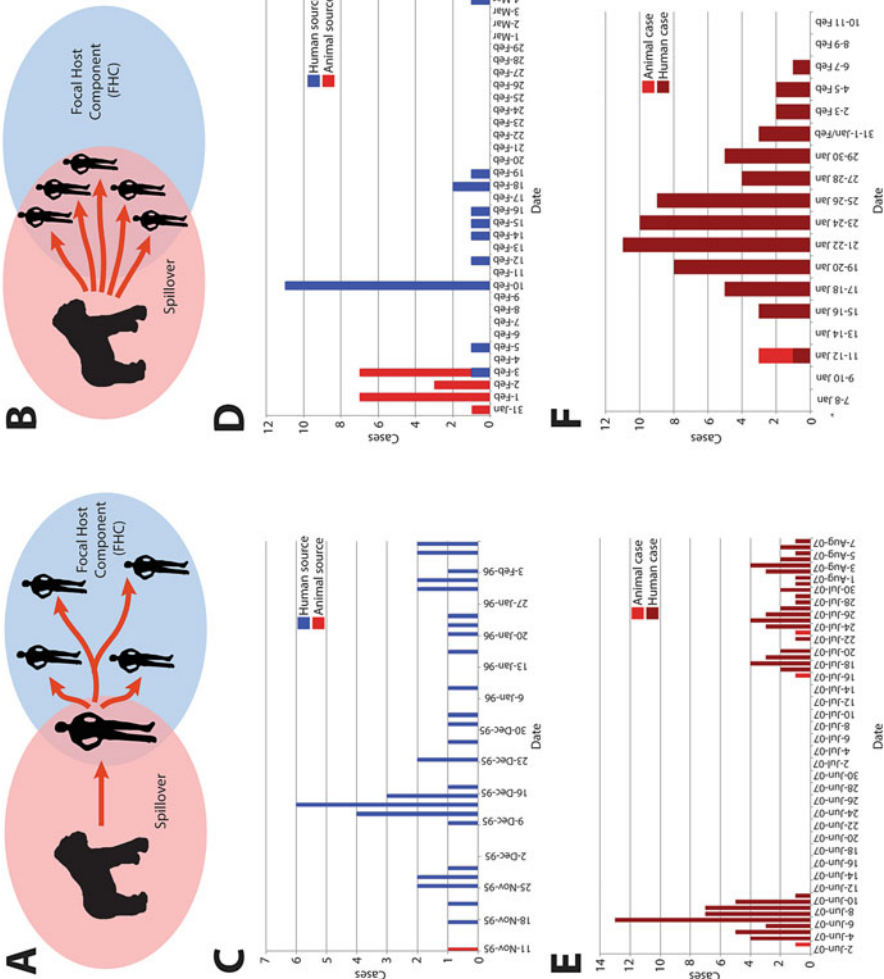
Fig. 8.4 Scenarios of Ebola spillover. In (**a**), the spillover is limited with the majority of transmission occurring in the host-epidemic focal host component (FHC). In (**b**), there is only a spillover epidemic with no FHC ($R_0 = 0$). Insets **c** and **d** illustrate Ebola outbreaks in Gabon (Georges et al. 1999) where both spillover types

individuals are infected, but in the first case, two separate parameters must be estimated to predict the pathogen emergence process (transmission rates in both the spillover and the FHC), while in the second case, only the transmission rate in the FHC is needed, given that a spillover event has occurred. It is possible that genetic data may allow us to differentiate between these two cases, though we will need to know something about the rates of Ebola virus strain evolution within animal and humans hosts, respectively. In the second case, however, estimating the probability that isolated spillover events occur over time requires long-term samples of outbreak rates and the assumption of stationary conditions (i.e., the environmental and human population factors involved remain unchanged over time). While the temporal dynamics of these two cases would be different, in a mixed ongoing epidemic, characterization and application of how the two stochastic processes, one at the spillover boundary and one in the FHC, are intertwined are essential to gaining the necessary insight into the outbreak etiology and efficacy of different management actions.

Explicitly integrating the separate stochastic processes of spillover and onward transmission facilitates consideration of new questions that are not routinely discussed in emerging infectious disease literature. Increasing our research focus on this integration from both the mathematical and conceptual perspective will be important to our ability to model the dynamics of coupled spillover and FHC transmission processes. Emphasis is given to the possibility that some spillovers will stutter to extinction even though we may have $R_0 \gg 1$ in the human population. Conversely, some spillovers with $R_0 < 1$ in the human population will, nevertheless, lead to outbreaks sustained by continuous transmission from animal to human spillover. When the public health focus is on the pathogen, not the strain (as in influenza), we can then consider the case of multiple spillovers of different strains with a distribution of R_0 in the human population. The public health question is then not so much will an HkNℓ (k = 1, ..., 18; ℓ = 1, ..., 11) variant of influenza spillover and seed an epidemic as it is how often will a reassorted influenza virus spillover and seed an epidemic. The spillover component is then the critical ingredient in an analysis.

8.4 Ongoing Quantitative Challenges at the Spillover Interface

The spillover interface is, epidemiologically, unique and complex; and, as we have highlighted here, unique quantitative approaches are correspondingly needed to describe the rate and dynamics of spillover. The most basic concepts like R_0 can

Fig. 8.4 (continued) (**a**, **b**) are illustrated. Red indicates human cases directly from animals; blue indicates human-to-human transmission. (**e**) and (**f**) illustrate livestock anthrax outbreaks with human spillover in Bengal (Ray et al. 2009) and Zimbabwe (Gombe et al. 2010). In both, human cases (dark red) were directly from animals (light red), illustrating anthrax is limited to the intermediary host/vector component (IHC)

be less meaningful and may need special formulations that more accurately summarize the different classes of epidemics we describe above. At the actual spillover boundary (Fig. 8.1), basic concepts like the force of infection break down. In normal epidemiology, for a pathogen circulating within a population, the force of infection λ is conventionally expressed as

$$\lambda = \frac{I}{N} \beta \tag{8.2}$$

where β is the transmission rate. Within a single species, contact rates can be defined based on assumptions of density or frequency dependence, using the number or proportion of infected individuals, respectively, to parameterize λ. Between two species, contact rates are harder to define based on I alone, and so the force of infection is a problematic concept at the spillover interface. Lloyd-Smith et al. (2015) suggested a customized definition of the **spillover force of infection**, adapted to the language we use here:

$$\lambda_s = \left(\frac{I_{RC}}{N_{RC}} \right) \times (RC : FHC \text{ contact rate}) \times \beta_s \tag{8.3}$$

where

$$\beta_s = P\,(\text{infection}|\text{contact}) \tag{8.4}$$

Parameterizing the RC:FHC contact rate—especially as a single model variable—poses a serious quantitative challenge. Increasingly complex models will be needed that break down the different processes at the RC:FHC interface—as well as those that separate the role of the IHC—helping researchers more readily conceptualize and parameterize models.

Recent work on Lassa fever has especially highlighted just how far models at the spillover interface have come in the last 5 years. A model recently published by Iacono et al. (2016) establishes a "unified framework" for modeling zoonotic spillover with horizontal transmission, at the most fundamental level based on the notion that spillovers are a Poisson point process with rate λ, such that the probability of a given number k of spillover events during interval τ is

$$P(k) = \frac{e^{-\lambda\tau}(\lambda\tau)^k}{k!} \tag{8.5}$$

They suggest that spillovers are a **self-exciting** process, as new human infections generate more human infections, but are also a **self-correcting** process, as acquired immunity in human populations depletes susceptible populations and decreases future transmission rates. Different framings of the relative importance of those processes lend themselves to different corresponding mathematical formulations, such as self-correcting Poisson processes or—if random variation in λ is stochastic enough to be important to model accuracy—a Poisson-gamma mixture with

feedback. In their model, the force of infection is expressed as a combination of zoonotic and human-to-human components:

$$\widehat{\lambda}(t) = S_H(t)\eta_R(N_R)Pr_R(N_R)\chi R + S_H(t)\eta_H(N_H)Pr_H(N_H, t)\chi_H \qquad (8.6)$$

where S_H is the susceptible human population size; Pr_R and Pr_H are the prevalence of infected rodents and humans, respectively; N_H and N_R are population sizes of humans and rodents, respectively; and χ_R is a parameter that represents "the ability of the reservoir to excrete a suitable dosage of the virus and the human response to it" (with a corresponding χ_H for human-to-human transmission). In their application to Lassa fever, the authors show that the flexibility of this model produces dramatic responses to subtle changes. For example, moving from a constant rate of spillover to a seasonally peaking process (as a mode of hypothesis testing) reduces human-to-human contributions to outbreaks from roughly 90% to 20%.

With expanding accuracy in models of the spillover process, simulation methods have now begun to be developed that appropriately predict spatial risk patterns for Lassa fever. A study by Redding et al. (2016) combined a (simpler) model of RC: FHC transmission (λ, which they term the "force of zoonotic infection") with habitat suitability modeling for reservoir hosts to develop an "environmental-mechanistic zoonotic spillover model." Models like these, which consider spatial variation in human-reservoir contact and spillover risk, represent a tremendous advancement in the quantification of the spillover interface. Most spatial patterns in zoonotic disease emergence are currently studied with more correlative methods like **ecological niche models**, which are tremendously powerful but subject to a number of user-end decisions, only relate patterns of occurrence to environmental variables (transmission risk rather than transmission rates), and suffer from problems relating to lack of consensus among conflicting models. Both modeling frameworks offer the possibility of extending models for predictions under global change; but models that explicitly and mechanistically account for human case burdens arising from spillover (rates, not risks) have a clear advantage when the data exists to parameterize them.

8.5 Conclusion

Articulation of zoonotic outbreaks as a set of processes that take place dynamically (Fig. 8.1) allows a deeper understanding of how to computationally categorize different classes of zoonotic diseases, with important implications to both public health policy and management of zoonotic outbreaks. Using this approach it becomes clearer why influenza is so different from many other zoonotic pathogens because the spillover-FHC concatenation can be bidirectional between humans and animals as well as animals and the environment. While R_0 is often ubiquitously applied to analysis of all infectious disease, this framework helps us understand why this concept is only part of the story for zoonotic diseases where key stochastic events and interdependent processes influence spillover probability at any or all

interfaces. This emphasis on the spillover component of zoonotic disease emergence points to a need for greater computational and mechanistic focus on spillover itself.

Compliance with Ethical Standards

Conflict of Interest All authors declare they have no conflict of interest.

Ethics Approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Alexander KA, McNutt JW (2010) Human behavior influences infectious disease emergence at the human–animal interface. Front Ecol Environ 8(10):522–526

Alexander KA, MacLachlan NJ, Kat PW et al (1994) Evidence of natural blue-tongue virus infection among African carnivores. Am J Trop Med Hyg 51(5):568–576

Alexander K, Kat P, House J et al (1995) African horse sickness and African carnivores. Vet Microbiol 47(1–2):133–140

Alexander KA, Blackburn JK, Vandewalle ME et al (2012a) Buffalo, bush meat, and the zoonotic threat of brucellosis in Botswana. PLoS One 7(3):e32, 842

Alexander KA, Lewis BL, Marathe M et al (2012b) Modeling of wildlife-associated zoonoses: applications and caveats. Vector Borne Zoonotic Dis 12(12):1005–1018

Alexander KA, Sanderson CE, Marathe M et al (2015) What factors might have led to the emergence of Ebola in West Africa? PLoS Negl Trop Dis 9(6):e0003, 652

Ali S, Keil R (2006) Global cities and the spread of infectious disease: the case of severe acute respiratory syndrome (SARS) in Toronto, Canada. Urban Stud 43(3):491

Allan B, Keesing F, Ostfeld R (2003) Effect of forest fragmentation on Lyme disease risk. Conserv Biol 17(1):267–272

Anishchenko M, Bowen R, Paessler S et al (2006) Venezuelan encephalitis emergence mediated by a phylogenetically predicted viral mutation. Proc Natl Acad Sci U S A 103(13):4994

Antia R, Regoes RR, Koella JC et al (2003) The role of evolution in the emergence of infectious diseases. Nature 426(6967):658

Blackburn J (2006) Evaluating the spatial ecology of anthrax in North America: Examining epidemiological components across multiple geographic scales using a GIS-based approach [Doctoral dissertation]. Louisiana State University, Baton Rouge

Blackburn JK (2010) Integrating geographic information systems and ecological niche modeling into disease ecology: a case study of *bacillus anthracis* in the United States and Mexico. In: O'Connell KP, Skowronski EW, Bakanidze L, Sulakvelidze A (eds) Emerging and endemic pathogens. Springer, Dordrecht, pp 59–88

Blackburn JK, McNyset KM, Curtis A et al (2007) Modeling the geographic distribution of *bacillus anthracis*, the causative agent of anthrax disease, for the contiguous united states using predictive ecologic niche modeling. Am J Trop Med Hyg 77(6):1103–1110

Blackburn JK, Curtis A, Hadfield TL et al (2010) Confirmation of *Bacillus anthracis* from flesh-eating flies collected during a West Texas anthrax season. J Wildl Dis 46(3):918–922

Blackburn JK, Hadfield TL, Curtis AJ et al (2014a) Spatial and temporal patterns of anthrax in white-tailed deer, *Odocoileus virginianus*, and hematophagous flies in West Texas during the summertime anthrax risk period. Ann Am Assoc Geogr 104(5):939–958

Blackburn JK, Van Ert M, Mullins JC et al (2014b) The necrophagous fly anthrax transmission pathway: empirical and genetic evidence from wildlife epizootics. Vector Borne Zoonotic Dis 14(8):576–583

Braack L, De Vos V (1990) Feeding habits and flight range of blow-flies (*Chrysomyia* spp.) in relation to anthrax transmission in the Kruger National Park, South Africa. Onderstepoort J Vet Res 57(2):141–142

Brown C (2004) Emerging zoonoses and pathogens of public health significance – an overview. Revue Scientifique et Technique-Office International des Epizooties 23(2):435–442

Camacho A, Kucharski A, Funk S et al (2014) Potential for large outbreaks of Ebola virus disease. Epidemics 9:70–78

Cherkasskiy B (1999) A national register of historic and contemporary anthrax foci. J Appl Microbiol 87(2):192–195

Childs J (2004) Zoonotic viruses of wildlife: hither from yon. In: Emergence and control of zoonotic viral encephalitides. Springer, Berlin

Childs JE, Richt JA, Mackenzie JS (2007) Introduction: conceptualizing and partitioning the emergence process of zoonotic viruses from wildlife to humans. In: Childs JE, Mackenzie JS, Richt JA (eds) Wildlife and emerging zoonotic diseases: the biology, circumstances and con sequences of cross-species transmission. Springer, Heidelberg, pp 1–31

Chuck S, Sande M (1989) Infections with *Cryptococcus neoformans* in the acquired immuno-deficiency syndrome. N Engl J Med 321(12):794–799

Cox-Singh J, Singh B (2008) Knowlesi malaria: newly emergent and of public health importance? Trends Parasitol 24(9):406–410

Daszak P, Cunningham AA, Hyatt AD (2000) Emerging infectious diseases of wildlife–threats to biodiversity and human health. Science 287(5452):443–449

Dearing MD, Dizney L (2010) Ecology of hantavirus in a changing world. Ann N Y Acad Sci 1195(1):99–112

Diekmann O, Heesterbeek JAP, Metz JA (1990) On the definition and the computation of the basic reproduction ratio r0 in models for infectious diseases in heterogeneous populations. J Math Biol 28(4):365–382

Dobson A (2004) Population dynamics of pathogens with multiple host species. Am Nat 164(S5): S64–S78

Dobson AP (2005) What links bats to emerging infectious diseases? Science 310(5748):628

Donnelly C, Woodroffe R, Cox D et al (2003) Impact of localized badger culling on tuberculosis incidence in British cattle. Nature 426(6968):834–837

Dragon DC, Rennie RP (1995) The ecology of anthrax spores: tough but not invincible. Can Vet J 36(5):295

Dragon D, Elkin B, Nishi J et al (1999) A review of anthrax in Canada and implications for research on the disease in northern bison. J Appl Microbiol 87(2):208–213

Duffy S, Shackelton LA, Holmes EC (2008) Rates of evolutionary change in viruses: patterns and determinants. Nat Rev Genet 9(4):267

Ferrari N, Cattadori I, Rizzoli A et al (2009) Heligmosomoides polygyrus reduces infestation of Ixodes ricinus in free-living yellow-necked mice, *Apodemus flavicollis*. Parasitology 136: 305–316

Fèvre E, Picozzi K, Fyfe J et al (2005) A burgeoning epidemic of sleeping sickness in Uganda. Lancet 366(9487):745–747

Fichet-Calvet E, Lecompte E, Koivogui L, Soropogui B, Doré A, Kourouma F, Sylla O, Daffis S, Koulémou K, Ter Meulen J (2007) Fluctuation of abundance and Lassa virus prevalence in *Mastomys natalensis* in Guinea, West Africa. Vector-Borne Zoonotic Dis 7(2):119–128

Getz WM, Pickering J (1983) Epidemic models: thresholds and population regulation. Am Nat 121:892–898

Getz WM, Gonzalez J-P, Salter R et al (2015) Tactics and strategies for managing Ebola outbreaks and the salience of immunization. Comput Math Methods Med 2015:736507

Georges AJ, Leroy EM, Renaut AA et al (1999) Ebola hemorrhagic fever outbreaks in Gabon, 1994–1997: epidemiologic and health control issues. J Infect Dis 179:S65–S75

Gombe N, Nkomo B, Chadambuka A et al (2010) Risk factors for contracting anthrax in Kuwirirana ward, Gokwe North, Zimbabwe. Afr Health Sci 10:159–164

Griffin D, Donaldson K, Paul J et al (2003) Pathogenic human viruses in coastal waters. Clin Microbiol Rev 16(1):129

Halperin DT (1999) Heterosexual anal intercourse: prevalence, cultural factors, and HIV infection and other health risks, Part I. AIDS Patient Care STDs 13(12):717–730

Haydon DT, Cleaveland S, Taylor LH et al (2002) Identifying reservoirs of infection: a conceptual and practical challenge. Emerg Infect Dis 8:1468–1473

Heesterbeek J (2002) A brief history of R0 and a recipe for its calculation. Acta Biotheor 50:189–204

Heeney JL, Dalgleish AG, Weiss RA (2006) Origins of HIV and the evolution of resistance to AIDS. Science 313:462

Hooper P, Zaki S, Daniels P et al (2001) Comparative pathology of the diseases caused by Hendra and Nipah viruses. Microbes Infect 3(4):315–322

Hudson P, Perkins S, Cattadori I et al (2008) The emergence of wildlife disease and the application of ecology. Princeton University Press, Princeton, NJ, pp 347–367

Hugh-Jones M, Blackburn J (2009) The ecology of *Bacillus anthracis*. Mol Asp Med 30(6):356–367

Iacono GL, Cunningham AA, Fichet-Calvet E et al (2016) A unified framework for the infection dynamics of zoonotic spillover and spread. PLoS Negl Trop Dis 10:e0004957

Johnson CK, Hitchens PL, Evans TS et al (2015) Spillover and pandemic properties of zoonotic viruses with high host plasticity. Sci Rep 5:14830

Jones K, Patel N, Levy M et al (2008) Global trends in emerging infectious diseases. Nature 451:990

Keele BF, Van Heuverswyn F, Li Y et al (2006) Chimpanzee reservoirs of pandemic and nonpandemic HIV-1. Science 313:523–526

Kilpatrick AM (2011) Globalization, land use, and the invasion of West Nile virus. Science 334:323–327

Kilpatrick AM, Kramer LD, Jones MJ et al (2006) West Nile virus epidemics in North America are driven by shifts in mosquito feeding behavior. PLoS Biol 4:e82

Kracalik IT, Malania L, Tsertsvadze N et al (2013) Evidence of local persistence of human anthrax in the country of Georgia associated with environmental and anthropogenic factors. PLoS Negl Trop Dis 7(9):e2388

Kracalik I, Abdullayev R, Asadov K et al (2014) Changing patterns of human anthrax in Azerbaijan during the post-soviet and preemptive livestock vaccination eras. PLoS Negl Trop Dis 8:e2985

Kracalik I, Malania L, Imnadze P et al (2015) Human Anthrax transmission at the urban–rural Interface, Georgia. Am J Trop Med Hyg 93:1156–1159

Krishna R, Mohiyuden S et al (1958) Tabanus flies as transmitters of anthrax-a field experience. Indian Vet J 38(7):348–353

Lagace-Wiens PR, Rubinstein E, Gumel A (2010) Influenza epidemiology past, present, and future. Crit Care Med 38:e1–e9

Lemey P, Pybus OG, Wang B et al (2003) Tracing the origin and history of the HIV-2 epidemic. Proc Natl Acad Sci U S A 100(11):6588–6592

Leroy EM, Epelboin A, Mondonge V et al (2009) Human Ebola outbreak resulting from direct exposure to fruit bats in Luebo, Democratic Republic of Congo, 2007. Vector Borne Zoonotic Dis 9(6):723–728

Lloyd-Smith JO, Cross PC, Briggs CJ et al (2005) Should we expect population thresholds for wildlife disease? Trends Ecol Evol 20(9):511–519

Lloyd-Smith JO, George D, Pepin KM et al (2009) Epidemic dynamics at the human-animal interface. Science 326(5958):1362–1367

Lloyd-Smith JO, Funk S, McLean AR et al (2015) Nine challenges in modelling the emergence of novel pathogens. Epidemics 10:35–39

McCormack RK, Allen LJ (2007) Disease emergence in multi-host epidemic models. Math Med Biol 24(1):17–34

Morris LR, Proffitt KM, Asher V et al (2016) Elk resource selection and implications for anthrax management in Montana. J Wildl Manag 80(2):235–244

Olival KJ, Hosseini PR, Zambrana-Torrelio C et al (2017) Host and viral traits predict zoonotic spillover from mammals. Nature 546(7660):646–650

Olsen CW (2002) The emergence of novel swine influenza viruses in North America. Virus Res 85(2):199–210

Olson PE, Hames C, Benenson A et al (1996) The thucydides syndrome: Ebola deja vu? (or Ebola reemergent?). Emerg Infect Dis 2(2):155

Orlandi P, Chu D, Bier J, Jackson G (2002) Parasites and the food supply. Food Technol Champaign Then Chicago 56(4):72–79

Papagrigorakis MJ, Yapijakis C, Synodinos PN et al (2006) DNA examination of ancient dental pulp incriminates typhoid fever as a probable cause of the plague of Athens. Int J Infect Dis 10(3):206–214

Parrish CR, Holmes EC, Morens DM et al (2008) Cross-species virus transmission and the emergence of new epidemic diseases. Microbiol Mol Biol Rev 72(3):457–470

Pepin KM, Lass S, Pulliam JRC et al (2010) Identifying genetic markers of adaptation for surveillance of viral host jumps. Nat Rev Microbiol 8(11):802–813

Petersen LR, Brault AC, Nasci RS (2013) West Nile virus: review of the literature. JAMA 310(3): 308–315

Pinzon JE, Wilson JM, Tucker CJ et al (2004) Trigger events: enviroclimatic coupling of Ebola hemorrhagic fever outbreaks. Am J Trop Med Hyg 71(5):664–674

Ray TK, Hutin YJ, Murhekar MV (2009) Cutaneous anthrax, West Bengal, India, 2007. Emerg Infect Dis 15(3):497

Redding DW, Moses LM, Cunningham AA et al (2016) Environmental-mechanistic modelling of the impact of global change on human zoonotic disease emergence: a case study of lassa fever. Methods Ecol Evol 7(6):646–655

Reis RB, Ribeiro GS, Felzemburgh RD et al (2008) Impact of environment and social gradient on leptospira infection in urban slums. PLoS Negl Trop Dis 2(4):e228

Rigaud T, Perrot-Minnot MJ, Brown MJ (2010) Parasite and host assemblages: embracing the reality will improve our knowledge of parasite transmission and virulence. Philos Trans R Soc Lond B Biol Sci 277(1701):3693–3702

Rimoin AW, Mulembakani PM, Johnston SC et al (2010) Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the democratic republic of congo. Proc Natl Acad Sci U S A 107(37):16,262–16,267

Smith RD (2006) Responding to global infectious disease outbreaks: lessons from sars on the role of risk perception, communication and management. Soc Sci Med 63(12):3113–3123

Smith GJ, Bahl J, Vijaykrishna D, Zhang J et al (2009) Dating the emergence of pandemic influenza viruses. Proc Natl Acad Sci U S A 106(28):11,709–11,712

Song H, Tu C, Zhang G et al (2005) Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. Proc Natl Acad Sci U S A 102(7):2430

Stapp P, Antolin MF, Ball M (2004) Patterns of extinction in prairie dog metapopulations: plague outbreaks follow el nino events. Front Ecol Environ 2(5):235–240

Tack AJ, Thrall PH, Barrett LG et al (2012) Variation in infectivity and aggressiveness in space and time in wild host–pathogen systems: causes and consequences. J Evol Biol 25(10):1918–1936

Taubenberger JK, Morens DM (2006) Influenza en 1918: La madre de todas las pandemias. Revista Biomedica 17(1):69–79

Turnbull PC, World Health Organization et al (1998) Guidelines for the surveillance and control of anthrax in humans and animals. World Health Organization, Department of Communicable Diseases Surveillance and Response, Geneva

Webster R, Shortridge K, Kawaoka Y (1997) Influenza: interspecies transmission and emergence of new pandemics. FEMS Immunol Med Microbiol 18(4):275–279

Wells R, Young J, Williams R et al (1997) Hantavirus transmission in the United States. Emerg Infect Dis 3(3):361

Wolfe ND, Dunavan CP, Diamond J (2007) Origins of major human infectious diseases. Nature 447(7142):279

Woods CW, Ospanov K, Myrzabekov A et al (2004) Risk factors for human anthrax among contacts of anthrax-infected livestock in Kazakhstan. Am J Trop Med Hyg 71(1):48–52

Yakob L, Bonsall MB, Yan G (2010) Modelling knowlesi malaria transmission in humans: vector preference and host competence. Malaria J 9(1):329

Yang Y, Halloran ME, Sugimoto JD et al (2007) Detecting human-to-human transmission of avian influenza a (h5n1). Emerg Infect Dis 13(9):1348

Zinsstag J, Roth F, Orkhon D, Chimed-Ochir G et al (2005) A model of animal–human brucellosis transmission in mongolia. Prev Vet Med 69(1–2):77–95

Zinsstag J, Dürr S, Penny M et al (2009) Transmission dynamics and economics of rabies control in dogs and humans in an African city. Proc Natl Acad Sci U S A 106(35):14996–15001