Modeling Spillovers of Emerging Infectious Diseases with Intermediate Hosts

DARTMOUTH

Katherine Royce

Honors Thesis

Feng Fu, Advisor
Department of Mathematics

Dartmouth College

May 29, 2019

Acknowledgements

I would like to thank my advisor, Feng Fu, for his constant optimism and guidance; Dana Williams, for encouraging me to pursue a thesis; and the mathematics department of Dartmouth College, for supporting my research during my entire undergraduate career. Additionally, this project owes a great deal to Noam Ross and Cale Basaraba of EcoHealth Alliance, who taught me how to mathematically model infectious diseases, and its even more distant beginnings to David Quammen and his book *Spillover*, which inspired me to seriously consider epidemiology as a career at age 13. Finally, without my parents' lifelong support for my studies in mathematics, I could not have approached this work, and I will always be grateful that they encouraged my unorthodox path.

Abstract

The World Health Organization describes zoonotic diseases as a major pandemic threat, and modeling the behavior of such diseases is a key component of their control. Many emerging zoonoses, such as SARS, Nipah, and Hendra, mutated from their wild type while circulating in an intermediate host population, usually a domestic species, to become more transmissible among humans, and this transmission route will only become more likely as agriculture and trade intensifies around the world. Passage through an intermediate host enables many otherwise rare diseases to become better adapted to humans, and so understanding this process with accurate mathematical models is necessary to prevent epidemics of emerging zoonoses, guide policy interventions in public health, and predict the behavior of an epidemic. In this thesis, we account for a zoonotic disease mutating in an intermediate host by introducing a new mathematical model for disease transmission among three species. We present a model of these disease dynamics, including the equilibria of the system and the basic reproductive number of the pathogen, finding that in the presence of biologically realistic interspecies transmission parameters, a zoonotic disease can establish itself in humans even if it fails to persist in its reservoir and intermediate host species. This result and model can be used to predict the behavior of any zoonosis with an intermediate host and assist efforts to protect public health.

Contents

List of Figures

Chapter 1

Introduction

This thesis presents a mathematical model that simulates the emergence of a zoonosis that mutates from its wild form to a human-transmissible form in an intermediate host population. It shows that interspecies transmission parameters determine the global stability of the system and that zoonotic diseases with intermediate hosts can persist in humans even if they fail to establish themselves in other species. This result mathematically confirms a key tenet of the field of global health, that human health is inextricably tied to that of other species. In this chapter, we introduce the project and review the current state of mathematical epidemiology.

1.1 Background

Zoonotic diseases, which originate in animals and infect humans, are one of the most concerning epidemic threats of the 21^{st} century and form 60% of all known infectious diseases [1]. These pathogens cause a billion cases of illness per year, inflict severe economic damage, and pose an increasing threat in a more connected world; indeed, endemic zoonoses are currently the greatest global burden on human health [1]. Public health threats such as HIV-AIDS, avian influenza, SARS, Ebola, Nipah, Hendra, and

rabies all trace their origin to nonhuman reservoir species, and it is likely that the next global pandemic will be a zoonosis [1]. The World Health Organization even cites "Disease X", a pathogen currently unknown to cause human disease that might evolve to become more transmissible among humans, as a priority for research and development to prevent a pandemic [2], indicating the severity of the threat to public health and the necessity for further research into zoonoses. Multihost pathogens are not threats to human health alone: rinderpest, foot-and-mouth disease, and other livestock diseases cause economic damage even though they do not infect humans [3], and zoonotic diseases form 50% of recognized livestock diseases [4]. Zoonoses have comprised a growing area of public health research for the last two decades [5], although recent research has shifted from concern over spillover from domestic animals to wild ones to concern over transmission from animals to humans.

The frequency of new pathogens emerging into the human population−rapidly increasing in incidence or geographic range to become a threat to public health−is increasing [4], and zoonoses comprise 75% of emerging infectious diseases [6]. Emergence of zoonoses is linked to human behavioral changes and increasing rates of interaction with wildlife, human travel, and global trade [7], as well as accelerating climate change [8]. These changes are predicted to increase with anthropogenic decisions, such as changing human population density, greater local and international trade, and intensifying agricultural practices and land use ([1], [4], [9]). The dynamics of a zoonosis in its reservoir host are frequently cited as an influence on its emergence in humans [1], but to our knowledge, no attempt has been made to quantify the entire course of an emerging zoonosis, from its origins in a wild reservoir host to, in the worst case scenario, a pandemic in humans. Indeed, [10] blames a desire to view zoonoses in a piecewise manner, as a concatenation of different epidemics rather than

a connected system, for the lack of quantitative understanding of zoonoses as a new type of disease. Explicitly understanding the dynamics behind this adaptive transformation is thus critical to public health efforts; however, no previous quantitative models examine the changes an emerging zoonosis undergoes as it spreads between different species.

Further adding to the air of mathematical mystique around zoonoses, recent research indicates that their transformation into a threat to humans does not occur in a single leap. Zoonotic diseases are classified on the basis of their human-to-human transmissibility [10], a critical distinction between pathogens with pandemic potential and pathogens that remain relatively rare ([1], [6], [8]). Currently, the classification of zoonoses uses a three-stage framework presented in [4] and modified in [10], which streamlines the five-stage framework of [9], dividing zoonoses based on their transmissibility in humans. Stage 1, pre-emergence, represents zoonoses circulating in an intermediate host but only capable of spillover into a dead-end human host, with no further transmission. Stage 2, localized emergence, defines diseases that can maintain stuttering chains in a human population with reinfection from animal hosts but are incapable of sustaining themselves in humans alone. Stage 3, pandemic emergence, classifies diseases that are fully adapted to humans and thus capable of causing outbreaks in our species alone ([4],[10]). In this thesis, we examine the process of pathogen evolution through these different stages to find that with a mutation to a human-transmissible strain in an intermediate host, a pathogen can maintain an endemic equilibrium in humans even in stage 1, suggesting that the rigid framework underlying epidemiology's stratification of zoonotic diseases based on their perceived threat to humans may be unwarranted.

In contrast to pathogens which evolved to infect humans, such as smallpox, the

biology of emerging zoonoses is adapted to a different host species, called the reservoir host. Zoonotic pathogens thus usually require one or more mutations from their wild type before becoming human-to-human transmissible [8]. Intermediate hosts−a non-reservoir animal species in which a zoonotic pathogen circulates−particularly domestic animals, provide greater opportunity for a pathogen to mutate to a human-transmissible form, because these species are biologically similar to the pathogen's wild reservoir and have greater contact with humans. Some of the most pressing unadressed questions in establishing the mathematical theory of zoonoses include better capturing disease dynamics within nonhuman species in order to characterize changes in the disease before it infects humans; focusing on the first singleton cases of human infection to understand how a pathogen actively adapts to humans; and developing a theory for the role of intermediate hosts in the emergence of the disease [8]. Overall, there is no unifying mathematical theory or set of principles that can be used to frame discussions of zoonotic spillovers, despite the frequent use of mathematical biology to assist with risk assessment and surveillance strategies for other types of diseases [8]. This gap in modeling spillover dynamics limits our understanding of zoonoses, as does a general lack of mathematical modeling of multihost pathogens and quantification of the rate of human-to-human transmission ([10], [11]). This thesis fills that gap by providing a mathematical model for a zoonosis emerging through an intermediate host.

1.2 The Role of Intermediate Hosts for a Zoonosis

Zoonoses are the product of a pathogen exploiting a new niche, sometimes one exposed by anthropogenic changes or induced by the amplification of its transmission

[1]. Zoonotic pandemics occur when the pathogen gains the ability to circulate in a human population, rather than infrequently causing infection in an individual dead-end host [12]. The major distinction in zoonotic spread within humans is whether the pathogen can spread beyond its primary individual host to infect other humans: whether the basic reproduction number R_0, the number of secondary cases produced by an index case in an entirely naive population, is greater than 1. The consensus in the field is that a pathogen's threat to public health is defined by its R_0 in humans [8]. A pathogen faces two barriers to becoming human-to-human transmissible: jumping from an animal host to a human, and adapting to its new host through mutation or reassortment [12]. However, overcoming the human-to-human transmissibility barrier is considered the greatest obstacle preventing a zoonosis from becoming a pandemic [12]. While such evolutionary changes can take place over a single individual infection, this modification is considered to be a result of the role that different animal hosts play in amplifying or transmitting a zoonosis to humans [1]. In fact, circulation in an intermediate host population, generally a domestic animal where the pathogen can mix with diseases caught from both wildlife and humans, provides zoonoses a key opportunity to mutate to a more effective pathogen in humans. There are four stages of a zoonotic disease's spread in an organism−exposure, cellular entry, replication, and transmission−any one of which offers the pathogen an opportunity to better adapt to a new host species [11]. The exposure and transmission stages of the pathogen's evolution can also be affected by anthropogenic factors such as the host species' population structure (for domestic animals) or resource and habitat availability [11], and so the dynamics behind the outbreak of a new zoonosis in humans are poorly understood [6]. However, it is widely believed that a species other than the reservoir host−particularly a domestic animal that is exposed to both wild and human diseases and has more

frequent contact with humans than its wild counterparts−can serve as an amplifier or transmission host to humans. Once established in an intermediate population, a pathogen has the opportunity to mutate to a human-to-human transmissible form and start an epidemic in humans before detection by public health authorities. It is therefore extremely important to develop a theory for a human-transmissible disease arising from a zoonotic pathogen in an intermediate host population; with such a framework, policymakers can move towards prevention of a human pandemic rather than amelioration of one [8].

As an example of the role of intermediate hosts, the adaptation of avian influenza, one of the most well-studied zoonoses, to humans requires a reassortment in domestic pigs or poultry. Avian influenza's success in a new host species is governed by its receptor binding specificity [12]; with circulation in domestic pigs, which express both human- and avian-influenza type receptors in their trachea, the virus has an opportunity to mutate to a type more dangerous to humans ([13], [14]). Further, as domestic animals, swine have more contact with humans than wild birds do and can thus spread a disease more quickly [14]. Domestic poultry can play a similar role for the disease, since circulation in a domestic poultry population may increase the pathogenicity of avian influenza among birds [15]. Indeed, through passage in chickens, an avirulent wild sample of avian influenza mutated to a highly pathenogenic form among chickens [16], indicating the importance of passage through an intermediate species to changing the disease. As a result, human movement of livestock, not avian migration, is the dominant factor in the spread of highly pathogenic avian influenza, even though wild birds are the reservoir of the disease [17]. The influenzas are perhaps the easiest example to understand, as reassortment of different hemagglutinin and neuraminidase subtypes within one infected pig can produce entirely new pathogens [13], but less

drastic mutations can alter the transmissibility or lethality of any pathogen. The intensification of the pig industry in Malaysia was identified as the key factor in the spread of Nipah virus encephalitus, which has bats as a reservoir host, to humans in the 1990s [7], and pigs were later confirmed as an intermediate host for the disease [18]. In this case, repeated introductions from bats, the pathogen's reservoir host, to pigs−and the disease dynamics that resulted−made Nipah virus able to persist in its intermediate host and thus infect humans [19]. These results support the general principle that the domestication of animals is linked to an increased risk of emergence of zoonotic diseases into the human population [1], and Table 1.1 shows a sampling of zoonoses for which an intermediate host has been identified.

Disease	Reservoir Host	Intermediate Host	Source
Nipah virus encephalitis	bats	pigs	[1], [7], [8], [5]
Hendra virus disease	bats	horses	[7], [8], [5]
SARS	bats	civets	[8]
Avian influenza	wild birds	domestic poultry, pigs	[15], [16], [20]
Menangle virus disease	bats	pigs	[7], [5]
Middle East Respiratory Syndrome	bats	camels	[21]
Campylobacteriosis	wild birds	domestic poultry	[22]
Japanese encephalitis	wild birds	pigs	[22]

Table 1.1: Zoonotic diseases with intermediate hosts

The importance of an intermediate host species to zoonosis dynamics is a result of the fact that most pathogens are less infectious to a non-reservoir species, a species barrier they can overcome by rapid adaptation in a new host [3]. While single-host pathogens evolve to an optimum level of virulence, multihost pathogens may be much less or much more virulent in a new species [3] and require adaptation to succeed in the new population. It has been proven that evolution favors minimizing the case fatality ratio in a reservoir host, but it is unclear how this dynamic changes in a new host species [23]. Nevertheless, dynamic emergence, where the non-human ecology of

a disease changes before its emergence in humans, is cited as a more pressing concern than static emergence, where the dynamics of the disease do not change until it is established in humans [8], because it is more difficult to gather data and distribute health interventions in animal populations than human ones. Zoonoses whose hosts have sporadic contact with humans, and thus opportunities to adapt themselves to humans through reassortment with human pathogens or stuttering chains of animal-human-animal transmission, can adapt to infect humans more effectively before the epidemic ceases [10]; as a result, most zoonotic diseases arise on farms [1], where humans and animals work in close contact. On the other hand, the presence of an intermediate amplifier host can provide an easier way to control a disease—by bringing its basic reproduction number in the entire multispecies system below 1—than direct interference with its wild reservoir host [11], offering hope for public health interventions.

Further, there is a dearth of theories for the role of intermediate hosts in pathogen emergence, despite the vital "bridging" role these species may play between wild reservoir species and humans [8]. Models which incorporate the multihost ecology that defines zoonoses are rare, with only six of 442 models surveyed in a recent study investigating this defining component of zoonotic disease [10]. Thus, it is currently unclear how to quantify the amplifier or transmission role that intermediate hosts are thought to play in the emergence of a zoonosis.

1.3 The Role of Mathematical Modeling

A sizeable literature exists on the utility of using ordinary differential equations to model a pathogen spreading between species [11]. Mathematical models of population

dynamics and zoonotic transmission are a crucial tool in understanding the nonlinear interactions that are a hallmark of zoonotic diseases, a type of subgroup dynamics which can lead to counterintuitive behaviors [10]. Models can enable experiments that would be unfeasible with real populations, predict future trends based on current data, and estimate key epidemic qualities such as the basic reproduction number [10] of a pathogen in a specific population.

There have been attempts to quantify the effect of pathogen mutations in humans alone. Models for tuberculosis sometimes include a distinction between latent and active forms of the disease [24]. [20] recognizes that the ability of avian influenza to mutate during an epidemic is a crucial determinant of its pandemic potential, but conceptualizes this mutation as occuring within humans rather than another species, ignoring the intrinsically zoonotic behavior of the disease. Modeling an SI-SIR domestic poultry-human system, [20] finds that once mutant avian influenza occurs in the human population, depopulating the avian one will not stop the spread of the disease. This paper suggests adding a constant inflow of disease from wild birds to domestic ones, as well as vital dynamics for the human compartment, but primarily considers the dynamics of a mutation occurring once the disease has already spread to humans, and considers only domestic poultry based on that population's greater importance than wild birds to the spread of the pathogen among humans [20]. [25] expands on this analysis by including a compartment for wild birds, as well as the capacity for isolation of infected humans. [25] also considers a mutation arising only in the human population, and finds a unique, globally stable endemic equilibrium when the basic reproduction number for the avian strain is greater than one. However, this paper also locates the mutation after the pathogen's spillover to humans: [12] cites two barriers, jumping to humans and efficient human-to-human

transmission, that a pathogen must overcome, and in well-known examples such as avian influenza, this change occurs in the "mixing vessel" of an intermediate host species [13]. Further, controlling a human epidemic of a zoonotic disease depends on controlling the basic reproduction number in both animals and humans [26], a control not studied in preceding papers.

While both vector-borne diseases and pathogens which mutate in humans provide a useful comparison for modeling the full range of a zoonotic disease, to our knowledge, no model yet exists that attempts to characterize a zoonosis mutating while circulating in an intermediate host population [8]. As their prevalence in the literature shows, mathematical models are a key tool for studying infectious diseases, and have been used to predict or prove behavior for many types of epidemic. However, few models focus on trans-species dynamics [10], and there are no mathematical models for zoonotic pathogens which contain a mechanism to differentiate between the disease's behavior in reservoir and intermediate hosts, despite the need for such analysis [8]. In this thesis, we present a model which incorporates this type of mutation. Here, intermediate hosts originally become infected with a purely animal disease from its reservoir hosts, but as the epidemic continues among intermediate hosts, a new strain develops that can spread among humans. This thesis fills the gap noted in [8] by introducing a mathematical model that simulates the entire course of a zoonosis mutating to a human-transmissible form in an intermediate host population. We investigate whether the presence of pathogen adaptation in intermediate hosts can amplify an epidemic among humans, with the goal of informing public health efforts to curb emerging infectious diseases.

The model presented here is based on the basic SIR model first presented by Kermack and McKendrick ([27], [28], [29]), as well as the introduction to multihost

SIR models found in [11]. As a baseline and example, we use parameters that most closely reflect highly pathenogenic avian influenza, recognized as a classical example of a zoonosis with an intermediate host [5] and for which the most data is available. Further, although we model a constant force of infection from the wild reservoir host, the model retains the capacity to implement seasonal variation or a sudden epidemic in that species as well by changing the equations describing the wild compartment. However, our model is intended to codify the idea of an intermediate host mathematically and therefore does not focus on a particular infectious disease. By changing its parameters, this model can be applied to study any zoonosis that passes through an intermediate host population, and its results are general to that theory.

1.4 Outline

This thesis investigates two questions: how to model adaptation of a zoonotic pathogen to a human-transmissible form in an intermediate host population and what effects these interspecies dynamics have on the epidemic in humans. We find that introducing a model that completely accounts for the spillover and interpopulation dynamics exhibited by emerging zoonoses links human populations to animal ones more deeply than previously thought: with nonzero contact rates between species and a nonzero mutation rate in an intermediate host, a zoonotic pathogen can establish itself in humans even if it fails to take hold in animal hosts or achieve an $R_0 > 1$ in the human compartment, refuting the transmissibility framework found in [4], [9], and [10]. This thesis introduces a theory of spillover through an intermediate host species that can be modified to study any zoonosis that exhibits this behavior, and sounds an alarm for researchers and policymakers by showing that zoonotic epidemics can persist in

human populations under more conditions than previously thought. Chapter 2, which introduces the model, provides justification for its organization. Chapter 3 gives a basic mathematical analysis of its epidemiological qualities and provides a global analysis of the three-species system. Chapter 4 provides numerical simulations of each possibility for the system, including a simulation of an avian influenza outbreak and a comparison of the effect of different parameters of the model on the equilibrium proportion of infected humans. Chapter 5 discusses the results and suggests directions for future research.

Chapter 2

The Model

In this chapter, we introduce the intermediate host model, showing how it builds on previous deterministic models of infectious disease, and discuss comparisons to other examples in the literature. We discuss the assumptions inherent to the model framework and give a survey of the methods used in this thesis.

2.1 Presentation

The traditional susceptible, infected, recovered (SIR) model originally developed by Kermack and McKendrick ([27], [28], [29]), shown below, accurately reproduces the standard epidemic curves for an infectious disease, and forms the basis for many different epidemiological models.

$$\frac{dS}{dt} = -\beta SI,$$
$$\frac{dI}{dt} = \beta SI - \gamma I,$$
$$\frac{dR}{dt} = \gamma I.$$

Here S, I, and R stand for the proportion of individuals that are susceptible, infected, and recovered, respectively. This deterministic framework depends on the transmission rate β and the recovery rate γ, parameters specific to the disease. This, the simplest version, considers one disease that confers lifelong immunity spreading within a closed, constant population of one species. There are no equilibria other than the disease-free state (i.e. $I(\infty) = 0$), as there is no external force of infection or influx of susceptible individuals. The basic reproductive number R_0 for this simple SIR model is

$$R_0 = \beta/\gamma.$$

To model a disease over a longer time frame, vital dynamics modeling birth (b) and mortality (m) rates are introduced:

$$dS/dt = b - \beta SI - mS,$$
$$dI/dt = \beta SI - \gamma I - mI,$$
$$dR/dt = \gamma I - mR.$$

This framework has a force b constantly introducing new susceptible individuals,

and the basic reproductive number for this model is

$$R_0 = \frac{b\beta}{m(m+\gamma)}.$$

The disease-free equilibrium is

$$(S^*, I^*, R^*) = (\frac{b}{m},\, 0,\, 0),$$

and the endemic equilibrium is

$$(S^*, I^*, R^*) = (\frac{m+\gamma}{\beta},\, \frac{m}{\beta}(R_0 - 1),\, \frac{\gamma}{\beta}(R_0 - 1)).$$

Other well-known modifications to the basic SIR model include adding classes for exposed or maternally-immune individuals; dropping the assumption of lifelong immunity so that individuals can become reinfected; or implementing a vaccination program with a given protection rate. To our knowledge, the main class of SIR models that include two or more species are those that consider vector-borne illnesses. However, since a vector-borne disease must infect both its host species (rather than opportunistically jumping to a new species) and follows set steps in its life cycle in both (rather than unpredictably mutating in a new host), a vector-borne SIR model merely adds more compartments for the pathogen to run through. Unlike vector-borne diseases such as malaria (see [30] and [31]), an emerging zoonosis does not need to infect another species as part of its life cycle. Instead, it opportunistically infects animals similar enough to its reservoir host, and−in the pattern of transmission considered here−mutates to a human-to-human transmissible form if given the opportunity. Dengue, which spreads between mosquitoes and humans, is another

example of a vector-borne disease, and its analysis draws useful parallels with the type of pathogen behavior modeled in this thesis. [32], a review paper of deterministic models of dengue, notes that the disease dynamics among the vector population are frequently simplified to a mere force of infection for the human one, since the lifespans of vectors are usually short. In contrast, a zoonosis model must consider population dynamics as well as disease dynamics in its non-human compartments. To our knowledge, this pattern of adaptive mutation rather than different stages in a pathogen life cycle has not yet been captured in a mathematical model. While a sizeable literature exists on mathematical models of vectorborne diseases, no model captures the unintentional opportunism of zoonoses or incorporates selective pressure on viruses [11]. Vector-borne diseases form a more widely studied type of pathogen, and provide a useful comparison for the type of behavior modeled in this thesis, but are a different type of dynamics than the opportunistic adaptation of zoonoses.

Attempts have been made to model zoonotic spillovers ([10], [11], [33]), but without incorporating changes in the pathogen's ecology over the course of an epidemic, these models are mathematically indistinguishable from those modeling a vectorborne disease with more hosts or a multispecies model. The key contrast with vectorborne diseases, not yet captured in a mathematical model, is that a zoonosis infects species other than its reservoir opportunistically, and−the most important distinction−mutates once within a new host. To model this behavior, we create three compartments, representing the pathogen's wild reservoir host, an intermediate host assumed to be a domestic animal, and humans. The wild, domestic and human populations are each modeled by a SIR system with vital dynamics and linked by transmission routes. An infected wild host can pass the disease to a susceptible domestic animal at a transmission rate p_d, and an infected domestic animal can pass

the human-transmissible strain of the disease to a human at a rate p_h. Finally, the model incorporates the hallmark of an emerging zoonosis: the pathogen's ability to mutate to a human-transmissible strain while circulating in a domestic host. To model this phenomenon, we introduce a category T (transmissible) for domestic animals in which the zoonosis has mutated—through reassortment, random mutation, or evolutionary pressure—to a human-transmissible form. This mutation happens at a rate μ in infected domestic animals, who then transition from the original infected category to the transmissible category and can infect other susceptible domestic animals with the new, human-transmissible strain. Figure 2.1 provides a representation of the connections between populations.

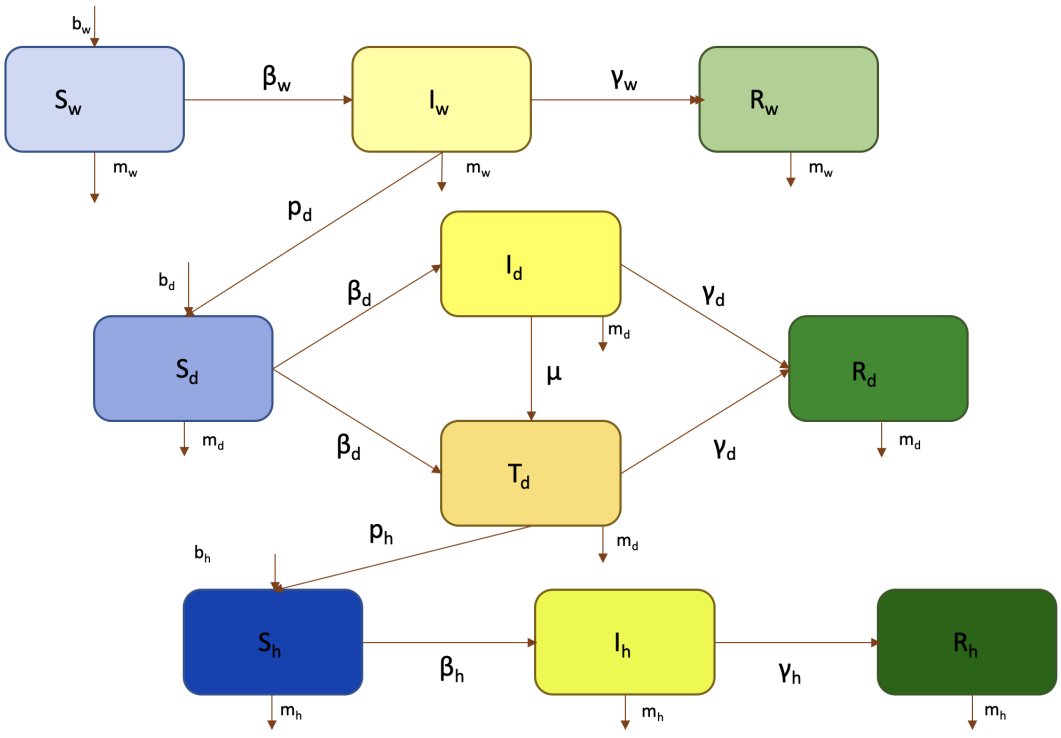

Figure 2.1: Model schematic. Model parameters are summarized in Table 2.2.

We use the traditional β_i and γ_i to represent the transmission and recovery rates

of the pathogen in species i, and represent births and deaths with b_i and m_i respectively. As discussed above, p_d represents the transmission rate from wild animals to domestic ones and p_h the rate at which the mutated version spreads from domestic animals to humans. The full system of 10 ordinary differential equations is shown in Table 2.1, with subscripts indicating the species (wild, domestic, or human) to which the compartment belongs. Table 2.2 defines each variable and parameter in the model.

Wild	$\mathrm{dS}_w/dt = b_w - \beta_w S_w I_w - m_w S_w$ $\mathrm{dI}_w/dt = \beta_w S_w I_w - \gamma_w I_w - m_w I_w$ $\mathrm{dR}_w/dt = \gamma_w I_w - m_w R_w$
Domestic	$\mathrm{dS}_d/dt = b_d - \beta_d S_d I_d - p_d S_d I_w - \beta_d S_d T_d - m_d S_d$ $\mathrm{dI}_d/dt = \beta_d S_d I_d + p_d S_d I_w - \mu I_d - \gamma_d I_d - m_d I_d$ $\mathrm{dT}_d/dt = \mu I_d + \beta_d S_d T_d - \gamma_d T_d - m_d T_d$ $\mathrm{dR}_d/dt = \gamma_d I_d + \gamma_d T_d - m_d R_d$
Humans	$\mathrm{dS}_h/dt = b_h - \beta_h S_h I_h - p_h S_h T_d - m_h S_h$ $\mathrm{dI}_h/dt = \beta_h S_h I_h + p_h S_h T_d - \gamma_h I_h - m_h I_h$ $\mathrm{dR}_h/dt = \gamma_h I_h - m_h R_h$

Table 2.1: ODE systems of our model with three host compartments (species), composed of wild reservoir hosts, intermediate domestic animal hosts, and human hosts.

S_i	susceptible individuals of species i
I_i	infected individuals of species i
T_d	intermediate hosts infected with human-transmissible strain
R_i	recovered individuals of species i
β_i	transmission rate among species i
γ_i	recovery rate among species i
b_i	birth rate among species i
m_i	natural mortality rate among species i
p_d	transmission rate from reservoir to intermediate hosts
p_h	transmission rate from intermediate hosts to humans
μ	mutation rate of the pathogen in the intermediate host population

Table 2.2: Parameter definitions.

2.2 Model Assumptions

We make several assumptions to clarify the essential dynamics of the system. Firstly, we equate the domestic animal recovery and transmission rates for both strains of the pathogen; the human-transmissible strain is different from the wild one only in that its transmission rate in humans is nonzero. Only domestic animals infected with the T strain can pass the disease to humans, although both strains circulate in the domestic population. The model does not account for coinfection in a domestic animal, since an individual infected with both strains is still capable of starting a human epidemic and is thus counted in the T category.

We further assume that the population of each compartment is constant over the course of the simulation, with each species' vital dynamics set at replacement rates, and thus calculate the proportion of susceptible, infected, and recovered animals in each species rather than the raw numbers present in each category. To maintain a focus on population biology and the potential for the spread of disease from infected individuals, we do not consider disease-induced mortality.

The parameters p_d, p_h, and μ, which measure the rate of transmission from wild to domestic animals, domestic animals to humans, and mutation rates in domestic animals, are intended to capture the rate of interactions between the different species and strains, an inherently unpredictable event, but the model is purely deterministic, rather than stochastic.

We intend this model to provide a general framework that can be modified to fit any zoonosis with an intermediate host, and provide the analysis in Chapter 3 with the goal of informing such a theory. However, to provide a baseline for the numerical simulations in Chapter 4, we use parameters corresponding to highly pathenogenic avian influenza, perhaps the most well-sourced zoonosis. Table 2.3 provides the base-

line values and the sources used in our examples.

Parameter	Value	Source
initial S_w	0.5	[34]
initial I_w	0.5	[34]
p_d	0.51	[34] figure 1
β_d	0.89	[35] table 1 for wild birds
γ_d	0.981	[35] table 1
b_d	1	assumed
m_d	1	assumed
p_h	0.207	[36]
β_h	0.078	[36]
γ_h	0.091	[36]
b_h	0.0118	CDC
m_h	0.009	CDC
μ	0.499	[34] figure 3

Table 2.3: Parameter values and sources for the model. Due to a lack of data for transmission parameters in wild animals, we assume β_w, γ_w, b_w, and m_w to be equivalent to their counterparts in domestic animals.

Reflecting the lack of data for zoonoses over their entire range of species, the sources used for these parameters reflect different strains of avian influenza. [37] calculates the transmission rate of H5N1 in Nigeria, while [36] cites information about H7N9 in China. The values are also attained using different data-gathering practices: [34] surveyed experts in Australian avian influenza for their assessment of the probability of domestic poultry becoming infected with low pathogenic avian influenza from wild birds, as well as that strain mutating to H5 or H7 higly pathenogic avian influenza (HPAI) on a farm, while [35] collected parameters about HPAI for an SEIR model. As stated in Table 2.3, we could not find a source for transmission parameters among wild birds, and thus assume their disease parameters to be equivalent to those in domestic poultry. The variety and inconsistency of these sources reflects the need for more data and research into the actual effects of particular zoonoses. Although it

is crucial to public health interventions based on a mathematical model to know the accuracy of each parameter, their specific values are relatively unimportant for the theoretical results presented here and are accordingly not the focus of this work.

2.3 Methods

To obtain the equilibria for the system, we set each of the 10 equations of Table 2.1 to 0 and solve for the population variables. We further analyze the stability of each equilibrium using the system's Jacobian about the point and establish the importance of the model's basic reproduction number as a threshold condition. The methods we use to analyze the model's R_0 are based on the next-generation matrix technique given in [38] and [39]. This method defines R_0 in a compartmental model, where it has been proven to remain a threshold condition for the stability of equilibria [39]. This approach is similar to that used to model the spread of avian influenza in farm and market populations of domestic poultry [40]; to analyze the effect of different growth laws in the avian population on the spread of avian influenza [41]; to give a model of a vector-host system for leishmaniasis [33]; to analyze SEIR models [42]; and to analyze models with vaccination [43]. Our work thus uses established mathematical epidemiology techniques to analyze a new model of infectious disease dynamics.

2.4 Conclusion

Our model extends the preexisting SIR framework such that it is well suited to study spillover effect by zoonosis with intermediate hosts. We use a variety of mathematical techniques such as the next-generation approach to analyze the dynamic behavior of our model. The parameters used reflect the current availability of data,

although the global analysis of the system will not change for different parameter values. The model's key innovations are linking three species together based on their proximity to humans and distinguishing between human-transmissible and non-human-transmissible strains of the pathogen, as no previous models simulate either intermediate hosts for zoonoses or a mutation to a human-transmissible form to study the entire range of an emerging infectious zoonosis.

Chapter 3

Analysis

In this Chapter, we analyze the mathematical qualities of the model, proving that a unique endemic equilibrium exists by analyzing each species compartment. We further show that the stability of each equilibrium depends on the system's R_0 and distinguish between the importance of intraspecies parameters−the transmission (β) and recovery (γ) rates of a species, as well as its birth and mortality rate (b, m)−and interspecies parameters governing connections between species −the contact rates p_d and p_h, as well as the rate of mutation μ to a human-transmissible form. We show that, if there is a nonzero number of infected wild animals, only the second type of parameters can alter the global stability of the system.

3.1 The Wild Compartment

The equilibrium states (S_w^*, I_w^*, R_w^*) in the wild compartment satisfy the following equations:

$$b_w - \beta_w S_w^* I_w^* - m_w S_w^* = 0, \tag{3.1}$$

$$\beta_w S_w^* I_w^* - \gamma_w I_w^* - m_w I_w^* = 0, \tag{3.2}$$

$$\gamma_w I_w^* - m_w R_w^* = 0. \tag{3.3}$$

By summing (3.1), (3.2), and (3.3), we obtain the total abundance of wild animals in equilibrium, b_w/m_w.

Theorem 1. *There is one disease-free equilibrium, E_f^w, at*

$$(S_w^*, I_w^*, R_w^*) = \left(\frac{b_w}{m_w}, 0, 0\right),$$

and a unique endemic equilibrium, E_e^w, at

$$(S_w^*, I_w^*, R_w^*) = \left(\frac{m_w + \gamma_w}{\beta_w}, \frac{b_w - m_w S_w^*}{\beta_w S_w^*}, \frac{\gamma_w I_w^*}{m_w}\right)$$

Proof. Factoring equation (3.2) yields

$$I_w^*(\beta_w S_w^* - \gamma_w - m_w) = 0,$$

which holds either if $I_w^* = 0$ (case 1) or if $\beta_w S_w^* - \gamma_w - m_w = 0$ (case 2).

In the first case, we obtain the disease-free equilibrium by substituting $I_w^* = 0$ into equations (3.1) and (3.3), producing equilibrium values of $S_w^* = \frac{b_w}{m_w}$ and $R_w^* = 0$.

The second case holds if $S_w = \frac{\gamma_w + m_w}{\beta_w}$. Substituting this value into equation (3.1), we obtain $I_w^* = \frac{b_w - m_w S_w^*}{\beta_w S_w^*}$. Solving equation (3.3) for R_w gives $R_w^* - \frac{\gamma_w I_w^*}{m_w}$. Since $I_w^* > 0$, this case produces an endemic equilibrium. □

It is a basic epidemiological result that a simple SIR model with vital dynamics, such as the system that models the wild compartment here, has $R_0^w = \frac{b_w \beta_w}{m_w(\gamma_w + m_w)}$. We prove the threshold value of R_0^w in the wild compartment by using its Jacobian,

$$J_w = \begin{bmatrix} -\beta_w I_w - m_w & -\beta_w S_w & 0 \\ \beta_w I_w & \beta_w S_w - \gamma_w - m_w & 0 \\ 0 & \gamma_w & -m_w \end{bmatrix}$$

Theorem 2. *E_f^w is stable if $R_0 < 1$ and E_e^f is stable if $R_0 > 1$.*

Proof. In the first case, let $R_0^w < 1$. We calculate that

$$J_w(E_f^w) = \begin{bmatrix} -m_w & -\frac{b_w \beta_w}{m_w} & 0 \\ 0 & \frac{b_w \beta_w}{m_w} - \gamma_w - m_w & 0 \\ 0 & \gamma_w & -m_w \end{bmatrix}$$

has eigenvalues $-m_w$ and $\frac{b_w \beta_w}{m_w} - \gamma_w - m_w$. Since $m_w > 0$ by assumption and $\frac{b_w \beta_w}{m_w} < m_w + \gamma_w$ by the restriction on R_0, both eigenvalues are negative and so E_f^w is stable when $R_0^w < 1$.

In the second, let $R_0^w > 1$. We have that

$$J_w(E_e^w) = \begin{bmatrix} -\frac{b_w \beta_w}{\gamma_w + m_w} & -\gamma_w - m_w & 0 \\ \frac{b_w \beta_w}{\gamma_w + m_w} - m_w & 0 & 0 \\ 0 & \gamma_w & -m_w \end{bmatrix}$$

with eigenvalues $-\frac{b_w\beta_w}{\gamma_w+m_w}, 0, -m_w$. Since all parameters are positive, these eigenvalues are all negative and thus E_e^w is stable. □

We have thus shown that one disease-free equilibrium and one endemic equilibrium exist among wild reservoir hosts, confirming the importance of $I_w > 0$ as a threshold condition for the spread of the disease.

3.2 The Domestic Compartment

In a similar manner, we can analyze the domestic compartment distinctly from the other two species, since interspecies interactions are limited to the force of infection $p_d S_d I_w$ attributed to the wild compartment. Any equilibrium $(S_d^*, I_d^*, T_d^*, R_d^*)$ in this compartment must satisfy the system

$$b_d - \beta_d S_d^* I_d^* - p_d S_d^* I_w^* - \beta_d S_d^* T_d^* - m_d S_d^* = 0, \tag{3.4}$$

$$\beta_d S_d^* I_d^* + p_d S_d^* I_w^* - \mu I_d^* - \gamma_d I_d^* - m_d I_d^* = 0, \tag{3.5}$$

$$\mu I_d^* + \beta_d S_d^* T_d^* - \gamma_d T_d^* - m_d T_d^* = 0, \tag{3.6}$$

$$\gamma_d I_d^* + \gamma_d T_d^* - m_d R_d^* = 0. \tag{3.7}$$

Note that by summing equations (3.4)-(3.7), we obtain the abundance of the domestic compartment at equilibrium, b_d/m_d. Since this compartment is subject to an external force of infection from the wild compartment, we also note that the existence of a disease-free equilibrium depends on this external influence.

Lemma 1. *A disease-free equilibrium, E_f^d, in the domestic compartment,*

$$(S_d^*, I_d^*, T_d^*, R_d^*) = \left(\frac{b_d}{m_d}, 0, 0, 0\right),$$

is only possible if $I_w = 0$ *or* $p_d = 0$.

Proof. Let $I_w > 0$ for some value of t and $p_d \neq 0$, and assume that a disease-free equilibrium exists with $I_d^* = 0$. We note that a disease-free equilibrium requires a nonzero proportion of susceptible individuals, so $S_d^* > 0$ as well. Substituting these values into equation (3.5), we obtain $p_d S_d^* I_w^* = 0$, a contradiction with our assumptions. Therefore $I_d^* \neq 0$. Substituting this value into equation (3.6), we also obtain $T_d^* \neq 0$. However, these condition imply that there are infected individuals of both types in the domestic animal population, a contradiction with our assumption that we are analyzing a disease-free equilibrium. By contradiction, any disease-free equilibrium in the domestic compartment must have either $I_w = 0$ or $p_d = 0$ in the complete system. □

Note that this result is deeper than one about the equilibrium state of I_w: if $I_w > 0$ at any time over the course of the epidemic, even if the disease later vanishes from the wild population, the pathogen will spread to the domestic species.

Assuming that there is a force of infection from the wild reservoir hosts, we analyze the possible endemic equilibrium values and show that there is a unique possibility in this compartment as well.

Theorem 3. *There is only one admissible endemic equilibrium* E_e^d *in the domestic compartment. At this equilibrium, we have* $S_d^* < \min\{b_d/(m_d + p_d I_w^*), (\gamma_d + m_d)/\beta_d\}$.

Proof. Adding equations (3.4)-(3.6), we obtain

$$b_d - m_d S_d^* - (\gamma_d + m_d) I_d^* - (\gamma_d + m_d) T_d^* = 0. \qquad (\star_1)$$

Further, from equation (3.6), we isolate

$$I_d^* = \frac{1}{\mu}(\gamma_d + m_d - \beta_d S_d^*)T_d^*. \qquad (\star_2)$$

Substituting $\star_2$ into $\star_1$, we get

$$T_d^* = \frac{b_d - m_d S_d^*}{(\gamma_d + m_d) + \frac{1}{\mu}(\gamma_d + m_d)(\gamma_d + m_d - \beta_d S_d^*)}. \qquad (\star_3)$$

Since the quantities I_d^* and T_d^* are both nonnegative, it follows immediately that the equilibrium value S_d^* must have a natural upper bound:

$$S_d^* \leq \frac{\gamma_d + m_d}{\beta_d} \leq \frac{b_d}{m_d}. \qquad (3.8)$$

Hence we can confirm the denominator in $(\star_3)$ is strictly positive.

We also note that from (3.7), we have $R_d^* = \frac{\gamma_d(I_d^* + T_d^*)}{m_d}$. We thus calculate the equilibrium values S_d^* by substituting $\star_2, \star_3$ into (3.4) and obtain, after rearranging:

$$\begin{aligned} b_d - p_d S_d^* I_w^* - m_d S_d^* &= \beta_d S_d^*(I_d^* + T_d^*) = \beta_d S_d^*(1 + \frac{1}{\mu}(\gamma_d + m_d - \beta_d S_d^*))T_d^* \\ &= \frac{\beta_d S_d^*(1 + \frac{1}{\mu}(\gamma_d + m_d - \beta_d S_d^*))(b_d - m_d S_d^*)}{(\gamma_d + m_d) + \frac{1}{\mu}(\gamma_d + m_d)(\gamma_d + m_d - \beta_d S_d^*)} \\ &= \frac{\beta_d S_d^*(b_d - m_d S_d^*)}{(\gamma_d + m_d)}. \end{aligned} \qquad (3.9)$$

We note that in the last step of the derivations above we cancel out the common factor $1 + \frac{1}{\mu}(\gamma_d + m_d - \beta_d S_d^*) > 0$, which is guaranteed by the inequality (3.8). It is easy to observe that there exist at most two possible equilibrium values of S_d^* as the roots of the quadratic equation (3.9), denoted by $S_{d(1)}^* < S_{d(2)}^*$, a consequence of our assumption that the transmission and recovery rates of both strains in domestic animals are equal.

We now proceed to prove only the smaller root $S^*_{d_{(1)}}$ is admissible for the long-term disease dynamics should there be nonzero disease burden (i.e., $I^*_d > 0$ and $T^*_d > 0$) in the domestic compartment. In fact, we can view S^*_d as the fixed point(s) satisfying

$$f(x) = g(x),$$

where $f(x)$ is a simple linear function, given by

$$f(x) = b_d - (p_d I^*_w + m_d)x,$$

and $g(x)$ is a quadratic function, given by

$$g(x) = \frac{\beta_d x(b_d - m_d x)}{(\gamma_d + m_d)}.$$

We can show that $f(0) = b_d > 0 = g(0)$, $f(b_d/(m_d + p_d I^*_w)) = 0 < g(b_d/(m_d + p_d I^*_w))$, and $0 > f(x) > g(x)$ for sufficiently large x. Furthermore, as both f and g are smooth continuous functions, according to the intermediate value theorem, there must exist two fixed points satisfying $f(x) = g(x)$, $S^*_{d_{(1)}} \in (0, b_d/(m_d + p_d I^*_w))$ and $S^*_{d_{(2)}} \in (b_d/(m_d + p_d I^*_w), \infty)$ (as also illustrated in Figure 3.1).

We have $b_d - p_d S^*_d I^*_w - m_d S^*_d = \beta_d S^*_d (I^*_d + T^*_d) > 0$, for nonzero disease burden $I^*_d > 0, T^*_d > 0$. Hence we must have $S^*_d < b_d/(m_d + p_d I^*_w)$. So we complete our proof that only the smaller root $S^*_{d_{(1)}}$ is admissible as the unique endemic equilibrium in the domestic compartment.

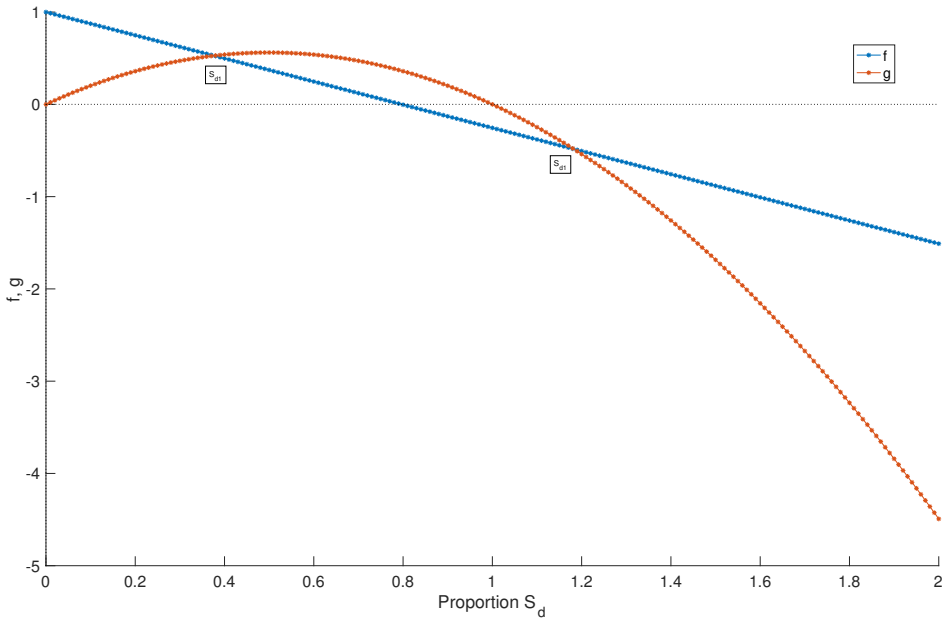

Figure 3.1: The graphs of $f(S_d^*)$ and $g(S_d^*)$; the x-coordinates of their intersection points give the proportion of domestic animals infected at the equilibria.

□

In line with our proof above, it is easy to directly check the discriminant of the quadratic equation in (3.9) is positive:

$$\Delta = [\beta_d b_d + (\gamma_d + m_d)(p_d I_w^* + m_d)]^2 - 4\beta_d m_d b_d(\gamma_d + m_d) > 0.$$

Then we obtain the endemic equilibrium for $S_d^* = S_{d(1)}^*$:

$$S_{d(1)}^* = \frac{\beta_d m_d + (\gamma_d + m_d)(p_d I_w^* + m_d) - \sqrt{\Delta}}{2\beta_d m_d}.$$

We have thus shown that, in the domestic compartment, there is one unique

endemic equilibrium $E_e^d = (S_d^*, I_d^*, T_d^*, R_d^*)$, where

$$\begin{aligned}
S_d^* &= S_{d(1)}^*, \\
T_d^* &= \frac{b_d - m_d S_d^*}{(\gamma_d + m_d) + \frac{1}{\mu}(\gamma_d + m_d)(\gamma_d + m_d - \beta_d S_d^*)}, \\
I_d^* &= \frac{1}{\mu}(\gamma_d + m_d - \beta_d S_d^*) T_d^*, \\
R_d^* &= \frac{\gamma_d (I_d^* + T_d^*)}{m_d}.
\end{aligned}$$

Further, as we prove above, this equilibrium must be admissible in the presence of a nonzero force of infection at any time from the wild host population ($p_d I_w^* > 0$).

3.3 The Human Compartment

To complete our understanding of the different species involved in the model, we analyze the system of equilibrium equations in the human compartment as follows,

$$b_h - \beta_h S_h I_h - p_h S_h T_d - m_h S_h = 0, \tag{3.10}$$

$$\beta_h S_h I_h + p_h S_h T_d - \gamma_h I_h - m_h I_h = 0, \tag{3.11}$$

$$\gamma_h I_h - m_h R_h = 0. \tag{3.12}$$

Adding (3.10) - (3.12) gives a total abundance of $\frac{b_h}{m_h}$ in the human compartment at equilibrium. We begin our analysis of this compartment by noting an identical result from the domestic one: a disease-free equilibrium can exist in the human compartment only if the force of infection from domestic animals is zero.

Lemma 2. *A disease-free equilibrium E_f^h in the human compartment, $(S_h^*, I_h^*, R_h^*) = (\frac{b_h}{m_h}, 0, 0)$, is only possible if $T_d = 0$ or $p_h = 0$.*

Proof. In a manner similar to the proof of Lemma 1, let $T_d > 0$ at any time over the course of the model and $p_h \neq 0$, and assume that a disease-free equilibrium exists with $I_h^* = 0$. By equation (9), we obtain $p_h S_h^* T_d^* = 0$, a contradiction with our assumptions and with the fact that $S_h^* \neq 0$ at a disease-free equilibrium. By contradiction, any disease-free equilibrium must have either $T_d = 0$ or $p_h = 0$. □

Thus, in the presence of any force of infection $p_h T_d$ from domestic animals, there must be an endemic equilibrium in the human compartment. We note again that if $T_d > 0$ at any time over the course of the epidemic, even if that population of animals vanishes at equilibrium, it is enough to seed the infection into the human compartment.

Theorem 4. *There exists only one admissible endemic equilibrium in the human compartment* $E_h^e = (S_h^*, I_h^*, R_h^*)$*, where* S_h^* *is given by the smaller root of the quadratic equation:*

$$b_h - p_h S_h^* T_d^* - m_h S_h^* = \beta_h S_h^* (b_h - m_h S_h^*)/(\gamma_h + m_h).$$

Proof. From equation (3.12), we know

$$R_h^* = \frac{\gamma_h I_h^*}{m_h}.$$

By adding equations (3.10) and (3.11), we obtain

$$b_h - m_h S_h^* - (\gamma_h + m_h) I_h^* = 0.$$

Accordingly, $I_h^* = \frac{b_h - m_h S_h^*}{\gamma_h + m_h}$. Substituting I_h^* into (3.10), we obtain

$$b_h - p_h S_h^* T_d^* - m_h S_h^* = \frac{\beta_h S_h^* (b_h - m_h S_h^*)}{\gamma_h + m_h}. \tag{3.13}$$

Defining the left-hand side as $f(S_h^*) = b_h - p_h S_h^* T_d^* - m_h S_h^*$ and the right-hand side as $g(S_h^*) = \frac{\beta_h S_h^*(b_h - m_h S_h^*)}{\gamma_h + m_h}$, as in the proof of Theorem 3, any endemic equilibrium in the human compartment must satisfy the fixed point(s) $f(S_h^*) = g(S_h^*)$ (see Figure 3.2).

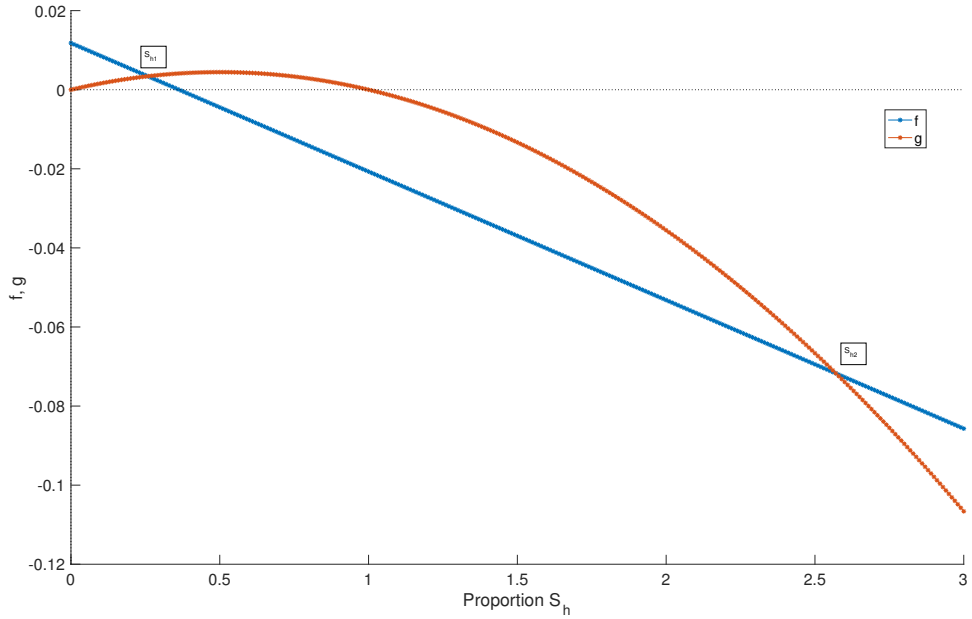

Figure 3.2: The graphs of $f(S_h^*)$ and $g(S_h^*)$; the x-coordinates of their intersection points give the proportion of humans infected at the equilibria.

f is a negatively-sloped line with its root at $f_1 = \frac{b_h}{p_h T_d^* + m_h}$. g is a concave parabola with roots at $g_1 = 0$ and $g_2 = \frac{b_h}{d_h}$. We thus have $g_1 < f_1 < g_2$, so there are two intersection points $S_{h(1)}^* < f_1$ and $S_{h(2)}^* > g_2$ (by using the intermediate value theorem). However, g_2 is the total compartment size in the human compartment; $S_{h(2)}$ is thus biologically impossible.

Solving the quadratic equation (3.13) directly and taking its smaller root, we

obtain the only viable endemic equilibrium:

$$S_{h^*_{(1)}} = \frac{\beta_h b_h + (m_h + \gamma_h)(p_h T_d^* + m_d) - \sqrt{[\beta_h b_h + (m_h + \gamma_h)(p_h T_d^* + m_d)]^2 - 4\beta_h m_h b_h (\gamma_h + m_h)}}{2\beta_h m_h}$$

□

We have thus shown that in the presence of a force of infection from domestic animals, there is an admissible endemic equilibrium in the human compartment at $E_h^e = (S_h^*, I_h^*, R_h^*)$, where

$$\begin{aligned} S_h^* &= S_{h^*_{(1)}}, \\ I_h^* &= \frac{b_h - m_h S_h^*}{\gamma_h + m_h}. \\ R_h^* &= \frac{\gamma_h I_h^*}{m_h}. \end{aligned}$$

3.4 System Stability and R_0

As shown in the previous sections, the endemic equilibria in each compartment are unique; under the assumption that there is a nonzero force of infection between species compartments and in the presence of circulating disease in the wild reservoir, we use the results of Theorems 1, 3, and 4 to obtain an endemic equilibrium at

$$E_e = (S_w^*, I_w^*, R_w^*, S_d^*, I_d^*, T_d^*, R_d^*, S_h^*, I_h^*, R_h^*).$$

The formula of these expressions can be found in detail above.

More precisely, the existence of such stable endemic disease equilibiria requires an exact condition, that is, the basic reproductive number of the entire system $R_0 > 1$.

Otherwise, there can exist a stable disease-free equilibria. In what follows, we will resort to the so-called next-generation approach as detailed in [38] and [39] to calculate R_0 for the system.

The system's R_0 is the spectral radius of FV^{-1}, where F describes the rate of appearance of new infections in each compartment of host individuals,

$$F = \begin{bmatrix} \beta_w S_w & 0 & 0 & 0 \\ p_d S_d & \beta_d S_d & 0 & 0 \\ 0 & 0 & \beta_d S_d & 0 \\ 0 & 0 & p_h S_h & \beta_h S_h \end{bmatrix}$$

and V describes the rate of transfer of individuals out of each compartment,

$$V = \begin{bmatrix} \gamma_w + m_w & 0 & 0 & 0 \\ 0 & \mu + \gamma_d + m_d & 0 & 0 \\ 0 & -\mu & \gamma_d + m_d & 0 \\ 0 & 0 & 0 & \gamma_h + m_h \end{bmatrix}.$$

We thus get

$$FV^{-1} = \begin{bmatrix} \frac{\beta_w S_w}{m_w(\gamma_w + m_w)} & 0 & 0 & 0 \\ \frac{p_d S_d}{\gamma_w + m_w} & \frac{\beta_d S_d}{\mu + \gamma_d + m_d} & 0 & 0 \\ 0 & \frac{\mu \beta_d S_d}{(\gamma_d + m_d)(\mu + \gamma_d + m_d)} & \frac{\beta_d S_d}{\gamma_d + m_d} & 0 \\ 0 & \frac{\mu p_h S_h}{(\gamma_d + m_d)(\mu + \gamma_d + m_d)} & \frac{p_h S_h}{\gamma_d + m_d} & \frac{\beta_h S_h}{\gamma_h + m_h} \end{bmatrix}.$$

R_0 is then the maximum of the eigenvalues of this matrix,

$$R_0 = \max\{\frac{\beta_w S_w}{\gamma_w + m_w}, \frac{\beta_d S_d}{\mu + \gamma_d + m_d}, \frac{\beta_d S_d}{\gamma_d + m_d}, \frac{\beta_h S_h}{\gamma_h + m_h}\}.$$

At the disease-free equilibrium, we have $S_w = b_w/m_w, S_d = b_d/m_d, S_h = b_h/m_h$. Therefore, the R_0 value in a population entirely composed of susceptible individuals is

$$R_0 = \max\left\{\frac{\beta_w b_w}{m_h(\gamma_w + m_w)}, \frac{\beta_d b_d}{m_d(\mu + \gamma_d + m_d)}, \frac{\beta_d b_d}{m_d(\gamma_d + m_d)}, \frac{\beta_h b_h}{m_h(\gamma_h + m_h)}\right\}. \quad (3.14)$$

We further establish that $R_0 > 1$ retains its traditional role as the threshold for determining the spread of an epidemic using an analysis of the system's Jacobian matrix at the disease-free equilibria. Since we are interested only in the total number of infected individuals, we consider the time evolution of disease burden across all three compartments in the form (I_w, I_d, T_d, I_h):

$$\begin{aligned}
dI_w/dt &= \beta_w S_w I_w - \gamma_w I_w - m_w I_w, \\
dI_d/dt &= \beta_d S_d I_d + p_d S_d I_w - \mu I_d - \gamma_d I_d - m_d I_d \\
dT_d/dt &= \mu I_d + \beta_d S_d T_d - \gamma_d T_d - m_d T_d \\
dI_h/dt &= \beta_h S_h I_h + p_h S_h T_d - \gamma_h I_h - m_h I_h.
\end{aligned}$$

The Jacobian matrix of this system above at the disease-free equilibrium $E_f = (0, 0, 0, 0)$ is

$$J(E_f) = \begin{bmatrix}
\beta_w S_w - (\gamma_w + m_w) & 0 & 0 & 0 \\
p_d S_d & \beta_d S_d - (\mu + \gamma_d + m_d) & 0 & 0 \\
0 & \mu & \beta_d S_d - (\gamma_d + m_d) & 0 \\
0 & 0 & p_h S_h & \beta_h S_h - (\gamma_h + m_h)
\end{bmatrix}.$$

We first establish results on the stability of the disease-free equilibrium E_f.

Theorem 5. *E_f is asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof. At $E_f = (0, 0, 0, 0)$, we have $S_w = b_w/m_w, S_d = b_d/m_d, S_h = b_h/m_h$. Thus, $J(E_f) =$

$$\begin{bmatrix} \beta_w b_w/m_w - (\gamma_w + m_w) & 0 & 0 & 0 \\ p_d S_d & \beta_d b_d/m_d - (\mu + \gamma_d + m_d) & 0 & 0 \\ 0 & \mu & \beta_d b_d/m_d - (\gamma_d + m_d) & 0 \\ 0 & 0 & p_h S_h & \beta_h b_h/m_h - (\gamma_h + m_h) \end{bmatrix}$$

.

If $R_0 < 1$, then the diagonal entries of $J(E_f)$, which are actually the eigenvalues of the Jacobian matrix $J(E_f)$, are strictly negative. Thus E_f is asymptotically stable if $R_0 < 1$. If $R_0 > 1$, then at least one of the eigenvalues of the Jacobian matrix $J(E_f)$ (its diagonal entries) is strictly positive. Therefore E_f is unstable if $R_o > 1$.

□

We then turn to the endemic equilibrium and establish similar results.

Theorem 6. *E_e is asymptotically stable if $R_0 > 1$ and unstable if $R_0 < 1$.*

Proof. According to our analysis of endemic equilibria above, we have

$$\begin{aligned} S_w^* &= \frac{\gamma_w + m_w}{\beta_w}, \\ S_d^* &< \frac{\gamma_d + m_d}{\beta_d}, \\ S_h^* &< \frac{\gamma_h + m_h}{\beta_h}. \end{aligned}$$

Substituting into the Jacobian matrix $J(E_e)$ the values for S_w^*, S_d^*, S_h^*, the diagonal entries of $J(E_e)$ are either zero or negative. Therefore E_e is asymptotically stable if $R_0 > 1$. Similarly we can prove E_e is unstable if $R_0 < 1$.

□

Thus R_0 retains its role as the threshold condition for an epidemic.

3.5 Threshold Parameters

The results above replicate the standard epidemiological finding that R_0 is a threshold condition for the system, but the interspecies connections in this model allow us to establish a more detailed result. By Theorem 2 and Lemmas 1 and 2, the stability of the equilibria depends on p_d, p_h and μ, the same parameters which control S_w, S_d, and S_h in the calculation of R_0. Indeed, only these parameters determine the results of the epidemic.

Theorem 7. *In the presence of a nonzero number of infected wild animals, E_f is stable if and only if $p_d, \mu, p_h > 0$.*

Proof. ($\Rightarrow$) If the disease-free equilibrium is stable, Lemmas 1 and 2 show that $p_d, I_w, p_h, T_d > 0$. Considering equation (6), the only way to obtain $T_d > 0$ is to have $\mu > 0$ as well.

($\Leftarrow$) If $p_d, p_h, \mu > 0$, a nonzero proportion I_w creates a positive force of infection in equation (5), and since $\mu > 0$ there is a positive force of infection in equation (6) as well. With $T_d^* > 0$ and $p_h > 0$, there is a positive force of infection in equation (9), and so $I_h^* > 0$, creating an endemic equilibrium in the human compartment. If all of these conditions hold, regardless of the values of β_i or γ_i in any species, there is a nonzero, constant force of infection for each species and so the system is forced into an endemic equilibrium. □

3.6 Conclusion

This model has a disease-free equilibrium and an endemic equilibrium, whose stability depends on p_d, p_h and μ. Isolating these parameters provides suggestions for possible interventions. The results of Theorem 7, in particular, show that while many parameters of the model can be changed by human intervention$-\beta_d$ could be lowered by increasing biosecurity on farms for domestic animals, for example, while much of public health and medicine offers strategies for changing β_h and $\gamma_h-$the only effective route for eliminating the possibility of a zoonotic epidemic in humans is to eliminate contact between species or the possibility of pathogen mutation, an impossible requirement in any real system.

Chapter 4

Numerical Simulations

To clarify the results of the theoretical analysis presented in Chapter 3, we present simulations of different cases of the model drawn from available data (summarized in Table 2.3). To elucidate the effects of the interspecies transmission parameters$-p_d$, p_h, and $\mu-$we simulate cases where the pathogen fails to establish itself in wildlife, in domestic animals, and in both populations, showing that the human population will still suffer an endemic disease even if animal populations remain relatively unaffected by a brief epidemic. We further isolate the effect of each parameter on I_d^*, T_d^*, and I_h^* by varying each in isolation, finding that only controlling the interspecies parameters can completely prevent an epidemic in humans.

4.1 Examples

We first simulate a zoonosis that establishes endemic equilibria in each host species, using the baseline parameters with $5\beta_w = 5\beta_d$ to ensure the spread of the pathogen.

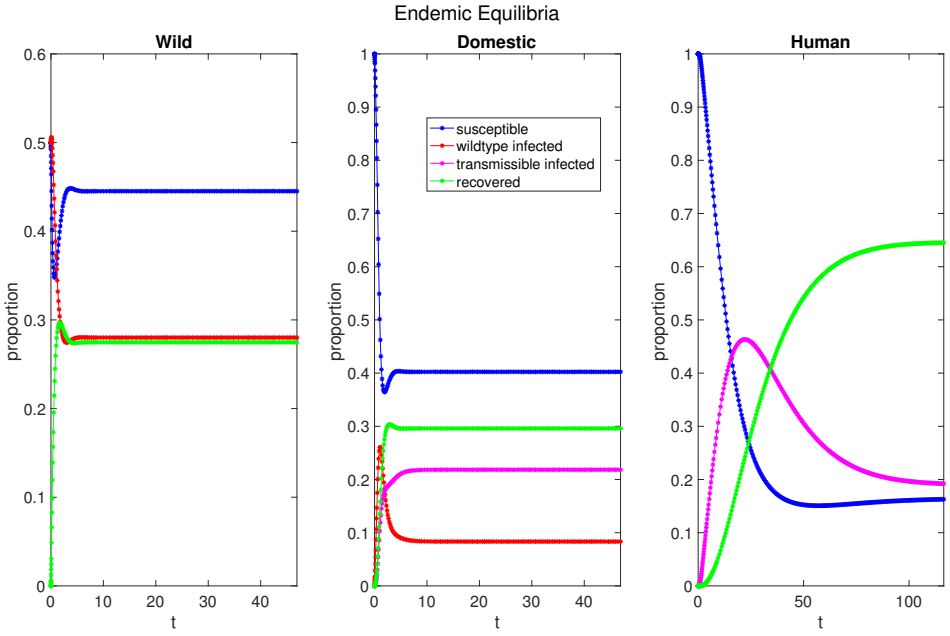

Figure 4.1: A simulation showing endemic equilibria in each species. Parameter values are as shown in Table 2.3, with β_w and β_d multiplied by 5 to ensure spread in each compartment.

The outbreak shown in figure 4.1 infects a maximum of 46.33% of the human population and stabilizes at 19.04% of the population infected, reaching equilibria in all three species by 150 units of time.

Next, to elucidate the effect of the mutation, we simulate an outbreak that fails to establish itself in the wild population (in this case, this species does not function as a reservoir host).

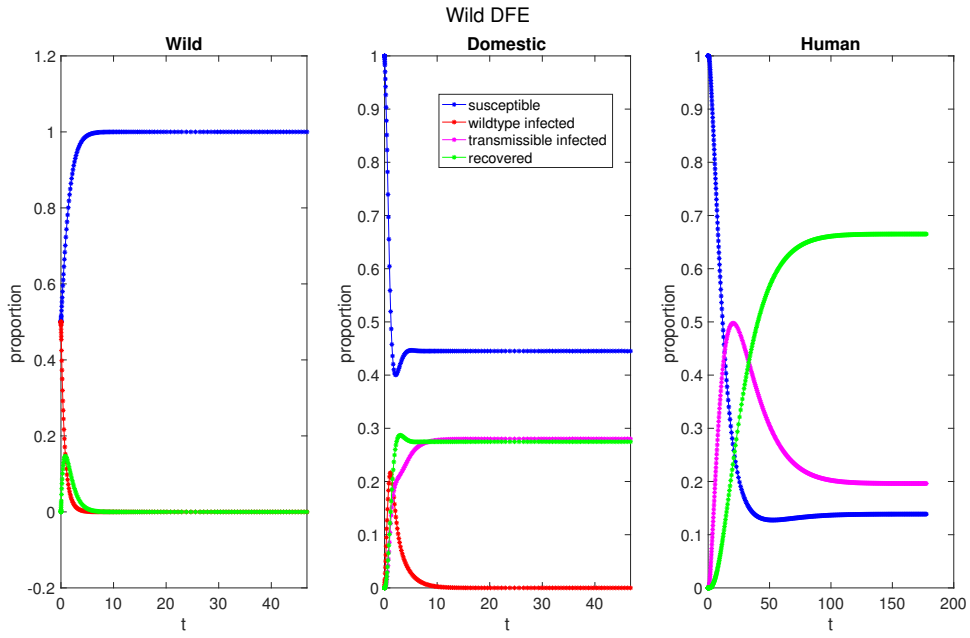

Figure 4.2: A simulation showing a disease-free equilibrium in the wild reservoir host species that spills over to endemic equilibria in the domestic intermediate host and humans. Parameters are as shown in Table 2.3, except with β_d multiplied by 5 to ensure an epidemic in the domestic compartment.

Figure 4.2 shows that even if the disease fails to persist in its wild reservoir host, it can still become endemic in the human population. A maximum of 49.75% of the human population was infected, with 19.62% infected at equilibrium by time 150. This case illustrates that even if the epidemic fails to take hold among wild animals, it can still spread to domestic animals and thus humans, illustrating the importance of p_d as a threshold parameter.

For our final example, we simulate avian influenza mutating from a low-pathogenic to a highly-pathogenic strain in an intermediate host. One of the best-known examples of a zoonosis with an intermediate host, avian influenza can spread from wild birds to

domestic poultry to humans, and this pathogen has widely available data. Seeding the model with the parameters shown in Table 2.3 (and assuming that $\beta_w = \beta_d, \gamma_w = \gamma_d$), we obtain the result shown in figure 4.3.

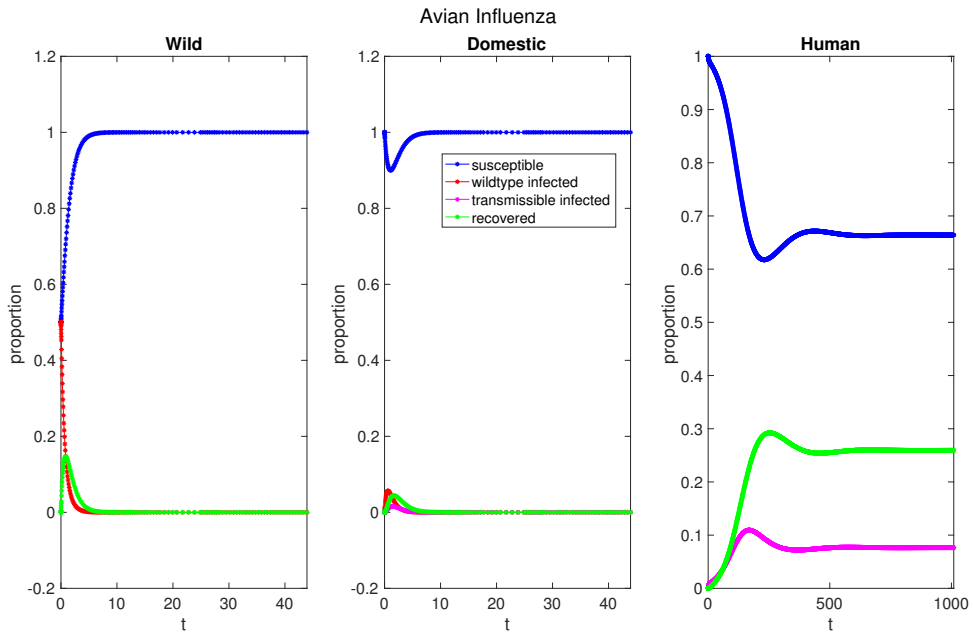

Figure 4.3: A simulation of low-pathogenic avian influenza mutating to high-pathenogenic avian influenza. Parameters are as shown in Table 2.3.

This example−which uses the most data publicly available−shows that even if a pathogen's R_0 is less than one in both wild and intermediate hosts, it can still establish itself in the human population. Here, both strains of avian influenza fade in the animal populations while establishing an endemic equilibrium in the human population, with a maximum of 10.94% and an equilibrium of 7.65% of the population infected over a time span an order of magnitude larger than that necessary in the previous examples ($t = 2000$, not shown in the figure). This result indicates that the unexpected behavior described in Chapter 3 and modeled above does appear in real

epidemics.

The results here are summarized in Table 4.1. The equilibrium proportion of infected humans is highest in row 2 because there are more domestic animals infected with the transmissible strain when the force of infection with the wildtype strain vanishes over time.

Situation	Max I_h	Equilibrium I_h	Time to Equilibrium
Endemic in all species	46.33%	19.04%	10^2
Disease-free in wildlife	49.75%	19.62%	10^2
Avian influenza	10.94%	7.65%	10^3

Table 4.1: A comparison of the maximal and equilibrium values for the percentage of infected humans for each representative strain.

These simulations illustrate that with nonzero transmission parameters, an initial infection in wild animals will spread to an endemic equilibrium in humans and domestic animals even if the pathogen fails to establish itself in its reservoir host (a biologically improbable situation), a worrying situation for public health officials.

4.2 Effects of Interspecies Transmission Parameters

In this section, we evaluate the effect of varying the interspecies transmission parameters p_d, μ, and p_h on the equilibrium values I_d^*, T_d^*, and I_h^* after 3000 units of time, in addition to β_d and β_h for comparison. To produce the graphs shown below, we vary the parameter in question from 0.01 to 5 (since values of 0, as shown in Chapter 3, inevitably lead to a disease-free equilibrium in the human compartment), with a step size of 0.1, holding the other values constant at the endemic equilibrium parameters detailed in section 4.1. Each simulation is run for 3000 timesteps, to ensure that

an equilibrium solution is reached. In the domestic compartment, varying the transmission parameters p_d and μ can change the relative prevalence of the wildtype and human-transmissible strains, as shown in Figures 4.4 and 4.5. (We do not examine the effect varying p_h has on the domestic compartment because that parameter does not appear in the equations governing its behavior.)

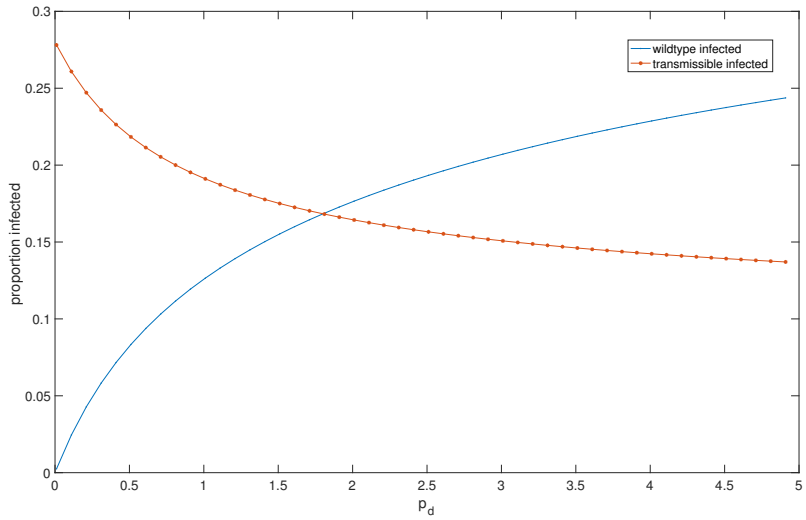

Figure 4.4: Graphing the proportion of domestic animals infected with the wildtype strain and the human-transmissible strain against p_d, the contact rate (spillover rate) between wild animals and domestic ones.

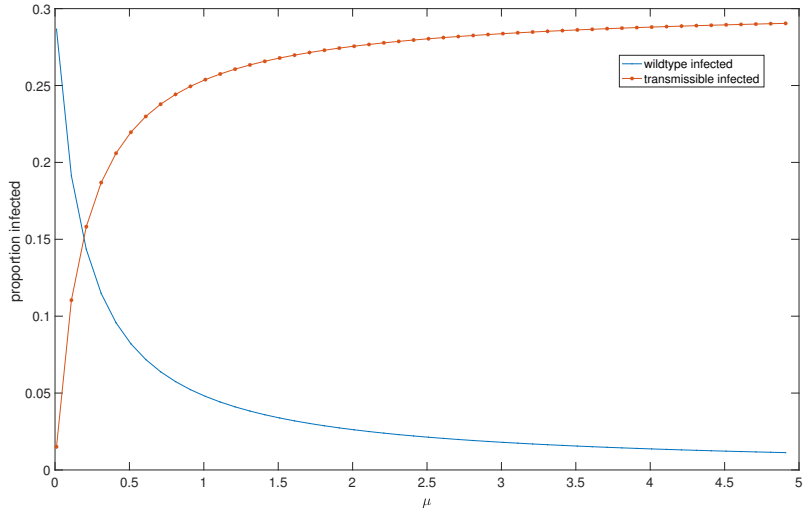

Figure 4.5: Graphing the proportion of domestic animals infected with the wildtype strain and the human-transmissible strain against μ, the rate of mutation from the wildtype strain to the human-transmissible strain.

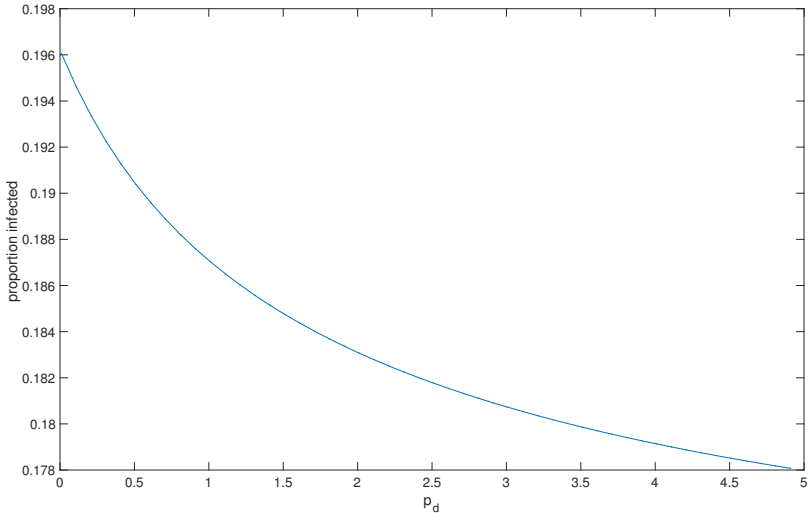

Figure 4.6: Graphing the proportion of infected humans against p_d.

Similarly, we vary p_d, μ, and p_h to examine the effect of these parameters on the proportion of infected humans, finding that while increasing the mutation and intermediate host-human contact rate increases this proportion, increasing p_d lowers it (see Figures 4.6, 4.7, and 4.8), as a larger contact rate between wild and domestic animals leads to a larger proportion of animals infected with the non-human-transmissible strain and thus unable to pass the disease to humans. Further, for comparison, we vary β_h from 0 to 5 using the same step length of 0.01. As shown in Figure 4.9, while increasing β_h can effect the proportion of infected humans, even decreasing β_h to 0 still leads to an endemic equilibrium, with $I_h^* > 0$.

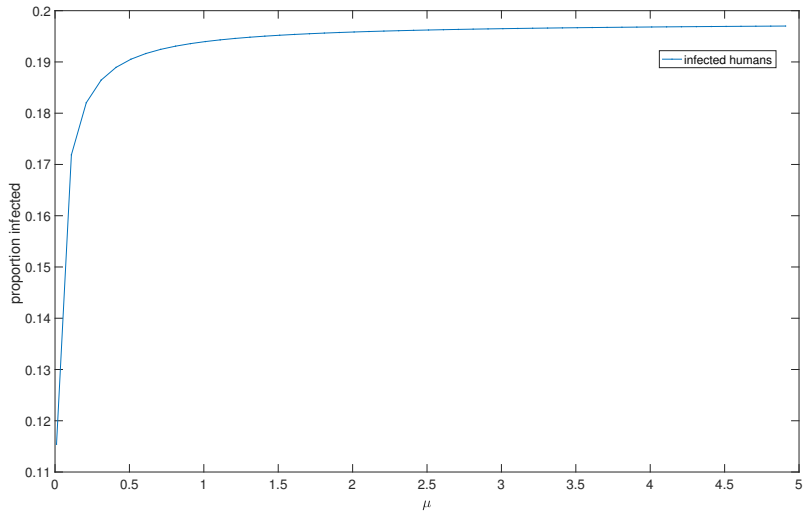

Figure 4.7: Graphing the proportion of infected humans against μ, the rate of mutation from the wildtype strain to the human-transmissible strain.

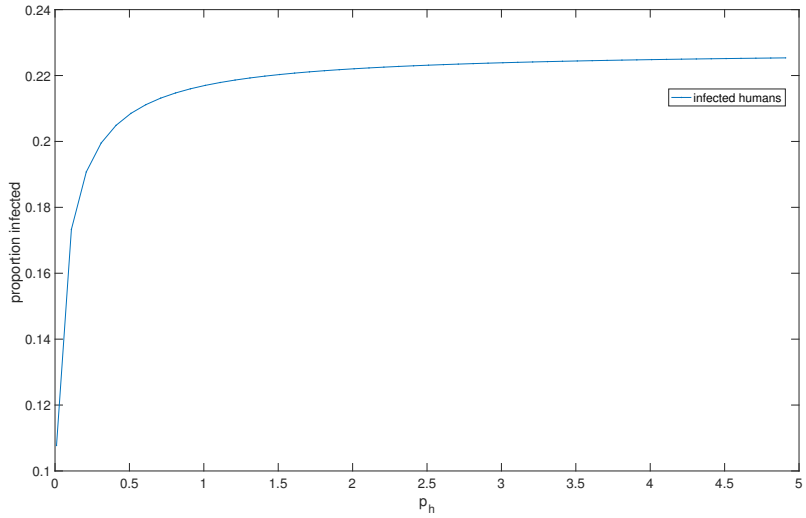

Figure 4.8: Graphing the proportion of infected humans against p_h, the contact rate (spillover rate) between domestic animals and humans.

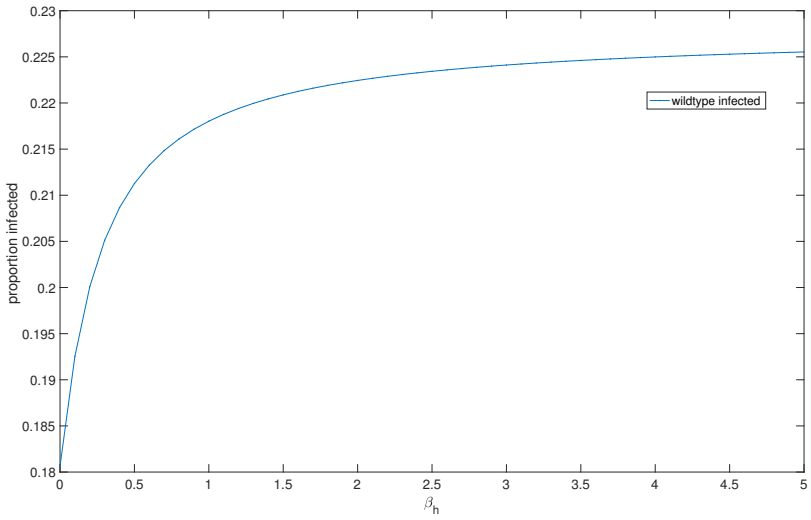

Figure 4.9: Graphing the proportion of infected humans against β_h, the transmission rate among humans. Here, setting β_h to 0 still gives rise to an endemic equilibrium of infected humans.

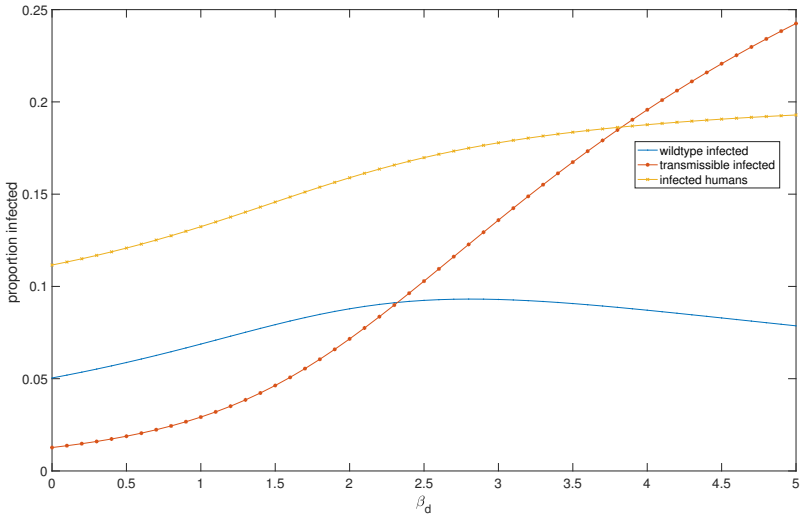

Figure 4.10: Graphing the proportion of infected humans and domestic animals against β_d, the transmission rate among domestic animals. Here, setting β_d to 0 still gives rise to an endemic equilibrium of infected humans.

The importance of the interspecies transmission parameters is reflected in Figures 4.9 and 4.10, which show that even when the transmission rates of the pathogen in humans or domestic animals is set to 0, the disease can reach an endemic equilibrium in humans. The effect of setting each parameter to in an otherwise endemic equilibrium, where the epidemic is expected to remain endemic in all three species as in 4.1 is summarized in 4.2.

These comparisons suggest that a lower number of animals infected with the transmissible strain has the potential to lower the proportion of infected humans, while even if the intraspecies parameters β_d or β_h are set to 0 the epidemic can spread to infect the human population. These results show that the interspecies transmission parameters are primary targets for intervention to lower the proportion of infected humans in this model.

Parameter	Maximum % of Infected Humans	Equilibrium % of Infected Humans
–	46.33	19.04
p_d	0	0
μ	0	0
p_h	0	0
β_w	49.77	19.62
β_d	18.81	11.16
β_h	36.13	18.06

Table 4.2: Comparing the effect of setting each transmission parameter to 0 in the endemic equilibrium of Figure 4.1.

4.3 Summary

To test the result from Chapter 3 that changing μ, p_h, and p_d matters more to the eventual number of infected humans than changing β_i or γ_i, the traditional parameters targeted in public health interventions, we varied the parameters p_d, μ, p_h, β_d, and β_h while holding the other values constant at an endemic equilibrium condition. The results of these numerical simulations show that varying p_d and μ can change the relative prevalence of domestic animals infected with the wildtype and human-transmissible strains, which in turn can change the proportion of infected humans. Further, only by setting one or more interspecies transmission parameters μ, p_d, p_h to 0 can the model avoid an endemic equilibrium in humans. In particular, the pathogen can persist in humans even if $\beta_h = 0$.

While varying traditional epidemic parameters such as β_i and γ_i can change the relative numbers of individuals in each compartment, Chapter 3 shows that only p_d, p_h, and μ control the global behavior of a zoonotic epidemic, a result shown in detail by the simulations in this chapter. These results show that a zoonotic pathogen can establish itself in the human population as long as it is seeded with an initial infection in the wild compartment and p_d, p_h and μ are nonzero, even if the human-transmissible strain is incapable of being transmitted among humans.

Chapter 5

Discussion

In this Chapter, we discuss the implications of this model and suggest directions for future research. The model goes a step further than [25], [36], and other attempts to quantify the interspecies spread of disease by accounting for the entire course of a zoonosis and the mutations that allow an animal pathogen to spread to humans. Further, the split between the effects of different parameters proved in Chapter 3 and exemplified in Chapter 4 offers suggestions both for interventions to mitigate the effects of an emerging zoonosis and future research based on this model.

5.1 Implications

The results of our mathematical analysis in Chapter 3 suggest that we can categorize the parameters of the model into two types. The first type is intracompartment parameters: the transmission and recovery rates β_i and γ_i for each species, which describe interactions in a single species. The second is intercompartment parameters, which govern interactions between members of two species. p_d and p_h, which indicate the spillover rate to domestic animals and humans, obviously fall into this category; μ

quantifies the rate of a mutation arising in domestic animals that makes the pathogen transmissible among humans, and so also qualifies. From Theorems 2 and 7, we see that it is only these second parameters, and the initial proportion of infected wild animals, that have the potential to alter the global dynamics of the three-species system to a disease-free equilibrium. The examples in Chapter 4 crystallize the result that parameters of the second type are threshold values for the global progression of an epidemic: changing values in the first category only changes the relative proportions of each type of individual present at an equilibrium, not the stability of the equilibria, while changing the values of parameters in the second category can change the global behavior of the pathogen.

This complete simulation of an emerging zoonosis shows that even in cases where the disease dies out in the wild compartment and would fail without an external force of infection in the domestic one, it can establish an endemic equilibrium in humans. Further, this result holds even if $\beta_h = 0$, reflecting a pathogen in Stage 1 of [4], [9], and [10]'s categorization for zoonoses that would not be deemed a pandemic threat under that framework. These simulations suggest that the threat posed by zoonoses is more detailed and probable than previously assumed: only by setting at least one of the transmission parameters to 0 can public health officials prevent an infection in wildlife from establishing a presence in humans, and it is extraordinarily unlikely that transmission routes between species or the mutation rate of pathogens can be entirely suppressed. While deterministic models such as the one presented here offer more certainly than stochastic models, which simulate interactions between individuals with random variables and offer more ways for an epidemic to attain a disease-free equilibrium, this result indicates that even the slightest possibility of contact between species or selection for a pathogen more suited to humans raises

p_d, p_h, or μ above 0 and thus can lead to an endemic infection in humans. While this endemic equilibrium or rates of transmission may be negligible in real populations, our results that the threat of an emerging zoonosis cannot be completely erased even with extraordinarily effective public health and medical interventions, confirming the focus on prioritizing zoonoses as mathematically sound and offering a warning for public health officials.

5.2 Future Research

The lack of large, publicly available data sets, especially regarding the prevalence of zoonotic infections in wild and domestic animals and the values for p_d, p_h, and μ, limits our ability to refine any model [11], and, as seen in Chapter 4, limits the accuracy of our theory. While some research attempts to approximate this data by assessing expert opinions as an explicit response to the lack of publicly available, unbiased data surrounding the spread of zoonoses [34], this type of research cannot replace population-level data. Gathering such data is thus critical to future modeling efforts in domestic and wild animal populations ([8], [10])−in particular, there is little data available for any infectious diseases in wild animals and interspecies contact rates−and should form a key component of future efforts.

This research introduces a model capable of replicating all stages of the emergence of a zoonosis with an intermediate host. To keep this work at a preliminary level and to maximize its use in more specialized contexts, we have not considered further modifications to the SIR prototype model such as loss of immunity (SIRS) or exposure time (SEIR), or possible variation patterns in the number of infected reservoir hosts, such as seasonal migration. Given adequate data, future research could add any

of these modifications, as well as others not mentioned here, and can thus adapt this model to any specific emerging zoonosis. In particular, approximately 25% of zoonotic pathogens are capable of some human-to-human transmission, but cannot persist without further introduction from an animal host [6]. These pathogens mutate over the course of many jumps back and forth from animal to human to animal in a phenomenon known as a stuttering chain, and incorporating this behavior could prove to change the model's dynamics significantly [10]. More broadly, future models should incorporate backwards transmission to wild animals and direct interactions between humans and wild reservoirs, as well as interactions between different pathogens in an intermediate host [10]. Even psychological and economic factors in the human population can change the dynamics of an emerging zoonosis [22], and so adding modifications indicating social change over the course of an epidemic−whether in the human population or in the human-controlled domestic animal one−can further refine a model. The modifications discussed above have the potential to introduce more exciting dynamics, such as backward bifurcations or strange attractors in the solution space [44], and this type of behavior would be mathematically intriguing to find.

Although this model introduces the idea of a mutation in an intermediate host, there may be more refined ways to model a zoonotic pathogen becoming better at infecting humans over time. Future models could make p_h, β_h, or μ a function of time to better simulate pathogen adaptation; we do not know if this greater detail will significantly change the global qualities of the model or if they are accurate reflections of pathogen behavior. More specifically, future models should investigate the effect of different transmission rates for the two strains circulating in the intermediate host, which will change the endemic equilibrium in domestic animals and thus humans.

Here, we have abstracted the process of mutation to a simple yes/no question regarding human transmissibility, neglecting the distinction between the different possible ways for a pathogen to mutate and the different possible degrees of change. The mutation rate of a zoonotic disease can depend on social factors such as culling in the intermediate host population, vaccination of infected individuals, and biosecurity, as well as biological ones such as RNA mutation or interstrain competition, and future research should investigate whether those different processes have noticeable differences on the number of infected humans or the mathematical structure of the model. There is also a lack of investigation of disease dynamics in individual hosts, with little data investigating the effect of different expressions of pathogen genotypes or animal superspreaders (individuals who infect many more secondary cases than average) on transmissibility in humans [10]. As this effect is the one abstracted by our parameter μ, delving deeper into individual-host pathogen dynamics such as cellular entry and replication [11] has the potential to improve our model. No emerging infected disease has been predicted before infecting humans [4], although progress is being made on identifying disease 'hotspots' [45], and this gap reinforces the importance of studying the factors that lead to successful spillover and define transmission rates between species [4].

This model is intended to provide the framework for quantitative, comprehensive study of zoonoses cited in [8] and other recent literature, and can thus be modified in many different ways suited to different pathogens.

5.3 Conclusion

This research suggests future avenues of exploration for both researchers and policymakers seeking to understand and control the spread of an emerging infectious zoonosis, and shows that interspecies connections are critical to controlling and understanding the effect an emerging zoonosis can have on human populations. We show that for the limited data that exists, pathogens such as avian influenza that have a high mutation rate and an intermediate host in close contact with humans can fail to establish themselves in animal populations while still establishing an endemic equilibrium in humans, and that with nonzero transmission parameters and an initial population of infected wild animals, a pathogen can fail to achieve traditional markers of success, such as stage 3 transmissibility, and still maintain an endemic equilibrium in the human population. This is a concerning result for public health, but offers areas in which policy rather than medical interventions can be more effective in controlling disease.

Chapter 6

Conclusion

With the ability to study the emergence of a zoonosis with an intermediate host exemplified for the first time by the model introduced here, scientists and policymakers alike have a more refined tool with which to study and confront one of the most well-recognized threats to global health: the emergence of a new pandemic into the human population. This model differs from already extant ones in that it charts the entire course of an emerging pathogen, proving that the course of a zoonosis in humans depends on its path through the wild reservoir and domestic intermediate host species. To our knowledge, this is the first model that accounts for the entire course−from infected wild animals, through mutation in an intermediate host, to an endemic equilibrium in humans−of the type of zoonotic pathogen cited as Disease X, the unknown pandemic threat the World Health Organization ranks in the highest tier of priorities for research and development, and so provides a significant step forward in its study.

This thesis fills a significant gap to infectious disease ecology: the introduction of a model that captures the unique properties of a zoonosis emerging in humans via

an intermediate domestic host [8]. We establish that it has one unique disease-free equilibrium and one endemic equilibrium, and that the stability of these points depends on p_d, p_h, and μ, the contact rates between species and the pathogen's rate of mutation. Accurately identifying and describing the dynamics of a pathogen circulating in wild and domestic animals provides an invaluable opportunity to avoid risk to humans [4], and can be used to inform the formation of health policies. This model can thus be used guide public health interventions for emerging zoonotic diseases.

That the interspecies parameters control the system's R_0 and are thus threshold conditions for this model suggests that the problem of controlling the spread of a zoonotic epidemic has less to do with intracompartment controls than with intercompartment ones: rather than efforts to control the transmission or recovery rates in one species, it is a more effective intervention to control p_d, p_h, or μ through better biosecurity or population control. This finding provides a blueprint for public health interventions in zoonoses, as well as a warning for officials hoping to prevent the spread of wildlife diseases to humans. In a ray of good news for public health officials, despite their importance as threshold conditions for the spread of a zoonotic epidemic, the interspecies parameters$-p_d, p_h$, and $\mu-$may be more susceptible to policy changes than the intraspecies parameters β_i and γ_i, at least when the domestic intermediate host is a livestock or pet species entirely under human control. Even before a zoonotic epidemic is detected in other species, restructuring agricultural systems and controlling livestock movements offer public health policymakers avenues to mitigate the effects of such a pathogen. Since accurate models can assist in appropriately allocating surveillance resources [8], these parameters can thus guide health officials in their response to and prevention of emerging zoonoses, policy changes which are essential in controlling zoonoses and mitigating their risk of emergence [7].

For example, by preventing disease circulation on farms, we can prevent pathogens such as avian influenza from becoming persistent human health risks ([1], [4]). Focusing on policy changes in domestic animal management−much easier and cheaper than human behavioral changes [7]−can be guided by this report and prevent other outbreaks.

Our results primarily offer a warning to public health officials: without drastic interventions to drive interspecies interactions or pathogen mutation rates to 0, which may be biologically impossible, zoonoses with the capacity to mutate in a human-adjacent intermediate host will spread to humans even if they are controlled in other species. More fundamentally to the field of mathematical epidemiology, this result confirms previously held beliefs−unquantified until now−about the philosophical importance of zoonoses to humanity. It is a pillar of the movement variously called "global", "one", or "planetary health" that humanity's connections to other species matter just as much to the progression of disease as does the pathogen's ability to infect individuals of the same species, and that human populations cannot insulate themselves from changes that affect other species. By mathematically linking the progress of a zoonotic epidemic to parameters governing interactions between species, this model shows that the framework of an interconnected human and natural world that implicitly underlies much of the analysis of global health in the last twenty years agrees with the mathematics of infectious disease, quantifying and confirming a widespread belief in global health.

References

[1] W. B. Karesh, A. Dobson, J. O. Lloyd-Smith, J. Lubroth, M. A. Dixon, M. Bennett, S. Aldrich, T. Harrington, P. Formenty, E. H. Loh, *et al.*, "Ecology of zoonoses: natural and unnatural histories," *The Lancet*, vol. 380, no. 9857, pp. 1936–1945, 2012.

[2] WHO, "List of blueprint priority diseases," July 2018.

[3] M. E. Woolhouse, L. H. Taylor, and D. T. Haydon, "Population biology of multihost pathogens," *Science*, vol. 292, no. 5519, pp. 1109–1112, 2001.

[4] S. S. Morse, J. A. Mazet, M. Woolhouse, C. R. Parrish, D. Carroll, W. B. Karesh, C. Zambrana-Torrelio, W. I. Lipkin, and P. Daszak, "Prediction and prevention of the next pandemic zoonosis," *The Lancet*, vol. 380, no. 9857, pp. 1956–1965, 2012.

[5] P. Daszak, A. A. Cunningham, and A. D. Hyatt, "Emerging infectious diseases of wildlife–threats to biodiversity and human health," *Science*, vol. 287, no. 5452, pp. 443–449, 2000.

[6] M. E. Woolhouse and S. Gowtage-Sequeria, "Host range and emerging and reemerging pathogens," *Emerging infectious diseases*, vol. 11, no. 12, p. 1842, 2005.

[7] A. A. Cunningham, P. Daszak, and J. L. Wood, "One health, emerging infectious diseases and wildlife: two decades of progress?," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 372, no. 1725, p. 20160167, 2017.

[8] J. O. Lloyd-Smith, S. Funk, A. R. McLean, S. Riley, and J. L. Wood, "Nine challenges in modelling the emergence of novel pathogens," *Epidemics*, vol. 10, pp. 35–39, 2015.

[9] N. D. Wolfe, P. Daszak, A. M. Kilpatrick, and D. S. Burke, "Bushmeat hunting, deforestation, and prediction of zoonotic disease," *Emerging infectious diseases*, vol. 11, no. 12, p. 1822, 2005.

[10] J. O. Lloyd-Smith, D. George, K. M. Pepin, V. E. Pitzer, J. R. Pulliam, A. P. Dobson, P. J. Hudson, and B. T. Grenfell, "Epidemic dynamics at the human-animal interface," *Science*, vol. 326, no. 5958, pp. 1362–1367, 2009.

[11] L. Allen, V. Brown, C. Jonsson, S. L. Klein, S. Laverty, K. Magwedere, J. Owen, and P. Van Den Driessche, "Mathematical modeling of viral zoonoses in wildlife," *Natural resource modeling*, vol. 25, no. 1, pp. 5–51, 2012.

[12] M. Richard, M. d. Graaf, and S. Herfst, "Avian influenza a viruses: from zoonosis to pandemic," *Future virology*, vol. 9, no. 5, pp. 513–524, 2014.

[13] G. Neumann, T. Noda, and Y. Kawaoka, "Emergence and pandemic potential of swine-origin h1n1 influenza virus," *Nature*, vol. 459, no. 7249, p. 931, 2009.

[14] W. Ma, K. Lager, A. Vincent, B. Janke, M. Gramer, and J. Richt, "The role of swine in the generation of novel influenza viruses," *Zoonoses and public health*, vol. 56, no. 6-7, pp. 326–337, 2009.

[15] K. J. Vandegrift, S. H. Sokolow, P. Daszak, and A. M. Kilpatrick, "Ecology of avian influenza viruses in a changing world," *Annals of the New York Academy of Sciences*, vol. 1195, no. 1, pp. 113–128, 2010.

[16] T. Ito, H. Goto, E. Yamamoto, H. Tanaka, M. Takeuchi, M. Kuwayama, Y. Kawaoka, and K. Otsuki, "Generation of a highly pathogenic avian influenza a virus from an avirulent field isolate by passaging in chickens," *Journal of virology*, vol. 75, no. 9, pp. 4439–4443, 2001.

[17] M. Gauthier-Clerc, C. Lebarbenchon, and F. Thomas, "Recent expansion of highly pathogenic avian influenza h5n1: a critical review," *Ibis*, vol. 149, no. 2, pp. 202–214, 2007.

[18] V. Sharma, S. Kaushik, R. Kumar, J. P. Yadav, and S. Kaushik, "Emerging trends of nipah virus: A review," *Reviews in medical virology*, vol. 29, no. 1, p. e2010, 2019.

[19] J. R. Pulliam, J. H. Epstein, J. Dushoff, S. A. Rahman, M. Bunning, A. A. Jamaluddin, A. D. Hyatt, H. E. Field, A. P. Dobson, and P. Daszak, "Agricultural intensification, priming for persistence and the emergence of nipah virus: a lethal bat-borne zoonosis," *Journal of the Royal Society Interface*, vol. 9, no. 66, pp. 89–101, 2011.

[20] S. Iwami, Y. Takeuchi, and X. Liu, "Avian–human influenza epidemic model," *Mathematical biosciences*, vol. 207, no. 1, pp. 1–25, 2007.

[21] E. de Wit and V. J. Munster, "Mers-cov: the intermediate host identified?," *The Lancet. Infectious diseases*, vol. 13, no. 10, p. 827, 2013.

[22] R. Goodwin, D. Schley, K.-M. Lai, G. M. Ceddia, J. Barnett, and N. Cook, "Interdisciplinary approaches to zoonotic disease," *Infectious disease reports*, vol. 4, no. 2, 2012.

[23] H. Gulbudak, V. L. Cannataro, N. Tuncer, and M. Martcheva, "Vector-borne pathogen and host evolution in a structured immuno-epidemiological system," *Bulletin of mathematical biology*, vol. 79, no. 2, pp. 325–355, 2017.

[24] A. Gumel, "Causes of backward bifurcations in some epidemiological models," *Journal of Mathematical Analysis and Applications*, vol. 395, no. 1, pp. 355–365, 2012.

[25] A. B. Gumel, "Global dynamics of a two-strain avian influenza model," *International Journal of Computer Mathematics*, vol. 86, no. 1, pp. 85–108, 2009.

[26] K. I. Kim, Z. Lin, and L. Zhang, "Avian-human influenza epidemic model with diffusion," *Nonlinear Analysis: Real World Applications*, vol. 11, no. 1, pp. 313–322, 2010.

[27] W. O. Kermack and A. G. McKendrick, "A contribution to the mathematical theory of epidemics," *Proceedings of the Royal Society of London. Series A, Containing papers of a mathematical and physical character*, vol. 115, no. 772, pp. 700–721, 1927.

[28] W. O. Kermack and A. G. McKendrick, "Contributions to the mathematical theory of epidemics. ii.the problem of endemicity," *Proceedings of the Royal Society of London. Series A, containing papers of a mathematical and physical character*, vol. 138, no. 834, pp. 55–83, 1932.

[29] W. O. Kermack and A. G. McKendrick, "Contributions to the mathematical theory of epidemics. iii.further studies of the problem of endemicity," *Proceedings of the Royal Society of London. Series A, Containing Papers of a Mathematical and Physical Character*, vol. 141, no. 843, pp. 94–122, 1933.

[30] L. Florens, M. P. Washburn, J. D. Raine, R. M. Anthony, M. Grainger, J. D. Haynes, J. K. Moch, N. Muster, J. B. Sacci, D. L. Tabb, *et al.*, "A proteomic view of the plasmodium falciparum life cycle," *Nature*, vol. 419, no. 6906, p. 520, 2002.

[31] H.-H. Chang, E. L. Moss, D. J. Park, D. Ndiaye, S. Mboup, S. K. Volkman, P. C. Sabeti, D. F. Wirth, D. E. Neafsey, and D. L. Hartl, "Malaria life cycle

intensifies both natural selection and random genetic drift," *Proceedings of the National Academy of Sciences*, vol. 110, no. 50, pp. 20129–20134, 2013.

[32] M. Andraud, N. Hens, C. Marais, and P. Beutels, "Dynamic epidemiological models for dengue transmission: a systematic review of structural approaches," *PloS one*, vol. 7, no. 11, p. e49085, 2012.

[33] N. Hussaini, K. Okuneye, and A. B. Gumel, "Mathematical analysis of a model for zoonotic visceral leishmaniasis," *Infectious Disease Modelling*, vol. 2, no. 4, pp. 455–474, 2017.

[34] M. Singh, J.-A. Toribio, A. B. Scott, P. Groves, B. Barnes, K. Glass, B. Moloney, A. Black, and M. Hernandez-Jover, "Assessing the probability of introduction and spread of avian influenza (ai) virus in commercial australian poultry operations using an expert opinion elicitation," *PloS one*, vol. 13, no. 3, p. e0193730, 2018.

[35] V. Henaux, M. D. Samuel, and C. M. Bunck, "Model-based evaluation of highly and low pathogenic avian influenza dynamics in wild birds," *PLoS One*, vol. 5, no. 6, p. e10997, 2010.

[36] Y. Xiao, X. Sun, S. Tang, and J. Wu, "Transmission potential of the novel avian influenza a (h7n9) infection in mainland china," *Journal of theoretical biology*, vol. 352, pp. 1–5, 2014.

[37] B. Bett, J. Henning, P. Abdu, I. Okike, J. Poole, J. Young, T. F. Randolph, and B. D. Perry, "Transmission rate and reproductive number of the h5n1 highly pathogenic avian influenza virus during the december 2005–july 2008 epidemic in n igeria," *Transboundary and emerging diseases*, vol. 61, no. 1, pp. 60–68, 2014.

[38] O. Diekmann, J. Heesterbeek, and M. G. Roberts, "The construction of next-generation matrices for compartmental epidemic models," *Journal of the Royal Society Interface*, vol. 7, no. 47, pp. 873–885, 2009.

[39] P. Van den Driessche and J. Watmough, "Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission," *Mathematical biosciences*, vol. 180, no. 1-2, pp. 29–48, 2002.

[40] Y. Li, P. Qin, and J. Zhang, "Dynamics analysis of avian influenza a (h7n9) epidemic model," *Discrete Dynamics in Nature and Society*, vol. 2018, 2018.

[41] S. Liu, S. Ruan, and X. Zhang, "Nonlinear dynamics of avian influenza epidemic models," *Mathematical biosciences*, vol. 283, pp. 118–135, 2017.

[42] M. A. Khan, Y. Khan, and S. Islam, "Complex dynamics of an seir epidemic model with saturated incidence rate and treatment," *Physica A: Statistical Mechanics and its Applications*, vol. 493, pp. 210–227, 2018.

[43] R. Anguelov, S. M. Garba, and S. Usaini, "Backward bifurcation analysis of epidemiological model with partial immunity," *Computers & Mathematics with Applications*, vol. 68, no. 9, pp. 931–940, 2014.

[44] P. G. Barrientos, J. Á. Rodríguez, and A. Ruiz-Herrera, "Chaotic dynamics in the seasonally forced sir epidemic model," *Journal of mathematical biology*, vol. 75, no. 6-7, pp. 1655–1668, 2017.

[45] P. Daszak, "Anatomy of a pandemic," *The Lancet*, vol. 380, no. 9857, pp. 1883–1884, 2012.