2019

The burden of zoonoses on public health: predicting zoonotic outbreaks usind different measures of pathogen richness

https://hdl.handle.net/2144/38681

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

THE BURDEN OF ZOONOSES ON PUBLIC HEALTH: PREDICTING ZOONOTIC OUTBREAKS USING DIFFERENT MEASURES OF PATHOGEN RICHNESS

by

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B.S., Duke University, 2015

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science
2019

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DEDICATION

I would like to dedicate this work to my family. First and foremost, my loving parents, Samia Mustafa and Mustafa Rahim, who have made countless sacrifices to support me in all of my life’s endeavors. This work and all of my other accomplishments are simply but a product of your love and encouragement. My younger brother, Umar Rahim, whose own hard work and dedication in overcoming all of his obstacles, serves to inspire me every day. My husband, Umer Ahmed, who has taught me what true love and equal partnership looks like. Thank you for pushing me to aspire and achieve, even in the moments that I did not think it would be possible. Last but not least, my beautiful, curious, and intelligent son, Kareem Ahmed-Rahim. I hope and pray every day that I am able to become the mother and role model that you deserve. I love you so much.

ACKNOWLEDGMENTS

I would like to thank Dr. Gwynneth Offner and Dr. Jean Spencer for not only serving as my thesis readers, but also for their patience, support, time, and extensive help throughout my graduate studies. I tremendously appreciated their willingness to always take time to mentor and guide me these past two years. I am grateful to have had such intelligent, helpful, and strong female mentors in graduate school. You both have inspired and encouraged me in my pursuit of higher education – thank you.

THE BURDEN OF ZOONOSES ON PUBLIC HEALTH: PREDICTING ZOONOTIC OUTBREAKS USING DIFFERENT MEASURES OF PATHOGEN RICHNESS

SANIA RAHIM

ABSTRACT

Zoonotic pathogens shared with wild or domesticated animals are the cause of more than 60% of human infectious diseases. These pathogens are responsible for millions of deaths annually and have resulted in costs of over a hundred billion U.S. dollars in the past three decades. Investigating different aspects of zoonotic pathogens can help inform policy decisions on public health, agriculture, and conservation of biodiversity. Because pathogens play essential roles in natural communities, studying the variables that influence pathogen richness is important in determining the biological principles governing biodiversity. Gaining a better understanding of the factors that influence these pathogens can allow for the development of effective and targeted action plans to deal with zoonotic disease outbreaks. The aims of this work were twofold: (1) to review the current literature and identify statistically significant predictors of pathogen richness, and (2) to analyze responses by public health agencies to recent zoonotic outbreaks. This work also discussed current gaps in the literature and suggested future areas of proposed funding and research.

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AIDS	Acquired immunodeficiency syndrome
CDC	Centers for Disease Control and Prevention
DALY	Disease-adjusted life years
EID	Emerging infectious disease
EVD	Ebola virus disease
HIV	Human immunodeficiency virus
IUCN	International Union for Conservation of Nature
kg	Kilogram
LDG	Latitudinal diversity gradient
ln	Natural logarithm
MERS	Middle East respiratory syndrome
p	Probability
SLOSS	Single large or several small
TPR	Total pathogen richness
WHO	World Health Organization
WNV	West Nile virus

INTRODUCTION

Over the past few decades, the majority of emerging infectious diseases (EIDs) affecting humans are caused by zoonotic pathogens that originate in wild and domesticated animals and are shared with humans. Zoonotic pathogens are responsible for millions of deaths annually and have caused hundreds of billions of U.S. dollars of economic damage in the past two decades (Karesh et al., 2012). Due to the significant public health and financial burden of zoonoses, effective approaches to zoonotic disease control and prevention are necessary. The origins of EIDs are significantly correlated with epidemiological and environmental variables (Yeh et al., 2018). These variables may be utilized to identify potential zoonotic disease hotspots. Thus, zoonotic disease research requires nuanced, cross-disciplinary understanding of ecological and evolutionary principles of animal, human, and environmental factors (**Figure 1**). This literature review explores zoonoses from a holistic perspective with the purpose of offering a more integrative and comprehensive outlook on zoonotic disease management. Furthermore, this information can be applied to public policy to inform on issues such as agriculture, conservation of biodiversity, and infrastructure.

The first part of this introduction briefly covers fundamental epidemiological principles and terminology necessary in understanding the modern-day burden of zoonotic diseases. The next part delves into basic principles of pathogen transmission. Finally, the last part considers major historical and epidemiological events that led to the development of modern-day spread and persistence of zoonotic diseases.

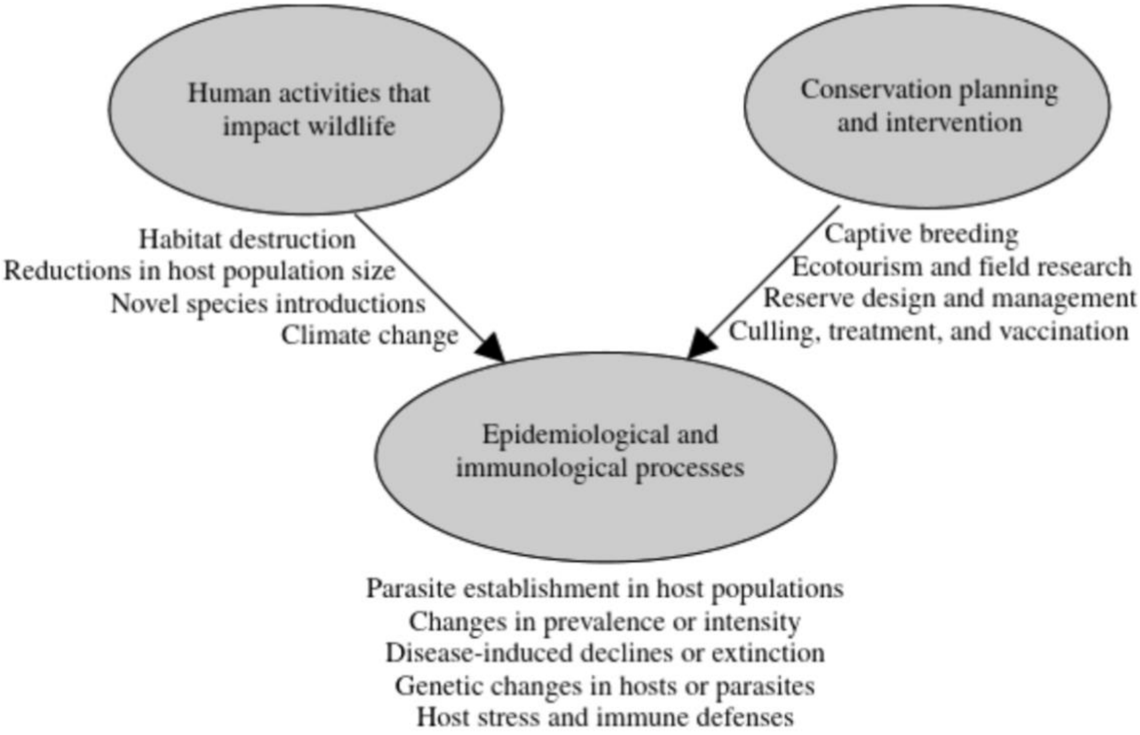

Figure 1. Overview of relationship between human behavior, conservation efforts, and infectious disease. Human activities such as habitat destruction lead to numerous changes in the flora and fauna of an area, most notably reductions in host populations and host range size. Reduced host population can lead to decreased genetic diversity, causing weakened immunocompetence in hosts. Furthermore, habitat fragmentation can generate novel stressors that also serve to weaken immunocompetence, thereby increasing risk of pathogen transmission and infection. Concerted conservation efforts, such as long-term monitoring of pathogens, implemented vaccination programs, and field research, can help to better manage and prevent future zoonotic outbreaks. Taken from (Nunn & Altizer, 2006).

Epidemiology of Zoonoses

Although the definition of epidemiology has expanded greatly in the past century, the field was initially developed to observe and manage outbreaks of communicable infectious diseases. A core tenet of epidemiology is that the outbreak of disease does not occur randomly. Rather, outbreaks occur because of variable distribution of risk factors in populations. An important function of epidemiology is to determine the risk factors that increase the probability of an outbreak happening.

The simplest model of disease causation is the epidemiologic triad, also known as the traditional model for infectious disease. The epidemiologic triad is comprised of an infectious agent, a susceptible host, and the environment (**Figure 2**). It is the interplay between these three variables that can establish disease in a population.

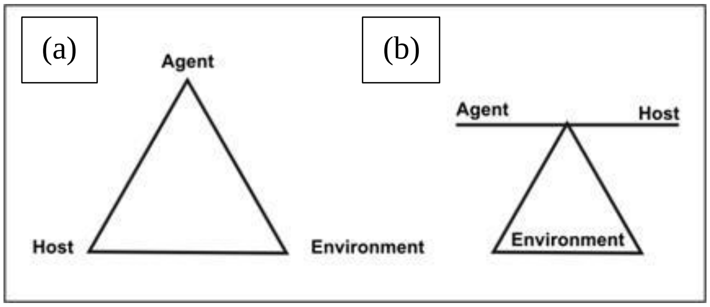

Figure 2. Interplay of epidemiologic triad. (a) This version depicts the agent, the host, and the environment as having equivalent influence over each other. **(b)** This version shows the agent and the host as being codependent, and together their interaction influences the environment. Taken from (Dicker et al., 2006).

An “agent” refers to any infectious microorganism that is capable of transmitting and causing infection in a host organism. This review refers to such infectious microorganisms as pathogens. In order to cause infection, the presence of a pathogen is necessary but not sufficient. A discussion of the factors that influence the ability of a pathogen to cause disease is discussed in detail later in this review. A “host” refers to a human who is susceptible to being affected. Variables such as physiological fitness, behavior, and lifestyle all affect opportunities for exposure. Lastly, the “environment” refers to all of the external factors that facilitate the interaction between the host and the pathogen. Environmental factors may include climatic variables, degree of urbanization, and host population density.

Epidemiologically, diseases can be classified according to the extent that they have spread within or among populations. The baseline amount to which a disease is observably present in a community is referred to as the “endemic” level of the disease. If the level of a disease suddenly increases above the endemic level of a particular population, it is referred to as an outbreak or “epidemic.” A pandemic refers to a large-scale epidemic that has spread to multiple regions across the globe.

Correct epidemiological practices are critical for the effective management of zoonoses. A zoonosis is a disease that originates in a vertebrate animal host and can be transmitted to a human host. Recent zoonotic outbreaks, such as Middle East respiratory syndrome (MERS), Ebola virus, West Nile virus (WNV), and Zika virus, have necessitated further research of the factors that increase the potential for zoonotic pathogen transmission and outbreaks.

Underlying Principles of Pathogen Transmission

Although the terms “pathogen” and “parasite” are used interchangeably in common vernacular and in the literature, there is a clear distinction. This work utilizes the definitions put forth by Nunn and Altizer (2006) to distinguish between the terms. “Pathogen” refers to any infectious, disease-causing organism that lives on another host organism. The term includes protozoa, helminths, viruses, fungi, bacteria, and arthropods. A pathogen obtains its nutrition by draining energy and resources from its host. “Parasite” refers to a narrower class of organisms that does not include viruses and bacteria and is often used in the literature to denote macroscopic organisms. Pathogens that can be transmitted from animals to humans are classified as “zoonotic pathogens.”

Transmission of pathogens from vertebrate animal hosts to humans, also known as zoonotic spillover transmission, is a nuanced and poorly understood phenomenon (Plowright et al., 2017). Although an in-depth discussion regarding the mechanism of zoonotic spillover is beyond the scope of this literature review, it is important to understand that there are numerous barriers that a pathogen must overcome to successfully transmit from animals to humans. A recent study by Plowright et al. (2017) proposed a theoretical framework outlining the potential barriers that a pathogen may encounter (**Figure 3**). The framework is composed of three phases (**Figure 4**). The first phase, “pathogen pressure,” takes into account the distribution, prevalence, and survival of pathogens for any particular host species. The second phase, “exposure,” considers the behavior of vertebrate animal hosts and humans that influences the likelihood of exposure. The third phase, “probability of infection," accounts for the genetic and immunological aspects of the vertebrate animal host and potential recipient human host.

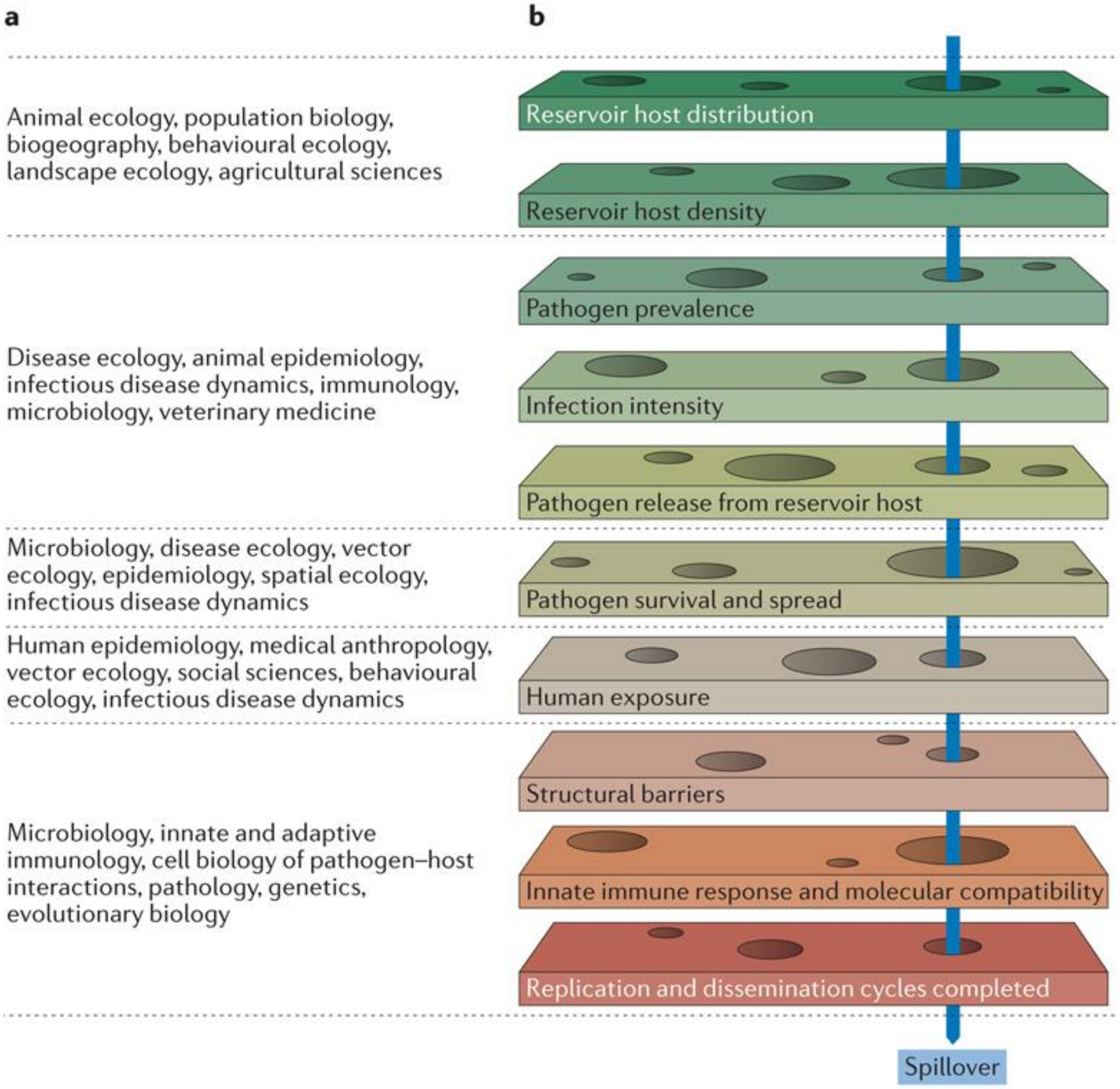

Figure 3. Proposed synthetic framework outlining barriers to zoonotic spillover transmission. (a) In order to understand the complexity behind zoonotic spillover, researchers in multiple disciplines are needed at every step of transmission. **(b)** Graphic illustration depicts the barriers that need to align in order for zoonotic spillover to occur. Holes in the illustration are representative of opportunities in space and time that a pathogen may have at every stage to evolve, adapt, and move to the next phase. Taken from (Plowright et al., 2017).

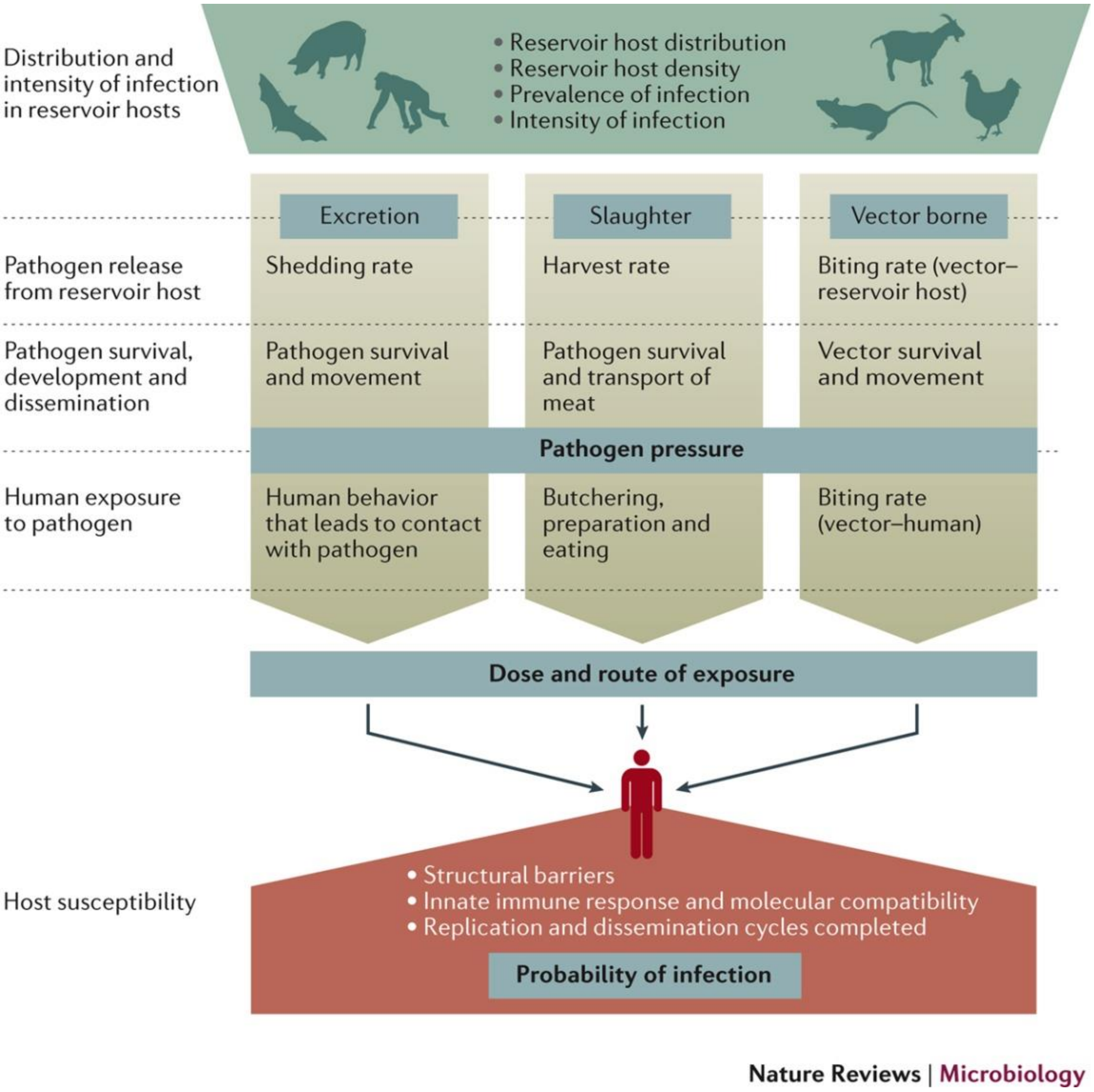

Figure 4. Paths and phases of zoonotic spillover transmission. Zoonotic spillover may occur within a variety of different pathways. Although each path poses unique challenges, the pathogen must ultimately be able to surpass each phase at the correct opportunity in order to successfully infect a human host. This process highlights the complex interplay between pathogen fitness, ecology, human behavior, and human fitness. Taken from (Plowright et al., 2017).

Zoonotic spillover transmission can occur in a myriad of ways (**Figure 4**). Once a zoonotic pathogen leaves its reservoir, or the habitat in which the pathogen grows and multiplies, it can then be shared through air droplets, fecal-oral transmission, vector-borne transmission, or exposure to infected bodily fluids. Although pathogens can be transmitted according to their characteristic methodology, it has become increasingly common for transmission to occur by atypical routes. For example, cysts of the organism *Giardia* can be transmitted through the fecal-oral route (**Figure 5**). Within the fecal-oral route, transmission may occur from person to person, from animals, or indirectly from water or food contaminated with animal feces (Sanyaolu et al., 2016). There is considerable risk for *Giardia* transmission through the fecal-oral route in food service establishments if proper food preparation methods and hygiene are not followed.

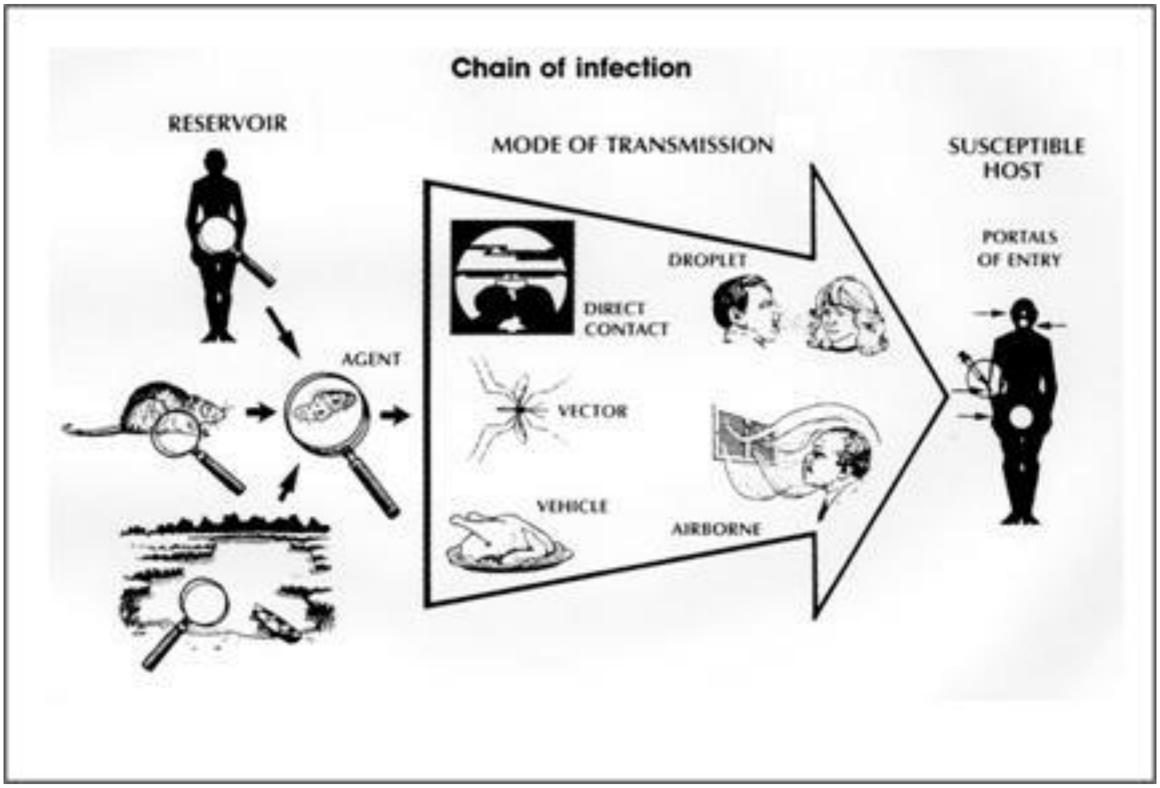

Figure 5. Chain of infection. There are three components to the chain of infection: a reservoir, a mode of transmission, and a susceptible host. Taken from (Dicker, Coronado, Koo, & Parrish, 2006).

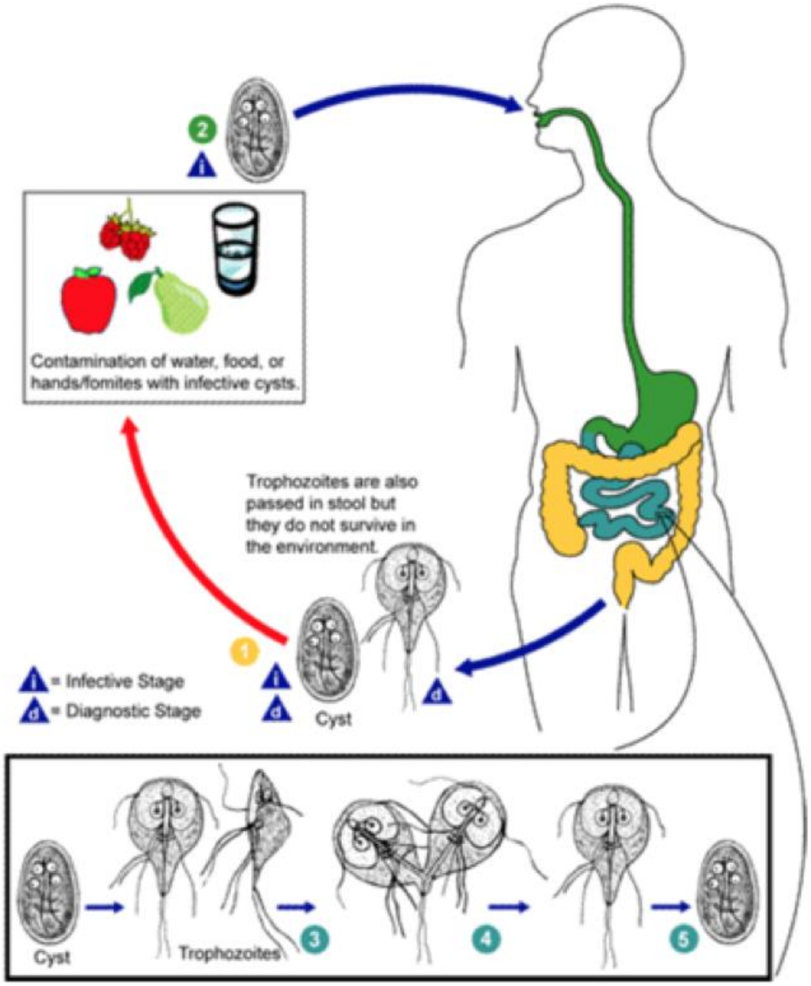

Figure 6. Example of life cycle of a zoonotic pathogen. *Giardia* is a common zoonotic pathogen of the gastrointestinal tract in domestic animals and humans. It is known to affect over 200 million people in Africa, Asia, and other regions in the world. *Giardia* cysts are shed into the feces of animals, and infection can occur after ingestion through fecal-oral transmission or through contaminated food or water. Giardiasis poses a significant public health burden because of its potential in causing major outbreaks and possible negative developmental effects in children. Taken from (Dicker et al., 2006).

Origins of Zoonoses in Humans

In order to effectively manage the widespread proliferation of zoonotic disease in the modern world, it is first necessary to understand the evolutionary history of zoonotic diseases and the events in history that led to their persistence and survival in human populations.

Although there is evidence that some zoonotic pathogens have had prehistoric relationships with their human hosts prior to the advent of significant anthropogenic changes (Harrison et al., 2018), the majority of modern-day zoonotic pathogens have only recently become established in human populations. Before the Agricultural Revolution, it is hypothesized that helminth infections were most likely common among humans living in hunter-gatherer groups. Helminths were probably transmitted through the consumption and exposure of unwashed and uncooked meats and foodstuffs. Furthermore, ectoparasites such as lice and mites were found to have coevolved with humans for the past 10,000 years (Ashford, 2000).

In recent human history, there have been three main events that most significantly influenced modern-day pathogen distribution (Barrett et al., 1998). These events, coined as "epidemiological transitions," describe critical shifts in human lifestyles and the corresponding environmental consequences that led to changes in zoonotic pathogen distribution and prevalence.

The first shift occurred approximately 10,000 years ago with the Agricultural Revolution in which small nomadic hunter-gatherer groups started living in larger, more agrarian communities. This first epidemiological transition led to the development of efficient food production, domestication of livestock and other wild animals, establishment of stable communities, and more sedentary lifestyles.

However, not all of these changes led to increased zoonotic pathogen exposure. It is believed that food production restricted the diets of humans living in agrarian communities because of the limited variety of crops and livestock compared with the food resources obtained through previous hunting and gathering communities (Nunn & Altizer, 2006). This production decreased the exposure to pathogens that were primarily transmitted through intermediate hosts.

The domestication of livestock and wild animals facilitated zoonotic spillover between animals and humans in a number of ways, such as positively influencing exposure opportunities between both groups. For example, human cases of rabies, an infectious viral disease most often transmitted from domesticated and wild animals to humans, are believed to have increased dramatically with the domestication of dogs around 4,000 years ago (Weiss, 2001). Domestication of animals also led to the creation of novel transmission routes for zoonotic pathogens. *Toxoplasma gondii*, the pathogen that causes toxoplasmosis in humans, was known to originally have a complicated life cycle involving multiple hosts. Recent genetic analyses have found that an alternative fecal-oral transmission route evolved around the same time as agrarian lifestyles became more common among humans (Yan et al., 2016).

These changes facilitated the development of more permanent human settlements, causing the birth rate of both human and animal populations to increase. However, larger population sizes led to increased accumulation of waste near human settlements that contaminated food and water and created novel sources of infection for humans. Expanding populations also resulted in a larger number of potential hosts, thereby ensuring the preservation of many contact-borne pathogens.

The second major shift occurred approximately during the Industrial Revolution in which populations moved from rural areas to densely populated urban centers, a process known as urbanization. Different levels of urbanization were found to affect species richness in different ways. Extreme urbanization in central urban areas reduced species richness, whereas moderate urbanization tended to produce varying results (McKinney, 2002).

In the earlier stages of the Industrial Revolution, the rapid expansion of human populations in urban centers caused an increase in the buildup of waste, allowing infectious diseases such as cholera, typhus, and plague to run rampant. Furthermore, significant infrastructure development led to increased trade and travel between remote areas that promoted faster spread and persistence of pathogens across the globe.

Rapid urbanization also gave rise to the creation of suburban areas and numerous changes to the natural environment, such as irrigation and dam building. Similar to the effects of moderate urbanization, these ecological modifications produced unpredictable consequences for zoonotic pathogens. For example, overall diversity of pathogen richness decreased, but novel evolutionary opportunities increased for pathogens and their transmission from vertebrate animal hosts to humans (Yan et al., 2016).

In some cases, anthropogenic changes led to an overall decrease in the prevalence and richness of zoonotic pathogens. Significant advances made in the scientific community allowed for better understanding of the importance of sanitation, improved city planning, and effective public health control strategies (Barrett et al., 1998). This dramatically decreased the prevalence of many infectious diseases and lowered mortality associated with infectious diseases.

According to Barrett and colleagues (1998), humans are in the midst of the third epidemiological transition characterized by the global proliferation of infectious disease and the evolution of antibiotic resistance. Although anthropogenic and demographic changes over the course of human history have both increased and decreased the prevalence and richness of zoonotic pathogens, throughout the past century it has been shown that the emergence of zoonotic diseases is largely on the rise. In a study conducted by Jones et al. (2008), the number of human EIDs was reported as steadily increasing since the 1940s (**Figure 7**). In addition, species richness was found to be a significant predictor of zoonotic EIDs that have a wildlife origin.

By learning how pathogen prevalence and richness were influenced by previous epidemiological transitions and by investing in multidisciplinary research on zoonotic spillover transmission, humans can craft effective management strategies to control zoonotic outbreaks.

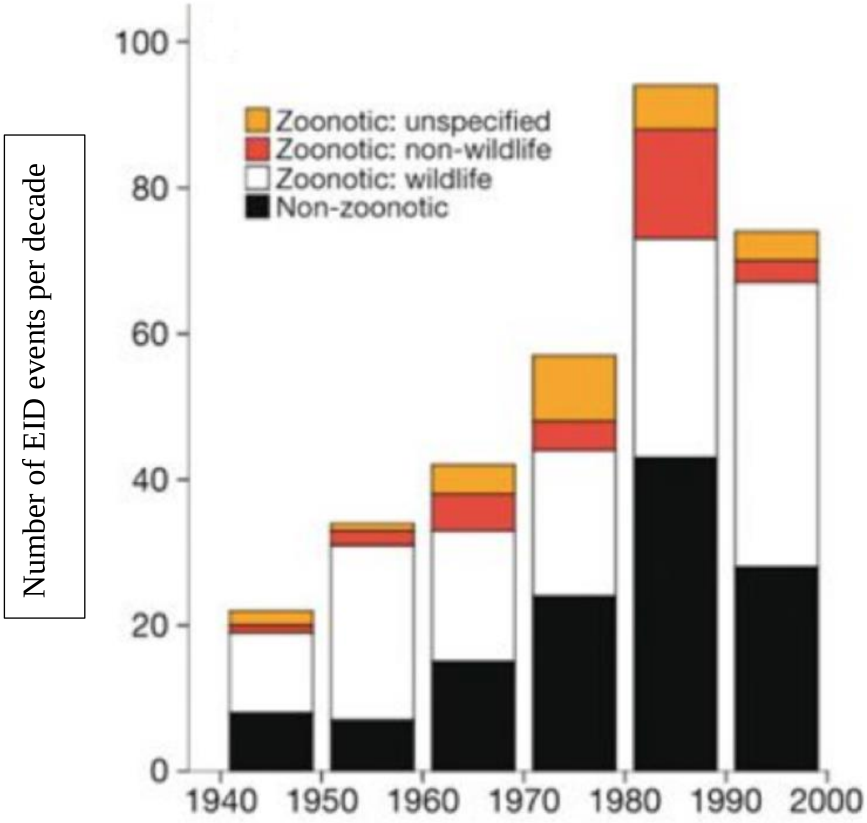

Figure 7. Number of emerging infectious diseases (EIDs) per decade, 1940-2000. The incidence of EIDs has significantly increased since 1940. After controlling for reporting bias, there is still a highly significant relationship between the number of EID events and time. This study provided one of the first pieces of analytical evidence for an increase in the burden of EID on global health with time. The spike in the 1980-1990 time range is largely due to EID associated with the HIV/AIDS pandemic. HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome. Taken from (Jones et al., 2008).

SPECIFIC AIMS

The purpose of this literature thesis is to analyze scientific articles in order to attain a more comprehensive understanding of zoonotic diseases. There are two specific aims that this work addresses:

(1) To review the current literature and identify the variables that have been found to have a significant correlation with zoonotic outbreaks.

(2) To analyze the efforts by national and international public health agencies at managing the most devastating zoonotic outbreaks of the past decade.

By focusing on these particular topics in the literature, this work can identify gaps in current zoonotic disease management strategies that may be resolved in future applications.

SIGNIFICANT PREDICTORS OF ZOONOTIC OUTBREAKS

In order to predict future zoonotic outbreaks, the past provides insight into which variables influence these events. Although there are a multitude of factors that mediate zoonotic spillover, latitude has long been a proxy for climate and biodiversity, both of which are implicated in influencing zoonotic pathogen transmission (Guernier et al., 2004). Because pathogen species richness is strongly correlated with both latitude and past zoonotic hotspots, this work utilized pathogen species richness as a measure of zoonotic potential (Guernier et al., 2004; Han et al., 2016).

A review was completed of more than 20 research papers that assessed or discussed various factors influencing pathogen richness. The factors that were identified were categorized into three main groups: host species characteristics, climate, and urbanization.

Host Species Characteristics

Host Body Size

Based on the island biogeography theory put forth by MacArthur and Wilson (1967), larger host species are believed to support greater population sizes, provide more niches for pathogen colonization, and encounter more pathogens because of increased surface area and increased feeding rates (due to higher energy requirements). Host body size has been shown to explain the diversity of parasitic arthropods and helminths infecting birds, fish, and some mammals (**Figure 8**) (Morand & Poulin, 1998).

According to recent studies that have tested this hypothesis, host body size is one of the most significant and widely used predictors of pathogen species richness across host and parasite taxa (Kamiya et al., 2014). Thus, host body size has a strong, well-supported positive effect on pathogen prevalence. However, in some of the literature, it has also been found that host group size is a better indicator of pathogen prevalence than host body size (Morand & Poulin, 1998; Nunn & Heymann, 2005).

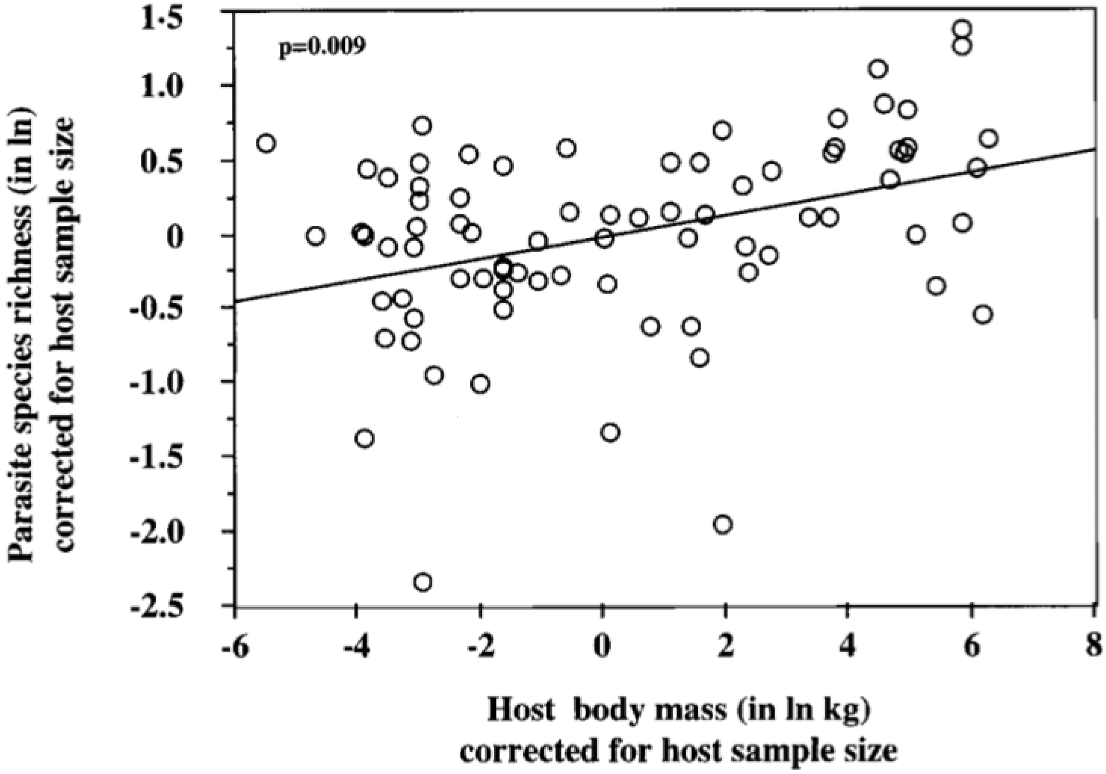

Figure 8. Relationship between host body mass and pathogen species richness. A non-phylogenetic (across-species) analysis shows that there is a positive correlation between host body size and pathogen species richness. ln = natural logarithm; kg = kilogram; p = probability value. Taken from (Morand & Poulin, 1998).

Host Population Density

Epidemiological theory states that host density is a significant indicator of the prevalence and richness of directly transmitted pathogens in animals. Although there are some older studies that downplayed the effect of host population density and pathogen species richness, such as Morand and Poulin (1998), there have been a plethora of other studies that have shown that host density plays a role in determining pathogen species richness. For example, analyses of the effects of host population density showed increasing richness of helminths, protozoa, and viruses (Nunn et al., 2003). Another study found that host population density is the key determinant of parasite species richness in nonhuman primates (Nunn et al., 2003). Furthermore, results of a recent meta-analysis indicated that hosts living in high population densities have higher parasite species richness than hosts living in low population densities (**Figure 9**) (Kamiya et al., 2014). Thus, it can be concluded that host density may be of great importance in predicting which host species are most heavily parasitized in free-living populations.

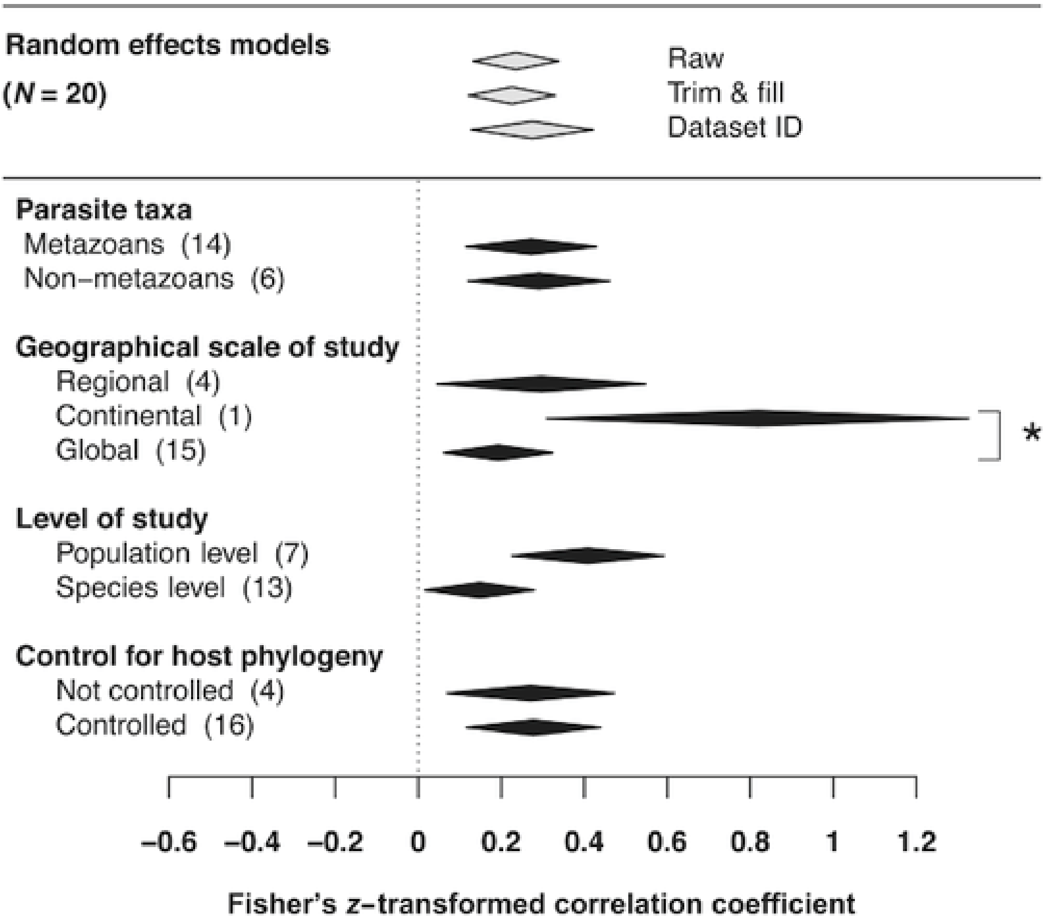

Figure 9. Forest plot of host population density and pathogen species richness. The plot shows the results of 20 comparative estimates looking at the relationship between host population density and pathogen species richness. The width of the black diamonds indicates a 95% confidence interval, with an asterisk representing a significant pairwise difference at an alpha level of 0.05. Taken from (Kamiya et al., 2014).

Host Species Richness

Because hosts serve as both habitats and dispersal agents for pathogens, it is important to determine if host species richness has an effect on pathogen species richness. Hechinger and Lafferty (2005) tested whether high host richness contributes to high pathogen species richness. The results showed that the diversity of upstream hosts, or hosts that carry pathogens in their developmental stages, was associated with the diversity of pathogens in a downstream host population. Thus, the authors were able to conclude that host species richness could potentially generate pathogen species richness in species with complex life cycles that sequentially use different host species. However, the study was not able to elucidate the precise pathways through which pathogen species richness increased. Two subsequent studies found possible mechanisms to explain the relationship between host species richness and pathogen species richness.

One study, conducted by Dunn and colleagues (Dunn et al., 2010), investigated the correlation between mammal richness and pathogen richness. This study proposed three ways by which host richness may affect pathogen richness: (1) greater number of alternative hosts or vector species could decrease the probability of local extinction in a particular pathogen (**Figure 10**), (2) greater host richness could mean a higher total richness of pathogens, and lastly, (3) patterns of alternative host species richness and parasite richness could simply reflect similar drivers of diversification such as temperature and precipitation. Another study confirmed that mammal richness was determined to probably capture additional variables that were important for causing pathogen richness (Aerts et al., 2018).

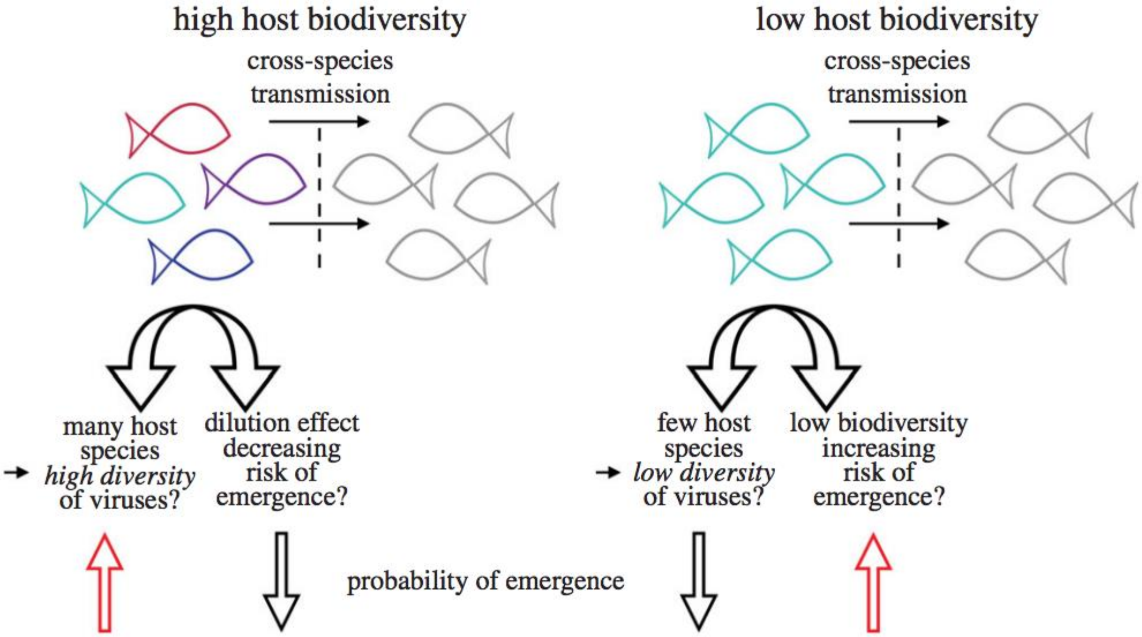

Figure 10. Effects of host biodiversity. This image depicts the potential effects of host biodiversity. As host species richness has been hypothesized to predict zoonotic potential, it is shown that increased richness of a host species corresponds with an increased zoonotic disease risk. In the illustration, red arrows depict increased emergence risk. Taken from (Geoghegan & Holmes, 2017).

A study by Johnson et al. (2016) also found three possible mechanisms through which increased pathogen species richness can occur (**Figure 11**). The "diversity-productivity" mechanism states that an increase may occur if increased host richness is correlated with an increase in total host species abundance. The second mechanism "propagule-pressure" proposes that variation in pathogen colonization leads to pathogen species richness. For example, if a new host species arrives with generalist pathogens that are able to become established on other vertebrate hosts, there should consequently be an increase in the average number of pathogens per host. Lastly, the "habitat-heterogeneity" mechanism suggests that the arrival of new host species increases the number of novel habitats for pathogens, thereby increasing pathogen richness at the level of the community rather than the individual.

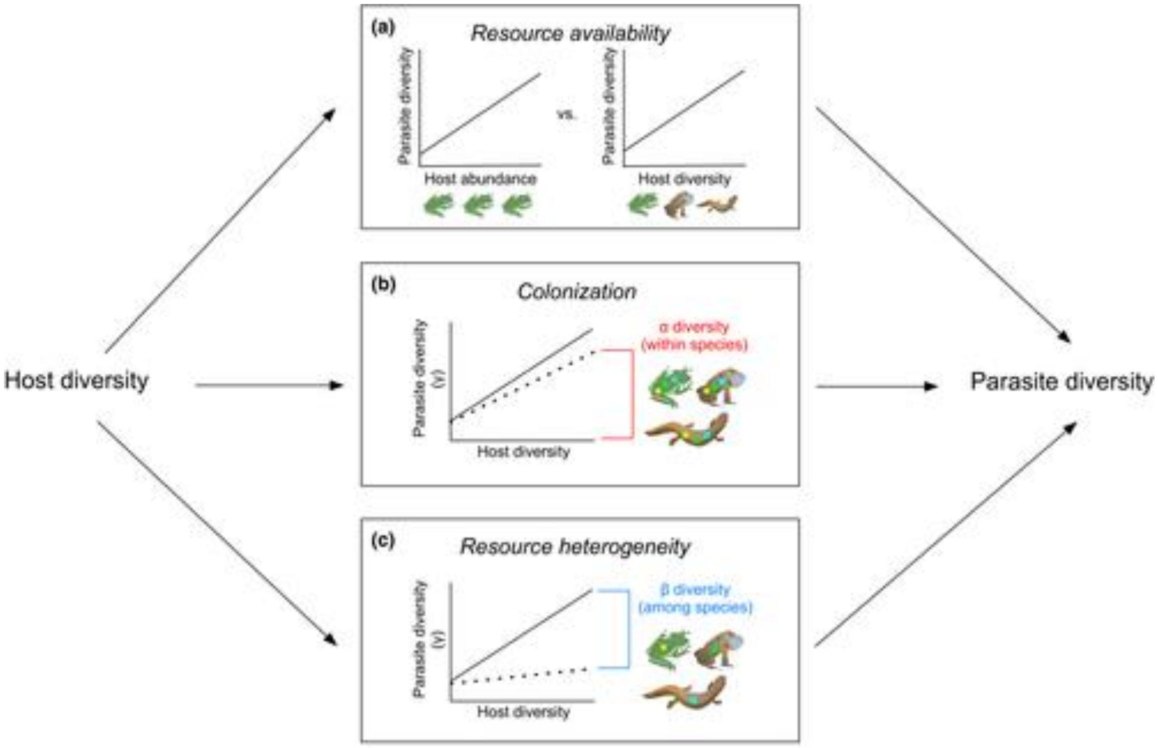

Figure 11. Host diversity promotes pathogen diversity. Host diversity influences pathogen diversity through three possible mechanisms: **(a)** resource availability, **(b)** pathogen colonization, and **(c)** resource heterogeneity. Taken from (Johnson et al., 2016).

Host Geographical Range

Hosts with expansive geographic ranges should encounter a greater variety of habitats and other host species, both of which lead to the hosts encountering a larger number of pathogens resulting in greater pathogen species richness (Poulin & Morand, 2004). A study conducted by Nunn et al. (2003) revealed that geographic range was significant in predicting species richness in protozoa; however, no consistent associations could be found in predicting virus richness (Lindenfors et al., 2007).

Climate

Studies have well documented the fact that species richness is strongly correlated with lower latitudes (Lindenfors et al., 2007). This is somewhat expected because harsher conditions at higher latitudes result in higher pathogen mortalities. Although this phenomenon, known as the latitudinal diversity gradient (LDG), has been investigated extensively in free-living organisms, there are comparatively few studies that have looked at the LDG and pathogen loads in the tropical and temperate zones (Bordes et al., 2011; Preisser, 2019).

One of the landmark studies in this field was conducted by Guernier et al. (2004), who discovered a strong positive correlation between proximity to the equator and total pathogen richness (TPR). This finding was further corroborated by both Dunn et al. (2010) and Jones et al. (2008) (**Figures 12 and 13**).

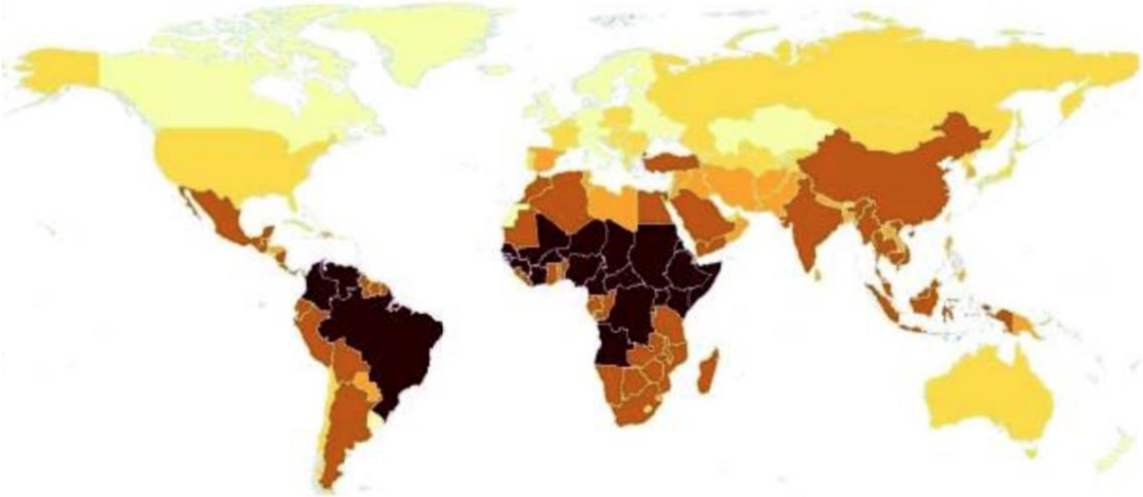

Figure 12. Geographical variation in human pathogen richness. This heat map depicts the geographical variation in human pathogen richness. The darker red regions represent greater richness. Taken from (Dunn et al., 2010).

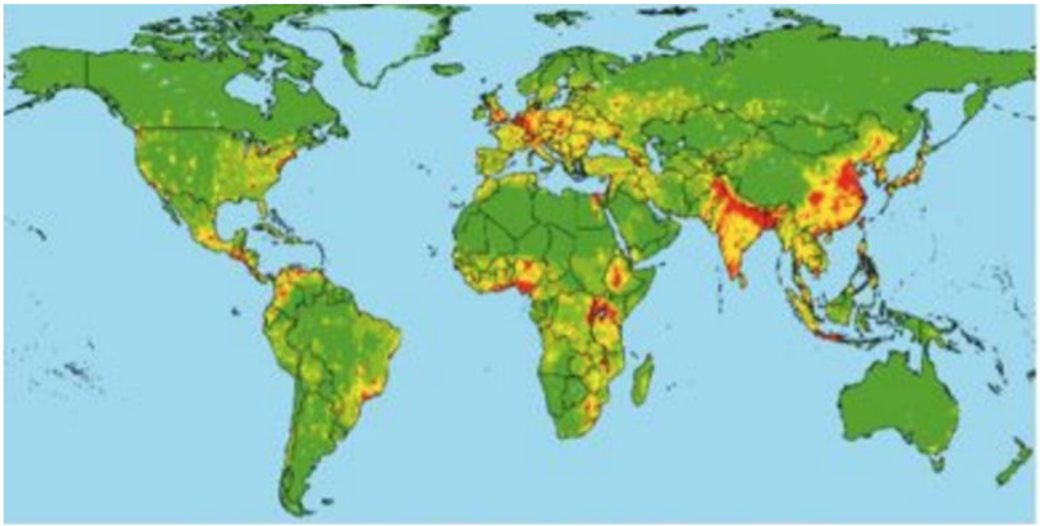

Figure 13. Global distribution of relative risk of human emerging infectious disease (EID) event. This heat map depicts the geographical variation in relative risk for a human EID event caused by a zoonotic pathogen with a wildlife origin. The relative risk is mapped on a linear scale from green (lower values) to red (higher values). Taken from (Jones et al. 2008).

Despite the evidence showing that TPR increased with proximity to the equator, there have been other studies with conflicting results. One such study conducted by Nunn and coworkers (Nunn et al., 2005) discovered that though protozoan pathogen species richness increased toward the equator in primates, there was a failure of viruses and helminths to fit into the LDG framework. Further highlighting the complex nature of the relationship between the LDG and pathogen species richness, a recent meta-analysis found that latitude was not an important predictor of parasite species richness (Kamiya et al., 2014). Rather, the study showed a weak but significant correlation between increased metazoan pathogen richness, such as viruses and helminths, and higher latitudes.

Although more comprehensive research into the mechanisms of the LDG and TPR is needed to elucidate these seemingly contradictory results, it is important to note that latitude is merely a substitute for a wide range of other climatic variables that may potentially affect species richness. Two major climatic variables, precipitation and temperature, appeared to have the most significant correlation with species richness (Guernier et al., 2004). Significant positive correlations between pathogen species richness and the maximum range of precipitation for all six categories of pathogens were found; however, monthly temperature range was only significant for predicting pathogen richness in three categories of pathogens: bacteria, directly transmitted viruses, and helminths.

Temperature has also been implicated as a significant variable in the evolutionary speed hypothesis, which predicts that increased species richness at lower latitudes is due to higher temperatures that increase mutation rates. Higher mutation rates in species can cause faster rates of speciation, thereby decreasing generation times and speeding up physiological processes such as catabolism and anabolism. Although more research is needed in this area, a recent study confirmed that richness patterns are dependent on rates of speciation (Gillman & Wright, 2014). Thus, higher species richness at regions near the equator may be a consequence of warmer temperatures, increased amounts of raw material upon which speciation can act, faster rates of speciation, and physiological tolerances that may bias particular species for warm climates (Currie et al., 2004).

Climate change may also substantially alter current pathogen species richness and prevalence. According to Epstein (2000), the suggestion was made that global warming would result in an expansion of tropical diseases, particularly vector-transmitted diseases. Though this may appear to be the case, a recent hypothesis proposed that shifted temperatures due to global warming would most likely change the range in both altitude and latitude of pathogen species' habitats (Harvell et al., 2008). Global warming has also affected the severity of certain diseases, such as malaria, in which transmission can increase to alarming rates as the climate gets warmer. However, the link between climate and infectious disease is complex, and climate change might not always lead to a net increase in the geographic distribution of infectious diseases or increased severity of pathogen-related threats.

Urbanization

Biodiversity Loss

Urbanization is a process that refers to the increasing concentration of human populations and human-generated landscapes that consist of built-up structures for human use. Urbanization causes a number of changes in the biotic and abiotic factors in an ecosystem that can greatly affect disease transmission dynamics, leading to serious public health concerns if changes are not carefully monitored (**Figure 14**) (Hassell et al., 2017). Urbanization can often lead to reductions in biodiversity and increases in species that thrive in urban environments (McKinney, 2002). A decrease in abundance and richness in other potential host species may cause certain parasites to become more extensive, infecting a higher proportion of the existing host species. In some cases, this may increase prevalence for infectious pathogens that affect urban-adapted wildlife, such as toxoplasmosis or rabies (Bradley & Altizer, 2007). Indeed, some studies that have been conducted in urban environments tend to show an increase in disease prevalence. Lehrer and colleagues (Lehrer et al., 2010) found a significant positive relationship with *Toxoplasma gondii* in woodchucks in areas where urban land covered more than 70%. This positive correlation was explained in part by higher densities of the definitive host in urban areas. However, studies of blood pathogen infection in blackbirds in Munich, Germany, actually found fewer infected birds in urban areas. This reduction in infection was attributed to a reduction in suitable vectors for the pathogen (Valkiūnas et al., 2018).

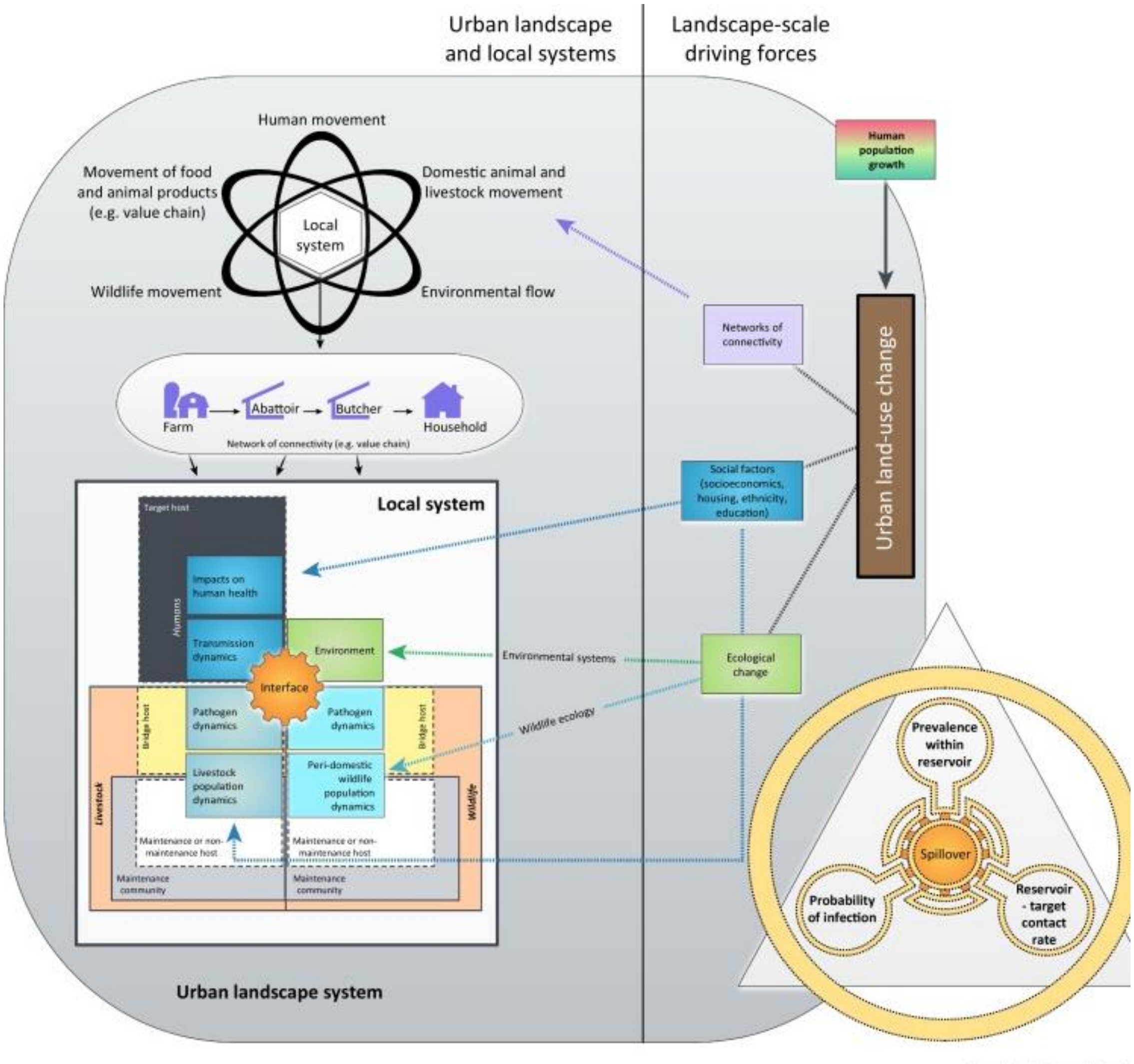

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Figure 14. Theoretical framework for the efforts of urbanization on zoonotic spillover. This simplified framework depicts the manner in which livestock and urban-adapted wildlife exist as either hosts or vectors for zoonotic pathogens. Thus, they act to either establish or maintain the zoonotic pathogen within the local population. Once spillover has occurred, further zoonotic spillover may happen in other populations. Taken from (Hassell et al., 2017).

Another process that has generated considerable attention and controversy is the “dilution effect.” The dilution effect proposes that high species richness is expected to result in lower disease risk for humans. Areas of high host species richness may lead to lower pathogen transmission if vectors feed on a variety of hosts that vary in their ability to further transmit the pathogen. Based on the current literature, richness of these pathogens is quite variable, and depending on the particular circumstances, urbanization may lead to an increase or even a decrease in pathogen richness (Bradley & Altizer, 2007). Due to the complex relationship between urbanization and pathogen species richness, researchers have suggested simplifying the complexity of urban environments into a network of various interfaces at which zoonotic spillover may occur (**Figure 15**) (Hassell et al., 2017). Although there is ongoing research regarding the epidemiological processes occurring at these interfaces, it is widely accepted that anthropogenic changes that increase exposure to urban-dwelling wildlife species inevitably increase zoonotic spillover (Plowright et al., 2011).

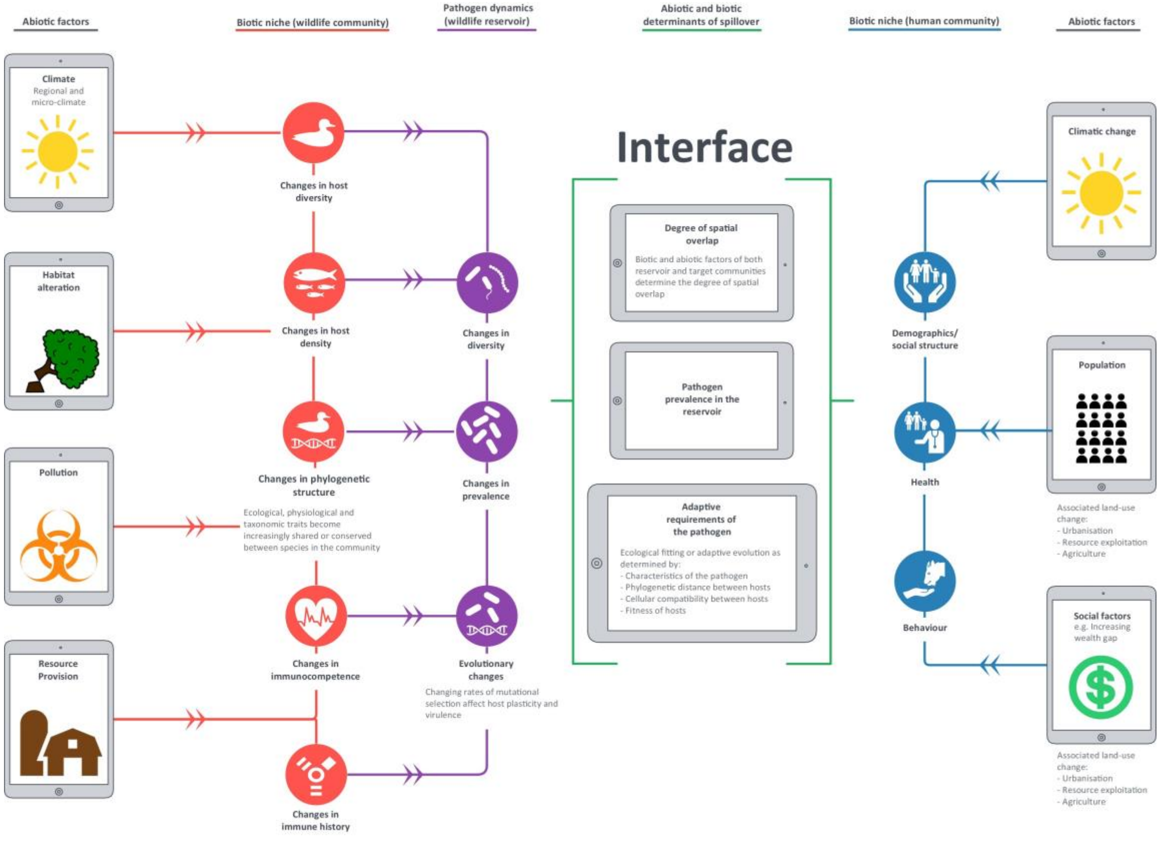

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Figure 15. Abiotic and biotic components of hypothetical wildlife-human interface. This flow chart represents the manner in which abiotic factors (such as climate, resources, pollution, and habitat modifications) and biotic factors (such as demographics, human behavior, and human health) determine zoonotic spillover. Taken from (Hassell et al., 2017).

Habitat Fragmentation and Loss

Urbanization produces a gradient of natural habitat loss that decreases from rural areas to the center of the urban area, or “urban core.” The habitats become increasingly fragmented, creating abundant but smaller patches. These fragmented landscapes contain more “edge habitat,” areas where an increase in cross-species transfer and acquisition of novel pathogens has been documented (Ries et al., 2004). This effect was seen among colobus monkeys in western Uganda, where individuals living at the edge of the forest were found more likely to be infected with multiple pathogen species as compared with individuals in the core of the forest (Gillespie & Chapman, 2006). This phenomenon has been partially explained by the fact that habitat loss reduces the number of habitats available for vertebrate animals. Habitat loss causes crowding, increased competition for food, and higher stress levels that lead to lower immunocompetence and a reduction in the vertebrate host animal’s resistance to infection.

In a study explaining the effects of habitat fragmentation, Fahrig (2017) reported that these effects were overwhelmingly positive with respect to biodiversity. However, a recent study conducted by Fletcher et al. (2018) systematically discredited many of these findings by claiming that they came from a narrow and potentially biased subset of data. **Table 1** summarizes the counterevidence to the claims that habitat fragmentation produces increased biodiversity (Fletcher et al., 2018).

Table 1. Counterevidence to Fahrig's Claims Regarding Habitat Fragmentation and Pathogen Species Richness[a]

Fahrig's "Zombie Ideas"	Fahrig's Evidence (Fahrig, 2017)	Counterevidence Not Considered
Habitat fragmentation has widespread negative effects.	76% of "significant" responses to habitat fragmentation from landscape studies were positive.	Haddad et al. (2015) provide a meta-analysis on long-term, patch-focused experiments, with edge and isolation effects controlling for habitat area and habitat heterogeneity. Effects are consistently negative (80% isolation; 82% edge) and increasingly so over time.
Small number of large patches contain more species than large number of small patches.	SLOSS (single large or several small) analysis on species richness: all 60 "significant" responses were positive (higher richness in many small patches).	Ramsey (1989) and Mac Nally and Lake (1999) argue that this type of analysis is flawed, yielding biased results (in the direction shown by Fahrig), and that it does not provide a means of assessing "significance."
Edge effects are generally negative.	No data. Authors of papers suggest that positive edge effects may drive positive responses to habitat fragmentation.	Ries et al. (2004), Fletcher et al. (2007), and Pfeifer et al. (2017) show variable edge effects. Pfeifer et al. (2017) meta-analysis shows that species with negative edge effects are 3.7 times more likely to be of conservation concern (International Union for Conservation of Nature [IUCN]-threatened), whereas positive responses include pest/invasive species.
		Meta-analysis on corridor effects shows positive effect of

Table 1 (continued).

Habitat fragmentation reduces connectivity.	No data. Authors of papers suggest that greater functional connectivity may drive positive responses to habitat fragmentation.	corridors (less fragmented), with 50% increase in movement ($n = 28$ studies) along corridors when controlling for habitat area (Gilbert-Norton et al., 2010).
Habitat specialists show greater negative responses.	No data. Pooled "endangered/ threatened/specialist": 29 of 30 significant responses to habitat fragmentation were positive.	Pfeifer et al. (2017) meta-analysis shows that negative edge effects are typically observed for specialist species, positive for generalist species.
Negative habitat fragmentation responses are stronger at low levels of habitat amount.	Proportion of negative responses to habitat fragmentation were similar when comparing <0.2 (31%) habitat to >0.2 (33%).	Theory emphasizes that specific thresholds are contingent on assumptions regarding movement (Hanski, 2015; Swift & Hannon, 2010; With & King, 2001). Fahrig's results do not support this claim when considering a larger threshold: <0.5 (33.3% negative) versus >0.5 (8% negative).
Negative fragmentation responses are stronger in the tropics.	Proportion of positive responses were similar for "subtropical/ tropical" versus other.	Lindell et al. (2007) meta-analysis shows that tropical birds are more likely to avoid edges than temperate birds.

[a]This table summarizes the major conclusions made by Fahrig (2017) and non-exhaustive summaries of counterevidence to refute those claims. Adapted from (Fletcher et al., 2018).

CURRENT PUBLIC HEALTH MANAGEMENT AND SURVEILLANCE OF ZOONOSES

As zoonoses increasingly comprise the majority of human EIDs, interdisciplinary collaboration and research are critical in managing and preventing future outbreaks. In learning from the management and shortcomings of past zoonoses, organizations such as the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have started using a "One Health" approach. According to the CDC:

> "One Health is defined as a collaborative, multisectoral, and transdisciplinary approach—working at the local, regional, national, and global levels—with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment (Centers for Disease Control and Prevention [CDC], 2018)."

This approach requires the participation of public health officials, veterinarians, ecologists, and physicians to effectively monitor the spread of zoonoses. The following sections highlight two contrasting examples of public health responses to zoonoses: one utilizing a more traditional approach for outbreak control and the other utilizing a "One Health" approach.

Ebola Virus Disease

Ebola virus disease (EVD) was first identified in the Democratic Republic of Congo in 1976 during an outbreak of more than 300 cases that caused over 85% fatality. Although there were smaller outbreaks documented since its identification, the 2013-2016 epidemic was the first time transmission was noted in West Africa and outside the African continent (**Figure 16**). The outbreak was also the largest in human history in terms of morbidity and mortality, affecting over 10 countries worldwide (Ajisegiri, et al., 2018). The management of EVD proved to be complicated because of the high-risk burial practices among local communities, weak health services, and inadequate responses from national and international agencies (Piot, Muyembe, & Edmunds, 2014).

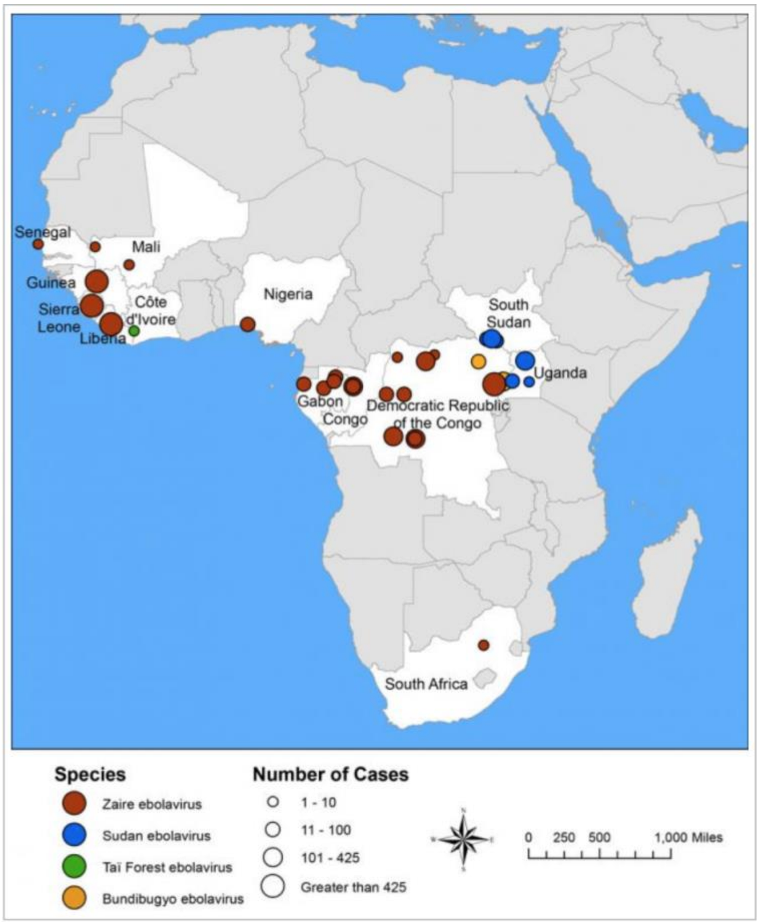

Figure 16. Ebola virus outbreaks since 1976. This map shows the geographic distribution of Ebola virus disease (EVD) across the African continent. The 2013-2016 EVD epidemic was the first time the virus was identified and sustained in a human population in West Africa. The different color dots represent various strains of the virus, and the sizes depict the number of cases. Taken from (Centers for Disease Control and Prevention [CDC], n.d.).

The WHO spearheaded the response to the Ebola epidemic, proposing a regional approach in managing the disease that aimed to be responsive to the unique needs of each region. Unfortunately, the response was largely reactionary and did not serve to preserve and improve local health care services. In some cases, the coordinated response to EVD served to disintegrate the local health systems as a result of patients dying from largely treatable conditions (Scott et al., 2016). Poor sanitation and hygiene led to the infection and subsequent death of large numbers of health care workers. The prohibition of travel at all international ports of affected countries also worsened local conditions, as it increased food insecurity in many households and reduced income potential for as many as 2 to 3 million people.

A critical analysis of the EVD response revealed a lack of understanding of the sociocultural factors that contributed to the outbreak. Poverty and chronic food shortages in many of the local populations pushed communities further into forests to look for food and fuel, exposing them to natural reservoirs of EVD. Combined with habitat fragmentation of many of the host species home ranges, zoonotic spillover transmission became inevitable.

Learning from the management of the 2013-2016 EVD outbreak has led to the conclusion that understanding a local region’s social, political, and cultural factors is crucial in implementing any type of public health response plans.

West Nile Virus

West Nile virus (WNV) was first isolated from a patient who presented with fever in the West Nile district of Uganda in 1937 (Smithburn et al., 1940). Since the first documented case, there have been several local outbreaks that occurred throughout Africa, Europe, and Asia. However, it was not until 1996 that the epidemiology and clinical presentation of WNV dramatically evolved. The WNV outbreak in 1996 near Bucharest, Romania, was the first to happen in an urban center and was the first in which patients presented overwhelmingly with neurological symptoms. The conditions that led to the rapid evolution and spread of WNV were attributed to the declining state of the city which facilitated the breeding of mosquitoes, a known vector for WNV, and the absence of physical barriers such as screens (Sejvar, 2003). Since that time, WNV has become endemic in various regions in both the Eastern and Western Hemispheres. One such region, the Po Valley area in Northern Italy, was the site of a recent study that attempted to analyze local disease management efforts that utilized a "One Health" approach (Paternoster et al., 2017).

First, the study noted that the local initiative addressed the multifaceted nature of zoonotic disease management by the creation of three multidisciplinary groups to deal with the animal, public, and environmental aspects of the disease. The task forces also created explicit rationale behind the disease management initiative to apply preventative measures in more targeted ways (**Table 2)**. Writing and sharing the rationale behind their initiative allowed effective public awareness campaigns to be created and disseminated to the general population (Paternoster et al., 2017).

Table 2. Rationale for West Nile Virus (WNV) Management in North Italian Regions[a]

A	**Economical**	West Nile neurologic disease causes high health care costs for human and equine patients. Moreover, it determines financial damage in the form of DALYs (disease-adjusted life years) for affected humans, lost manpower for employers, and lost investments for owners of commercially used horses. In addition, a continuous screening of blood donations from previously affected areas during the entire WNV circulation period is costly.
B	**Emotional/Psychological**	Patients (human, horse) affected by neurologic disease are suffering. This suffering extends to the family and friends of the affected patients—especially in fatal cases.
C	**Environmental**	Possibly due to climate and environmental changes, mosquitoes—including the ones carrying WNV—have a higher chance of survival during winter (overwintering), leading to the establishment of WNV endemic areas in Northern Italy.
D	**Social**	There is a lack of knowledge in the general population regarding mosquito biology, their breeding habitats, and their potential to carry disease.

[a]This table shows drivers for the WNV management initiative. Adapted from (Paternoster et al., 2017).

In addition, the disease management initiative developed a national early detection system that aimed to monitor known vectors and hosts of WNV, including mosquitos, wild birds, humans, and horses. The surveillance plan was composed of four parts: active surveillance of target bird hosts, passive surveillance of dead target bird hosts, active surveillance of mosquito vectors, and syndromic surveillance of human patients who presented with neurological disease (Paternoster et al., 2017).

The integrated and holistic "One Health" approach taken by these researchers was found to have increased efficiency in detection of infected blood, adoption and implementation of evidence-based preventative public health measures, and reduction in overall health care costs (Paternoster et al., 2017). Thus, adopting a "One Health" approach can improve health outcomes and have favorable economic consequences as well.

CONCLUSIONS AND FUTURE DIRECTIONS

As zoonotic pathogens persist in making up a significant portion of human EIDs, the social, public health, and economic burden of managing zoonoses continues to skyrocket without adequate understanding and management. This literature review highlighted the importance of conducting zoonotic research within a holistic perspective. This work further provided a comprehensive introduction into the fundamental principles of zoonotic spillover as well as the historical factors that contributed to zoonotic pathogens becoming endemic in certain populations.

The overarching goal of this literature review was to find common themes and trends in the current literature that could aid in developing systematic public health strategies in managing zoonoses. Because pathogen species richness has strongly correlated with hotspots of past zoonotic outbreaks, this work used pathogen species richness as a measure of zoonotic potential for a particular region. Several variables associated with climate, urbanization, and host-specific characteristics were found to be positively correlated with pathogen species richness.

Finally, this review looked at two examples of recent public health efforts aimed at managing zoonoses. In analyzing both EVD and WNW control efforts, the adoption of a “One Health” approach in zoonotic disease management yielded more positive and effective economic, social, and public health outcomes as compared with more traditional control methods.

In conclusion, pathogens play essential roles in natural communities. Studying the variables that influence their transmission, species richness, and establishment is key in discovering the biological principles that determine zoonotic spillover. Research into these variables would have immense potential in informing researchers on how to develop more integrated and multidisciplinary strategies in monitoring and preventing major zoonotic outbreaks.

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