The Socioeconomic and Ecological Drivers of Avian Influenza Risks in China and at the International Level

by

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ABSTRACT

Avian influenzas are zoonoses, or pathogens borne by wildlife and livestock that can also infect people. In recent decades, and especially since the emergence of highly pathogenic avian influenza (HPAI) H5N1 in 1996, these diseases have become a significant threat to animal and public health across the world. HPAI H5N1 has caused severe damage to poultry populations, killing, or prompting the culling of, millions of birds in Asia, Africa, and Europe. It has also infected hundreds of people, with a mortality rate of approximately 50%. This dissertation focuses on the ecological and socioeconomic drivers of avian influenza risk, particularly in China, the most populous country to be infected. Among the most significant ecological risk factors are landscapes that serve as "mixing zones" for wild waterfowl and poultry, such as rice paddy, and nearby lakes and wetlands that are important breeding and wintering habitats for wild birds. Poultry outbreaks often involve cross infections between wild and domesticated birds. At the international level, trade in live poultry can spread the disease, especially if the imports are from countries not party to trade agreements with well-developed biosecurity standards. However, these risks can be mitigated in a number of ways. Protected habitats, such as Ramsar wetlands, can segregate wild bird and poultry populations, thereby lowering the chance of interspecies transmission. The industrialization of poultry production, while not without ethical and public health problems, can also be risk-reducing by causing wild-domestic segregation and allowing for the more efficient application of surveillance, vaccination, and other biosecurity measures. Disease surveillance is effective at preventing the spread of avian influenza, including across international borders. Economic modernization in general, as reflected in rising per-capita GDP, appears to mitigate avian influenza risks at both the national and sub-national levels. Poultry vaccination has been effective in many cases, but is an incomplete solution because of the practical difficulties of sustained and widespread implementation. The other popular approach to avian influenza control is culling, which can be highly expensive and raise ethical concerns about large-scale animal slaughter. Therefore, it is more economically efficient, and may even be more ethical, to target the socio-ecological drivers of avian influenza risks, including by implementing the policies discussed here.

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CHAPTER 1

INTRODUCTION

This dissertation examines the socio-ecological drivers of avian influenza risk in China and at the international level. Avian influenzas, such as H5N1 and H7N9, have become a major threat to human and livestock health in recent decades. Propagated by both "natural" pathways, such as waterfowl migration, and anthropogenic means, such as the trade of live poultry, they have spread across the world. My research focuses on China, the largest country to be infected by the disease, but also examines how China's epidemic dynamics fit into the larger, global context of avian influenza risks.

Previous research on avian influenza risks has generally not taken a socio-ecological, system-level view of the phenomena. More specifically, socioeconomic factors that facilitate or contain epidemic spread are usually overlooked in studies that are often discipline-specific. My doctoral research has attempted to contribute to the literature by taking a more interdisciplinary approach, analyzing the interactions between ecological and socioeconomic factors, and drawing out the policy implications that follow from that analysis. My dissertation is comprised of five chapters, including a literature review and a concluding review of policy solutions.

The next chapter provides an overview of the general epidemiological conditions of modern China, with emphasis on how environmental and demographic changes wrought by industrialization, urbanization, and globalization have changed the risks posed by infectious diseases to people and livestock. It uses avian influenza, and particularly the highly pathogenic H5N1 strain, as an exemplar of the type of epidemics that are increasingly typical of modern China's epidemiological conditions.

Chapter 3 takes a macro-level analysis of the socio-ecological drivers of avian influenza risk in China. Although there have been numerous studies of environmental factors influencing the spread of H5N1 avian influenza in the country (it was first discovered in 1996 and has been in circulation in the country for over a decade), few have explicitly incorporated socioeconomic and administrative factors, such as biosecurity and public health controls. By using provincial-level data, this study identifies key management variables such as the presence of epidemic control agencies as being important to mitigating disease risk.

Chapter 4 focuses more explicitly on a specific mechanism of disease transmission at the landscape level – namely, how protected areas separate agricultural land, with their attendant populations of susceptible poultry, from migratory birds, which have been identified as an important agent of avian influenza spread. It puts forward the hypothesis that conserving biodiversity – in this case migratory birds, which are prevalent throughout China during the breeding and wintering seasons – may also mitigate the spread of avian influenza, thus offering a win-win scenario.

Chapter 5 takes an international outlook, analyzing avian influenza's epidemic dynamics as a function of migratory birds, the "natural" pathway, and the live poultry trade, the socioeconomic pathway. Over the past two decades, H5N1 (again the focus of the analysis) has spread throughout Asia, Europe, and Africa. This chapter attempts to analyze the risk factors for its spread in three key regions which have been heavily impacted, and which are also framed by regional trade agreements: the Association of Southeast Asian Nations (ASEAN), the Economic Community of Western Africa (ECOWAS), and the European Union (EU). This study identifies how spread dynamics differ based on different regional and national ecological conditions, management and regulatory standards, and socioeconomic characteristics.

Finally, Chapter 6 summarizes and synthesizes the policy implications of the abovementioned analyses. It reviews the history of attempts to contain or mitigate avian influenza outbreaks in China and across the world. The review assesses both the benefits and drawbacks of certain interventions, such as livestock culling, vaccination, and land-use zoning. Overall, a primary conclusion of this policy review is that prevention/mitigation is more economically efficient than suppression/adaptation. Going forward, as new avian influenzas continue to emerge and existing strains evolve, it will be necessary to tackle the basic socio-ecological drivers of epidemics, as opposed to merely trying to contain outbreaks after they occur.

Overall, I hope the research presented in this dissertation will contribute to the understanding of avian influenza epidemics as socio-ecological phenomena and to the development of effective policy responses. The risks analyzed in this dissertation will continue to exist, and perhaps even worsen, for the foreseeable future. Therefore, it is imperative to study and manage them in a systematic way, perhaps most importantly at the interface between wild birds and poultry. Highly pathogenic avian influenza H5N1, the primary focus of this dissertation, is one of many avian influenzas, and it will likely be joined by novel strains in the coming years and decades. However, I believe the results of this doctoral research can provide general insights that will apply to these other avian influenzas as well, given the epidemiological similarities among them.

CHAPTER 2

A REVIEW OF ZOONOTIC DISEASE RISKS IN CHINA

*A version of this chapter was published in *Ambio* in 2017 as “Economic Growth, Urbanization, Globalization, and the Risks of Emerging Infectious Diseases in China: A Review,” with my committee members Drs. Charles Perrings, Ann Kinzig, Jim Collins, Ben Minteer, and Peter Daszak.

2.1. Introduction

Today, an increasingly urban and interconnected world faces growing threats from emerging infectious diseases (Bradley and Altizer, 2007; Kapan et al., 2006; McMichael, 2004). This is of particular concern in the developing world, where managing fast-spreading epidemics in the growing number of megacities is a pressing challenge (Rees, 2013). Recent epidemics have underscored the importance of linkages between host habitats and the global network of cities. The Ebola virus, for example, has long survived among wildlife reservoirs in the hinterlands of Africa, “breaking out” in towns and cities in conspicuous but otherwise local epidemics. As in earlier outbreaks, the 2014 epidemic is thought to have origins in the consumption of wild animal protein, while its spread occurred in densely populated African cities. The international threat it posed stemmed from the increasing air travel connections between these and other cities around the world.

In the case of arboviruses like Zika, dengue, chikungunya, West Nile, and malaria, whose vectors have found ready habitat in urban areas, the primary mechanism for the spread of disease from one city to the next is international trade and travel (Alirol et al., 2011; Hay et al., 2005; Kraemer et al., 2015; Tatem et al., 2006; Weaver, 2013). The same is true of coronaviruses such as Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS). The latter emerged in Saudi Arabia in 2012, having been transmitted between animal reservoirs such as camels and their human handlers. It has since spread throughout the surrounding region, and travel-related human infections have been recorded in Europe, North America, and East and Southeast Asia (Parlak, 2015; Zumla et al., 2015). Urbanization and globalization have made outbreaks of these diverse zoonoses difficult to control, even with unprecedented levels of international cooperation (Chan, 2014; Khan et al., 2013; Kraemer et al., 2015; Weaver, 2013).

For most emerging infectious diseases prevention is better than cure – ex ante mitigation of disease risk is more economically efficient than ex post adaptation to an outbreak (Graham et al., 2008; Langwig et al., 2015; Murphy, 1999; Voyles et al., 2014). Among mitigation strategies, vaccination has been a widespread and long-established practice for many DNA viruses such as chicken pox or small pox. However, vaccination remains problematic for most RNA viruses, including Ebola, SARS, and avian influenza, due to their higher mutation rate; vaccination is simply not a feasible way to prevent the emergence of many novel zoonoses, which will inevitably encounter immunologically naïve populations. Therefore, mitigating the risks from emerging and re-emerging zoonoses requires preemptive measures against their socio-ecological drivers (Pike et al., 2014). Identifying areas where the convergence of risk factors are occurring with greatest intensity, and at the largest scales, is a logical first step in the development of a mitigation strategy. In this regard, China may be an important outlier among countries.

Assessment of the risks posed by zoonotic diseases requires an understanding of how socioeconomic, and ecological conditions affect two phenomena: emergence (the irruption of a pathogen originating in wildlife or livestock into human populations) and spread (the transmission of disease among both animals and people). In this article, I review the evidence for changes in zoonotic risks in China. More particularly, I show how income growth, urbanization, and globalization affect the likelihood of emergence and spread, using SARS and avian influenza as topical and representative examples, but also referring to other diseases when relevant. I discuss the policy implications of changes in the epidemiological environment in China, and consider how the mitigation of zoonotic risk in China could benefit the global risk environment.

China's rate of economic growth over the last twenty-five years has been exceptional. Real per-capita GDP (in purchasing power parity terms) rose from 1,516 USD in 1990 to 12,608 USD in 2014, an average annual growth rate of over 9 percent. While this has generated the resources necessary to improve biosecurity and healthcare, it has also increased the likelihood of disease emergence and transmission. The presence of major migratory bird pathways (conduits for the transmission of influenzas), habitats that encourage mixing between wild and domesticated birds, and a dramatic increase in demand for fresh meat have increased the likelihood of disease emergence. At the same time, urbanization and the growth of international trade and travel have increased the likelihood of disease spread (Alirol et al., 2011; Gong et al., 2012; Li et al., 2012a; Li et al., 2012b; Wang et al., 2008; Zhu et al., 2011). In 1990, only one quarter of China's population lived in cities; today, over 54% are urban residents, and by 2030 there will be at least one billion city-dwellers, or 70% of the population (Peng, 2011a). Concurrently, China's integration into international networks of trade and travel has occurred rapidly. Between 1990 and 2015, China's exports to the rest of the world grew annually by around 17 percent, and although exports in this period were dominated by manufactures, exports of food and live animals grew at an only slightly lower rate. More importantly for China's exposure to global disease risk, imports of food and live animals were 7-8 times larger than exports in 1990, and have since grown by around 15 percent per year (World Bank, 2016).

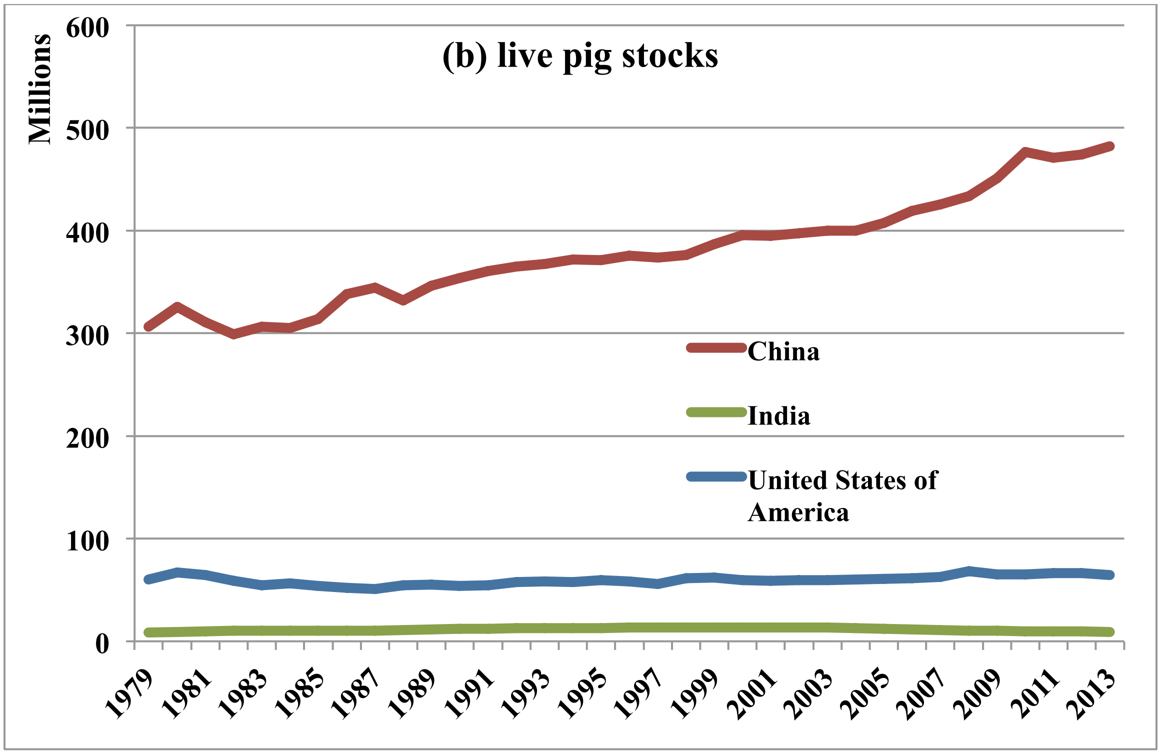
2.2. Economic Growth, Meat Consumption, and Zoonotic Risks in China

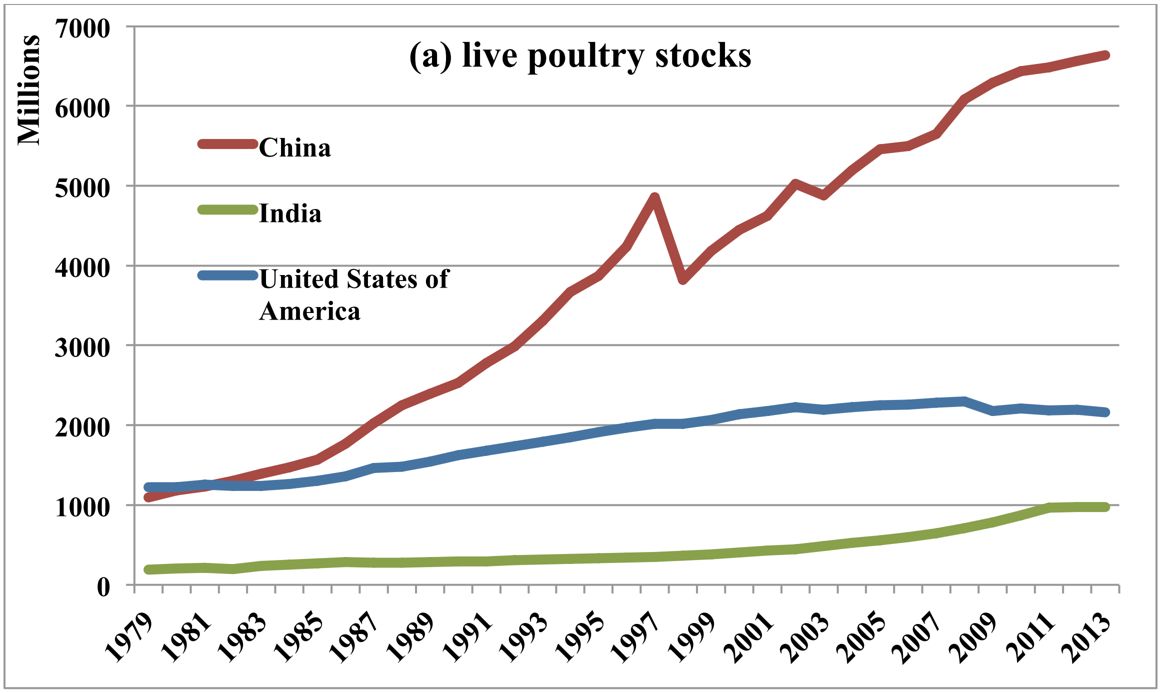
The epidemiological boundary separating humans from wildlife- and livestock-borne pathogens has been breached repeatedly throughout history. At the turn of the 20th century, it was estimated that 61% of all known human pathogens and 75% of all emerging diseases were zoonotic (Taylor et al., 2001). Zoonotic "spillover" into human populations can occur in numerous ways. Direct contact between people and pathogen-carrying animals through, for example, the consumption of infected wildlife or livestock is a common pathway of emergence (Murray and Daszak, 2013; Patz et al., 2004).

Increasing per-capita income has led to increasing per-capita meat consumption, and this has occurred more rapidly in China than in any other major economy. Tracking rapid rates of GDP growth and rural-to-urban migration, China's meat consumption has risen by around one-third since the turn of the century (Figure 1). The pattern of consumption is also changing: while pork remains the main source of animal protein, chicken consumption and production are increasing more rapidly. Between 1968 and 2005, the growth in poultry numbers was around ten times the growth in pig numbers

(Wang et al. 2008). Nor has the growth rate of these stocks slowed. In 2013, China had the world's largest stocks of poultry and swine, at 6.63 billion and 482 million individuals respectively. By comparison, U.S. stocks stood at 2.16 billion and 64.8 million individuals (FAO 2013).

Figure 1. The growth of China's poultry (1a) and pig (1b) stocks since 1979, compared to India and the United States.





What makes the changing pattern of meat consumption significant for infectious disease transmission in China is a persisting social preference for live and freshly slaughtered meat (the primary interface for animal-to-human transmission of many zoonoses) (Pi et al., 2014). As the consumption of meat grows in the coming decades, so will contact between consumers and live or freshly slaughtered animals. Over the next decade, per-capita consumption of chicken is expected to grow at an annual rate of 2.4%, compared to 1.5% for pork. While meat imports will likely increase, most of the growth in supply is expected to be from domestic sources. Annual production of poultry, pork, and beef is projected to rise from 70 million metric tons (mmt) today to 90 mmt by 2024 (Westcott and Trostle, 2014). The resulting increase in the levels and densities of pigs and poultry enlarges the potential pathogen reservoirs for zoonoses, especially influenzas.

A central mechanism that brings human, livestock, and wild animal populations together in China is the extensive network of wet markets – markets that sell live and freshly slaughtered domesticated and wild animals. Although found in many parts of the world, wet markets are particularly common in East and Southeast Asia. In China, they are the primary source of meat purchases, particularly of poultry. In Shanghai, for example, where highly pathogenic avian influenza (HPAI) H7N9 first emerged in 2013, 120 million of the approximately 190 million chickens consumed annually were purchased at wet markets (Pi et al., 2014).

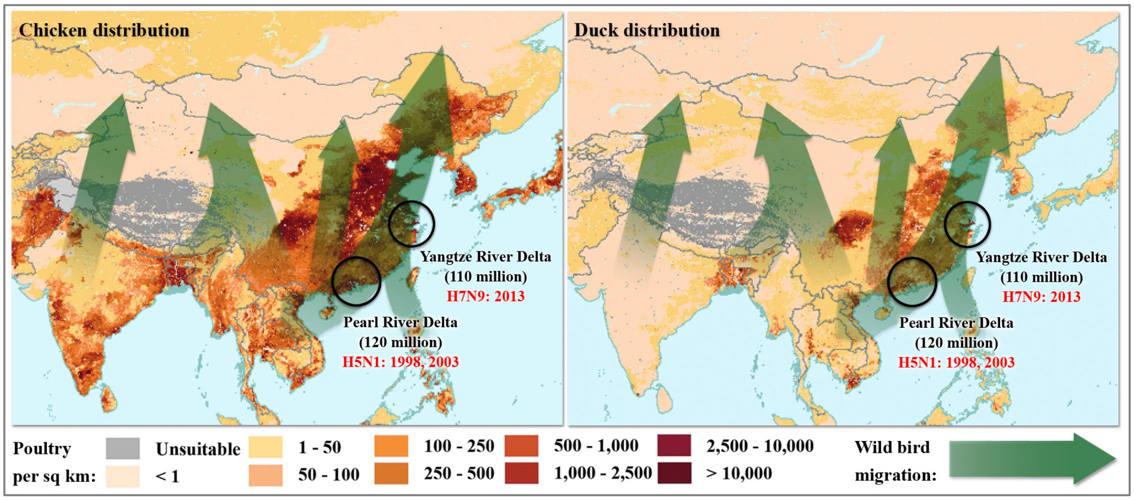
The spillover of H5N1 and H7N9 into human populations in China has been closely linked to these markets (Yu et al., 2007; Yu et al., 2014). Wet markets are frequently under-regulated, have unhygienic environments with inadequate sanitation, and are subject to poor surveillance and little biosecurity (Woo et al., 2006). Although the role of wet markets is expected to diminish in the coming decades, they will still account for a significant, perhaps even the majority, share of poultry sales (Pi et al., 2014). Income growth among urban consumers will increase the demand for meat, much of it bought in wet markets. Indeed, dietary preference for freshly slaughtered meat and the enduring popularity of wet markets will remain important drivers of zoonotic risk for the foreseeable future.

2.3. Urbanization and Disease Spread

The growth of cities and changing agricultural conditions have shaped infectious disease ecology in China since at least the Tang Dynasty (7th – 10th Century CE), creating and connecting reservoirs of pathogens and vectors (Jannetta, 1993). However, the speed and scope of urbanization over the past three decades have been significantly greater than at any other time in the past, creating a primarily urban population for the first time in China's history. The rate of urbanization has also been markedly higher than that of other industrialized and industrializing countries. For instance, in 1979, at the start of its own economic liberalization program, India had an urbanization level of 18.6% compared to China's 22.7%. Today, China's urbanization has reached 54.4% compared to India's 32.4% (UN 2015).

In China, this has expanded the interface of contact between humans, wildlife, and livestock. Urbanization and associated land-use changes, in conjunction with rising meat consumption, have brought reservoirs of wildlife diseases into closer contact with livestock and people (Daszak, 2000; Daszak et al., 2001; Myers et al., 2013; Wang et al., 2008). In particular, the emergence of HPAI strains has become more likely in southern China, where the growth of an increasingly affluent urban population has driven an increase in poultry production and land-use changes that brings humans, domesticated animals, and wildlife into closer contact (Davis, 2005; Wallace et al., 2010) (Figure 2).

Figure 2. The intersection of dense chicken and duck populations, human populations (concentrated by urbanization), and migratory birds increases the likelihood of interspecies transmission and the emergence of new influenza strains.



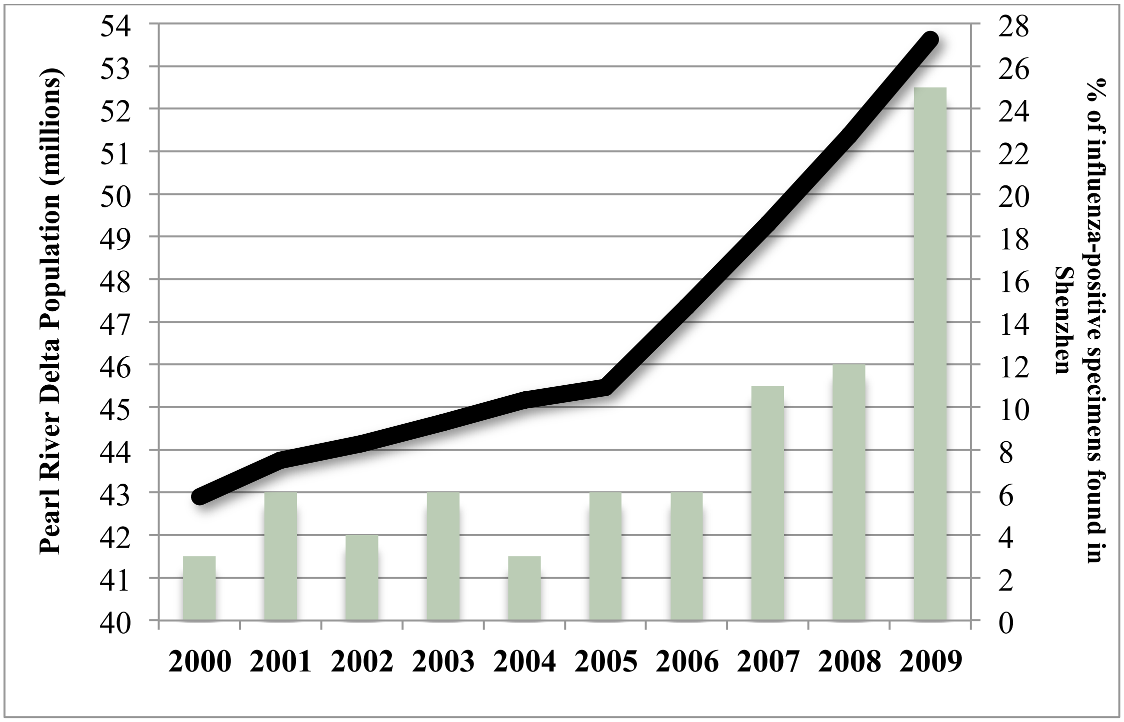
Sources: Generalized bird migration routes adapted from Fang et al. (2008); poultry distribution data from Robinson et al. (2014).

Changes in the configuration of natural, agricultural, and built-up land cover, as well as in the biotic and abiotic fluxes among them, also affect disease risks to people (Meentemeyer et al., 2012; Reisen, 2010). Large and growing populations of livestock – particularly poultry – distributed across China are ideal sites of viral mutation and interspecies influenza transmission, most notably between wild and domesticated birds. China is also crossed by multiple migratory flyways, which allow numerous waterfowl and other bird species to carry avian influenza into and out of the country (Chen et al., 2005b; Kilpatrick et al., 2006; Prosser et al., 2011; Takekawa et al., 2010). Across East Asia, intensively cultivated rice fields are populated by poultry and ducks, but are also ready habitats for HPAI-carrying waterfowl (Gilbert et al., 2014; Gilbert et al., 2008;

Martin et al., 2011; Paul et al., 2010) (Figure 2). The growing number of species infected by recent outbreaks of avian influenza suggests that epidemic risks are growing as a result (Webby and Webstter, 2003). Livestock populations are also staging posts for pathogens to enter human populations. For instance, poultry farming in China's urban and peri-urban areas increases the likelihood of H5N1 spread (Fasina et al., 2007; Kapan et al., 2006).

The risk of pathogen spread from diseases contracted in wet markets is exacerbated by the concentration and interconnectedness of human populations associated with urbanization (Fang et al., 2008; Hogerwerf et al., 2010; Paul et al., 2010). Wet markets in urban areas are now recognized to be the primary locus of infection for H7N9 (Gilbert et al., 2014). The high density of people makes cities, particularly the large cities that have appeared rapidly in China, force multipliers of pathogen transmission (Alirol et al., 2011). Patel and Burke (2009) argue that the outbreak of SARS in Hong Kong in 2002 and 2003, "demonstrated how dense urban living could ignite a global health crisis." The first phase of the SARS epidemic involved its spread through the interconnected metropolises of the Pearl River Delta (PRD) (Li et al., 2012b; Wang et al., 2008; Zhu et al., 2011). The PRD was also an epicenter for HPAI H5N1 (see Box 1), and remains a potential hotspot for other influenzas (Figure 3), though this has yet to be reflected in public health policies in the area (Fabre and Rodwin, 2011).

Figure 3. The increasing population of the Pearl River Delta urban area (black) and the annual rise in influenza-positive specimens from Shenzhen, one of its primary cities (gray).



Sources: Urbanization data from Guangdong Statistical Yearbook (2013); Shenzhen influenza-positive specimen data from Cheng et al. (2013).

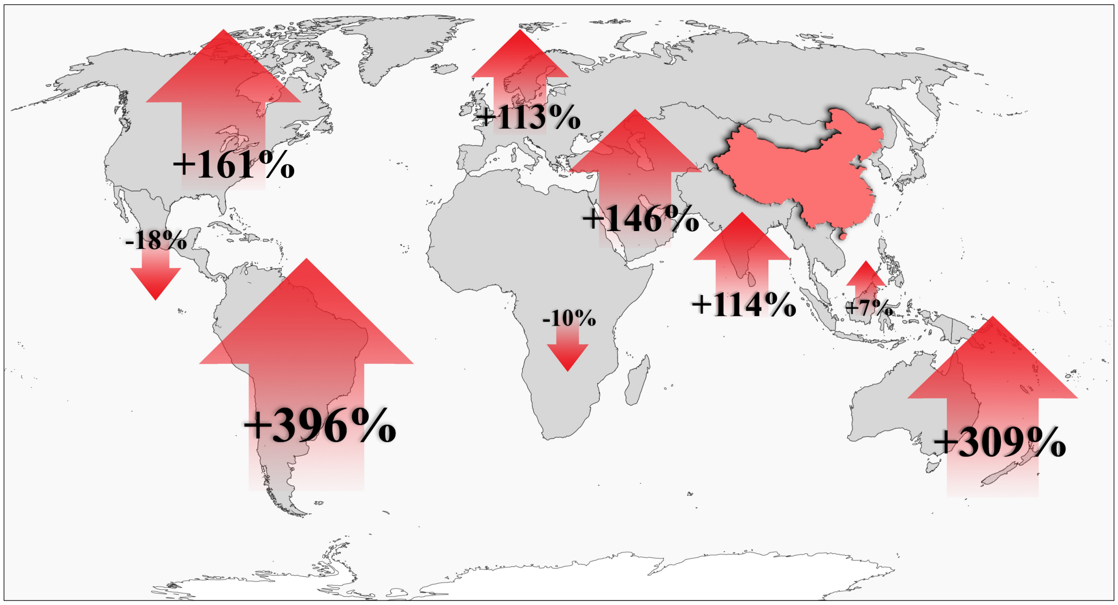
One reason for the effectiveness of cities as force multipliers, relative to rural areas, is the higher prevalence of a range of communicable and non-communicable diseases, including sexually transmitted diseases and cancers. Such conditions increase vulnerability to infection (Alirol et al., 2011; Gong et al., 2012; Li et al., 2012b), while co-morbidity can magnify the potential virulence of zoonotic pathogens and thus their spread (Weiss and McMichael, 2004). In many Chinese cities, public health management has not kept pace with demographic and economic changes. Despite progress in recent decades, immunization coverage for even common infections such as tuberculosis, measles, and tetanus remains inadequate (Gong et al., 2012). Infection risk is also related to the social inequality and dislocations caused by urbanization. In the Pearl River Delta in 2009, for instance, 80% of migrants did not have access to medical insurance (Fabre and Rodwin, 2011). This deprivation may deter people from seeking preventative care, or even immediate care after possible infection.

HPAI H5N1 is an important example of these aforementioned dynamics. It first emerged in southern China in the late 1990s. After several outbreaks, contained with varying degrees of efficacy, it has now spread across the world, infecting people, poultry, wild birds, and other wild and domesticated animals. Income growth has driven an increase in China's protein consumption, which has resulted in a nearly 6-fold increase in domestic poultry stocks since 1979 (FAO 2015). Urban wet markets are still the primary sources of poultry purchases – in Shanghai, for instance, 120 million of the 190 million chickens sold in 2013 were from wet markets (Pi et al. 2014). That year, Shanghai, China's largest city at 25 million people, was the site of HPAI H7N9's emergence. The most likely areas of future H7N9 spread in China are urban areas with a high density of wet markets (Gilbert et al. 2914). China is also traversed by several migratory bird pathways, bringing growing and ever-denser populations of poultry and people into contact with influenza-bearing wild birds (Chen et al. 2005; Takekawa et al. 2010). The heavily urbanized areas of southern China – such as the metropolitan Pearl River Delta, home to over 100 million people and a high concentration of poultry production – is at particular risk for the emergence of HPAI, and may be an important outlet for its spread within China and internationally (Davis 2005; Wallace et al. 2010).

2.4. China and the Globalization of Infectious Disease Risks

The epidemiological implications of disease co-morbidity – including the risks of "super spreaders" – are perhaps even more significant at the international level. For instance, had the first SARS carrier reached the dense precincts of Durban, with its high incidence of AIDS, rather than the more ordered and hygienic environment of Toronto, the outcome may have been much worse (Weiss and McMichael, 2004). Of course, the probability that an infection is transmitted abroad to a given city depends on the volume of trade and travel involved, but since trade between China and South Africa has been growing more rapidly than trade with China's main international markets, this is not a trivial observation. China is now the world's largest trading nation, and in recent years its trade to nearly every region of the world has increased significantly (Figure 4). The global infectious disease risks created by China's trade growth stem from the fact that international markets facilitate the movement of pathogens around the world as freely as commodities and people (Perrings et al., 2010a, b; Tatem et al., 2006).

Figure 4. The percent increase in the volume of commodities exported from mainland China to different global regions between 2001 and 2011.



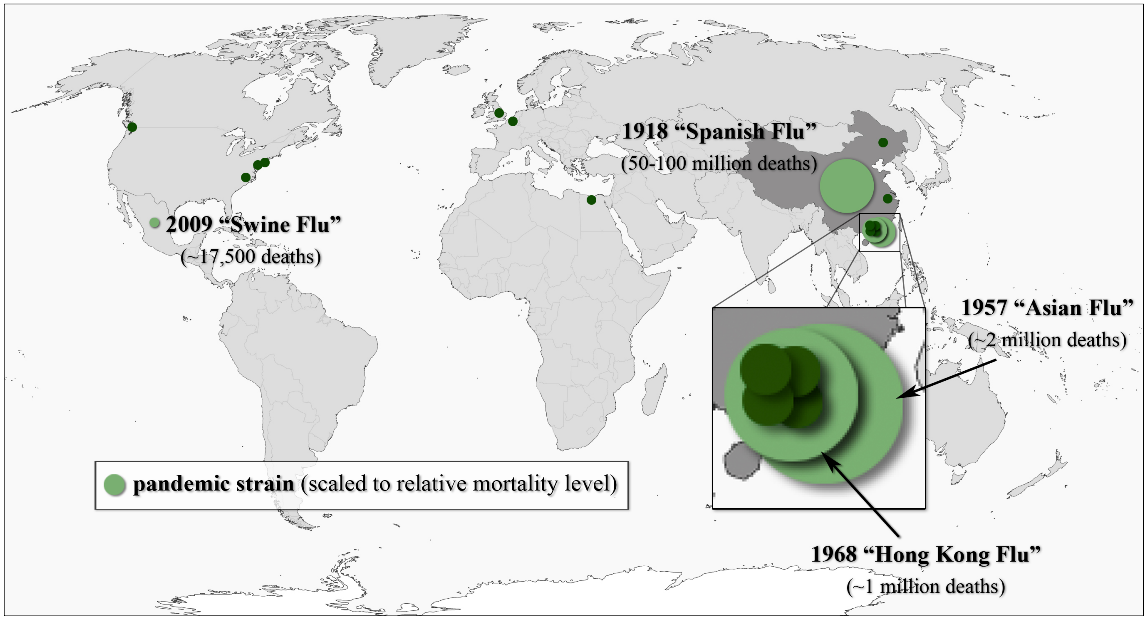
Source: Food and Agricultural Organization (http://www.faostat.org/).

In history, there have been several notable moments when trade and travel have bridged the natural epidemiological discontinuities created by geography. The most famous of these is the Black Death of the 13th-14th Centuries, during which the plague bacillus *Yersinia pestis* spread from China to Europe along trade routes maintained by the Mongol Empire. The same disease had also earlier spread across Eurasia from China in the 6th Century (Wagner et al., 2014). That outbreak, known as the Plague of Justinian, had killed tens of millions across the Mediterranean region and critically damaged the economic and geopolitical fortunes of the Byzantine Empire (McNeill, 1998). Not all epidemics have Chinese origins, though. Several centuries later, overseas expansion by European powers led not only to the political and economic subjugation of foreign peoples, but also to the introduction of many new species – pests and pathogens among them (Crosby, 1986). The growth of maritime trade facilitated massive movements of people, plants, and animals, as well as the pathogens that these passengers and cargo carried, across the world's oceans. The so-called Columbian Exchange had particularly severe effects on human health on both sides of the Atlantic. Old World diseases such as smallpox, typhoid, typhus, and measles were introduced to the Western Hemisphere by colonizers, resulting in significant depopulation and a decisive shift in the balance of power (Crosby, 2003; Diamond, 1999; McNeill, 1998).

Nevertheless, China has remained a persistent and important source of infectious zoonotic disease. For instance, a plague outbreak in southwestern China engulfed the country and then spread to the rest of the world in the late 1800s. The spillover was likely mediated by rat-borne fleas, brought into contact with people due to ecological encroachments from settlement expansion (Benedict, 1996). This plague first spread to the port cities of the Chinese coast and thence to Southeast Asia, the United States, and Europe. In the western U.S., the bacillus remained epizootic among rodent species well into the 20th Century (McNeill, 1998).

The archetypal modern pandemic – the one that remains a touchstone for thinking about global infectious disease risk – is the 1918-1919 Spanish Flu. The severity of this pandemic was in large part a result of the integration forced by global conflict. Propagated by the movements of millions of servicemen during and after World War I, this strain of H1N1 influenza may have infected as many as 500 million people, or a quarter of the world's population, and killed as many as 50-100 million (Taubenberger and Morens, 2006). Recent forensic studies tracking mortality rates and other contemporary evidence suggest that, contrary to its name, this pandemic actually originated in China (Humphries, 2014; Langford, 2005). Indeed, China has been the epicenter of influenza both before and after the “Spanish Flu”. At least two of four historically documented pandemics originated in China before 1918, as did both of the subsequent pandemics (Potter, 2001) (Figure 5).

Figure 5. The geographic distribution of confirmed outbreaks of novel and/or pandemic influenza strains since 1900. Of the four pandemic strains, three emerged in China.



The mechanism behind the global spread of diseases after 1918 has been the ever-closer integration of the world economy. Habitat suitability and transport distance determine the potential dispersal patterns of infectious disease vectors(Tatem et al., 2006), while the relative costs and benefits of trade and infectious disease determine the likelihood that pathogens will be spread this way (Perrings, 2014). The potentially high cost of the SARS epidemic led to prompt preventive action, but the volume of travel meant that the pathogen still managed to reach every continent. In East Asia alone, SARS resulted in at least a 2% decline of GDP (Brahmbhatt, 2005). It has been estimated that the economic losses from a major influenza pandemic could be as high as $7.3 trillion (12.6% of global GDP) – a downturn on par with the Great Depression – and cause over 140 million deaths (McKibbin and Sidorenko, 2006).

2.5. Policy Implications of China's Zoonotic Disease Risks

Given its role as the "cradle of influenza" (Davis, 2005), and many other zoonoses, China should be a focus of international efforts to mitigate future infectious disease risk. It is likely that the factors that facilitated the global spread of the 1894 plague and the 1918-1919, 1957, and 1968 influenza pandemics that originated in China are even more forceful today. The lesson of recent decades is that zoonoses such as HPAI, SARS, and Ebola cannot be reliably contained at the local, national, or even continental level. It follows that infectious disease risk mitigation is a product not only of the probability of emergence, but also of the probability that an outbreak will be propagated to other parts of the world.

Design and implementation of risk mitigation strategies require an understanding of the factors affecting the probability that zoonoses will emerge, and the likely pattern of their spread (Castillo-Chavez et al., 2015; Daszak, 2005; Daszak et al., 2001; McMichael, 1999, 2004). With regard to China, in particular, this involves understanding the way that income growth, urbanization, and globalization interact with predisposing socio-ecological conditions (including changes in the interface between wild and domestic species, and cultural practices surrounding the consumption of those species) to alter the likelihood of emergence.

We also need an improved understanding of the role of more widespread processes in changing epidemiological environments. Climate change is expected to alter ecosystem processes and functioning in ways that will influence the emergence and re-emergence of infectious diseases worldwide (Morens et al., 2004; Piao et al., 2010), particularly for vector-borne pathogens (Chretien et al., 2015; Hales et al., 1999). In China, climate change, including changes in the El Nino-Southern Oscillation (ENSO), is expected to increase human vulnerability to a spectrum of infectious diseases such malaria, dengue, and Japanese encephalitis (Bai et al., 2013; Bi et al., 2005). Mitigating the infectious disease risks of climate change – both for vector-borne and directly-transmissible zoonoses – requires a deeper understanding of how it interacts with urbanization and globalization to alter the vulnerability of human populations (Tong et al., 2015). Encouragingly, a recent survey of provincial public health workers in China found that the large majority had "accurate" (i.e., in line with existing scientific consensus) perceptions and knowledge about climate change and its likely impacts on infectious diseases (Wei et al., 2014).

A second requirement for successful policy is to look beyond standard epidemiological measures for risk indicators. For avian influenza, outbreaks among wild birds, poultry, and people reveal patterns that suggest new indicators (Figure 2). The urban areas bestriding the Pearl River and Yangtze River deltas were the emergence areas for H5N1 and H7N9, respectively. Empirical studies have shown how both outbreaks were facilitated by similar socio-ecological changes (as discussed in preceding sections). Because of this, it has been argued that wet markets could be used as an early-warning system to detect emerging zoonoses (Webster, 2004), and that control measures could focus on the norms and incentives underlying human-to-animal interactions in the marketplace (Gao, 2014; Goldman et al., 1999; Pi et al., 2014; Woo et al., 2006).

A third requirement is to enable public health infrastructures to respond to a range of threat indicators. SARS and HPAI, and the experiences of dealing with other zoonotic risks in recent years, have motivated Chinese policymakers to improve their capacity to respond to emerging infectious diseases. Responsiveness, information dissemination, and infectious disease surveillance have all improved since the initial SARS and H5N1 outbreaks (Wang et al., 2008). The Ministry of Health has created the world's largest online, real-time, case-based reporting system, called the China Information System for Disease Control and Prevention, with coverage from the national down to the county level (Gong et al., 2012; Li et al., 2012a; Li et al., 2012b; Wang et al., 2008). This system is connected to a network of Center for Disease Control and Prevention (CDC) institutes (http://www.chinacdc.cn/en), which collaborates with government-funded labs and other academic organizations focused on zoonotic diseases (Wang et al., 2008; Zhang et al., 2008). As of 2014, there were 3,490 CDC institutes across China (NBS, 2015). Nonetheless, surveillance and the overall public health infrastructure still has several weaknesses, namely under-coverage of rural areas (where zoonoses, particularly those borne by livestock, may originate), lack of training for health professionals in poorer areas, and a low per-capita level of funding (Tong et al., 2015).

Indeed, these weaknesses may have been reflected in the fact that management of zoonotic diseases has largely been ad hoc. The reactions to HPAI outbreaks included widespread wet market closures and trade restrictions. While this limited the spread of H7N9 after its initial occurrence (He et al., 2014; Webster, 2004; Yu et al., 2014), it was also very costly to authorities, vendors, and consumers, and is unsustainable as a policy framework for the long run (Gao, 2014). Additionally, given the significant traditional values attached to wet markets and the live animal trade, policies of that kind may abrade cultural sensibilities. For instance, abrupt and prolonged closures of live animal markets may deprive people of a traditional venue for social interaction (Gao, 2014; Goldman et al., 1999; Woo et al., 2006). Improving public awareness and knowledge has been one form of intervention, but more generally, management has tended to take the form of response rather than prevention. But given the changing zoonotic risks, mitigation (e.g., management at the human-animal-wildlife interface in anticipation of mutation and spillover) is likely to be more cost effective than adaptation (e.g., reducing contact rates through social distancing and trade and travel restrictions after an outbreak) (Pike et al., 2014).

A fourth requirement is to build the collective capacity to mitigate international risk. Evidence that this has received higher priority in recent times is China's greater involvement in World Health Organization (WHO) initiatives (Wang et al., 2008; Zhang et al., 2008). The U.S. Agency for International Development also has active programs in China assessing the risks of emerging zoonoses (e.g., the Emerging Pandemic Threats program: http://www.usaid.gov/ept2/). Such ventures may provide an important medium for "science diplomacy" – i.e., using research collaboration and the exchange of ideas as a platform to improve geopolitical relationships – between the two largest economies, and trading nations, in the world (Hoetz, 2012). Additionally, Chinese health workers have, since 2001, received training from the WHO and the U.S. Center for Disease Control, although as of 2014 only 194 had graduated from the program (Tong et al., 2015). As with domestic disease surveillance and management efforts, this has implications for the allocation of resources needed to support initiatives and institutions.

Finally, the underlying research efforts to model risk at different spatial scales and inform policy need to include factors that affect not only the abundance of susceptible, latent, infectious, and recovered individuals, but also the likelihood of contact and transmission. There would be value in exploiting a class of models in economic epidemiology that addresses the decisions made by people and policymakers that affect the likelihood of both host contact and infectious disease transmission (Perrings et al., 2014). Income growth, rising trade in goods and services, and the demographic and land-use changes caused by urbanization all affect private infectious disease risk management, and so should inform the public response. The development of infectious disease models for China that capture such risk factors would have the potential both to enhance management domestically, and to comprehend the risks from trade and travel links with the rest of the world.

In certain respects, the nature of infectious disease risk mitigation is similar to the nature of climate change mitigation. In both cases, there is a closing window for timely action. In both cases, too, the mitigation of global risk depends heavily on the efforts of a small number of countries, each of which has a disproportionate impact on global risk

(Pike et al., 2014). To that end, improving the management of infectious disease risk in China is a necessary, though not sufficient, condition for managing such risks globally.

6. Concluding Remarks

It has been argued that the world has been undergoing an epidemiological transition, in which rising incomes and the dissemination of improved technologies and good practices has shifted the burden of disease away from communicable towards non-communicable diseases (McKeown, 2009; Sepulveda and Murray, 2014). In part this is because development generates greater resources for biosecurity and the prevention and treatment of infectious disease. There is ample evidence that an epidemiological transition is underway in China. Rising affluence has lessened the burden of infections that once were socially devastating, such as malaria and tuberculosis, but has increased non-communicable diseases, such as cancer, heart disease, and obesity (Yang et al., 2008). At the same time, globalization has increased the potential for domestic infections to be exported to countries where infectious diseases are still the greater part of the disease burden (Bygbjerg, 2012). Indeed, emerging infectious diseases have been identified as one of a few “catastrophic risks” facing humanity in the 21st Century, especially for developing countries (Rees, 2013). In China – which, despite its remarkable development in recent decades remains an “emerging” economy – novel zoonotic risks have accompanied the classic health trends of the epidemiological transition (Cook and Drummer, 2004).

Large developing countries such as India, Indonesia, and Nigeria have a similar set of pre-disposing socio-ecological risk factors to China – e.g., large and growing human and livestock populations, high levels of interaction between species, and large-scale ecological change. As the forces of economic modernization accelerate, so could the zoonotic risks that such countries face. Unlike China, many of these countries are still in the early stages of the epidemiological transition. While they are becoming more exposed to disease risk through the growth of trade and travel, they still experience many of the public health conditions that increase vulnerability to infections. For instance, "silent epidemics" – i.e., those caused by high-risk pathogens that have not received international attention, and that are only pervasive at a local scale – may yet flare into epidemics of global impact. A salient example is buffalopox, an emerging and re-emerging zoonosis that has recorded many animal outbreaks and human cases in South Asia. The pathogen dynamics indicate a reasonably high level of transmissibility between livestock and people, and the forces of income growth, urbanization, and globalization could contribute to its further spread (Singh et al., 2007; Venkatesan et al., 2010).

The degree to which China's public health authorities and researchers, along with their international collaborators, keep pace with income growth, urbanization, and globalization – and how these changes interact with China's pre-disposing socio-ecological conditions – will be a major force shaping global epidemiology. China is not the only emerging infectious disease hotspot, but it is among the most important. As the world continues to navigate a potentially new era for infectious diseases, the management of risk in China will be critical to the management of risk everywhere.

CHAPTER 3

A PROVINCIAL-LEVEL ANALYSIS OF HIGHLY PATHOGENIC H5N1 AVIAN INFLUENZA RISKS IN CHINA

*A version of this chapter was published in *Philosophical Transactions of the Royal Society B* in 2017 as “Conservation, Development, and the Management of Infectious Disease: Avian Influenza in China, 2004-2012,” with my advisor Dr. Charles Perrings.

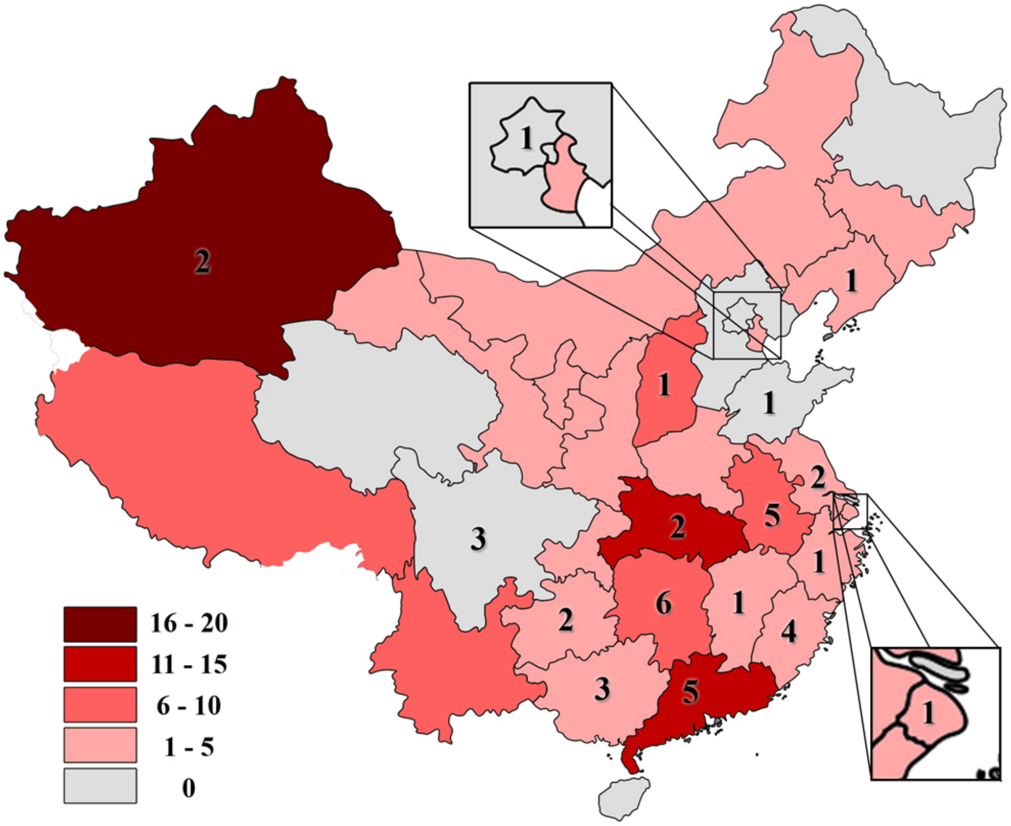
3.1. Introduction

A common ecological consequence of economic development is the promotion of some species and the suppression of others (Millenium Ecosystem Assessment, 2005). Crops, livestock, and positively valued wild species are promoted along with the ecosystems on which they depend. Pests, pathogens and their vectors are suppressed. The ecological context within which such decisions are taken, however, means that there are tradeoffs to be made. The promotion of domesticated species frequently compromises the existence of wild species. Similarly, the conservation of wild species can threaten domesticated species. Aside from competitive or predatory interactions between wild and domesticated species, the susceptibility of both to common pathogens means that either can impact the disease risks faced by the other. A change in disease risk for domesticated species, for example, is amongst the potential benefits or costs of a change in the abundance of wild disease vectors and host species. The dilution effect explored in several papers in this special issue is an example of the benefits from increasing the richness and abundance of wild reservoirs (Faust et al., 2017; Kilpatrick et al., 2017a; Millins et al., 2017; Wood et al., 2017). Conversely, the transmission of zoonotic and enzootic diseases to domesticated species in proximity to wild reservoirs is an example of the costs. Both may be influenced by the patterns of land use change associated with economic development and urbanization (Jones et al., 2013; McMichael, 2004; Wood et al., 2017).

In this paper I consider the relationship between poultry production, waterfowl conservation, and the risks posed by highly pathogenic avian influenza H5N1 (henceforth H5N1) in a rapidly developing and urbanizing economy. More particularly, I model the risk of H5N1 outbreaks in both poultry and people as a function of land use change, urbanization, commercial integration, biosecurity and public health in China. H5N1 was first identified in China in 1996, and has since posed a threat to both animal and human health nationally and internationally (King et al., 2006; Pfeiffer et al., 2011; Wang et al., 2008). The pathogen has spread throughout China, with poultry outbreaks and human infections nearly ever year (see Figure 6), each of which poses a risk to the rest of the world (Davis, 2005). In addition to a high mortality rate for human cases, infections are fatal to both waterfowl and domesticated birds, thereby having the potential to cause significant ecological and economic damage (Thomas and Noppenberger, 2007).

Figure 6

Total H5N1 poultry outbreaks and human cases across mainland Chinese provinces, 2004 – 2012. The shades of red represent the number of poultry outbreaks. The black numerals within the provinces indicate the number of human cases.



Sources: Emergency Prevention System for Animal Health (EMPRES). Food and Agriculture Organization of the United Nations (FAO) and World Organization for Animal Health (OIE). URL: http://empres-i.fao.org/eipws3g/.

In order to understand H5N1 risks, I consider two sets of risk factors. One is the set of environmental factors that determine the likelihood of contact and pathogen transmission between wild and domesticated birds. The other is the set of socioeconomic factors that determine value at risk and hence the biosecurity measures taken to reduce the probability of infection. Amongst environmental factors, most attention has been focused on the abundance and distribution of wild birds. These factors include vegetation cover, surface water, and climate (Gilbert and Pfeiffer, 2012). Less attention has so far been paid to socio-economic factors affecting the abundance and distribution of domesticated poultry, and the biosecurity measures applied in their production and marketing. This is partly due to limitations of the available data. Many socio-economic data are reported at the national level and, unlike biophysical variables, cannot be ascertained by remote sensing, or are not readily disaggregated into finer-grained units. There are, for example, few studies of the role of socio-economic risk factors at provincial (the unit of analysis in this paper) or local scales (Gilbert and Pfeiffer, 2012). Yet many environmental management and public health decisions that affect disease risks are devolved to sub-national levels (Qi et al., 2008; Qi and Zhang, 2014).

3.2. Avian Influenza Risk Factors

High rates of interprovincial inequality[1] across a range of development indicators are a defining feature of economic growth in China (see Table 1) (Jones et al., 2003). Provinces differ greatly in their infrastructure, industrial composition, and average income (Li and Xu, 2009; Sun, 2013). This unevenness reflects differences in both the distribution of natural resources (Demurger et al., 2002), and patterns of human-

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[1] In China, municipalities – Beijing, Shanghai, Chonqing, and Tianjin – and “autonomous regions” – e.g., Inner Mongolia and Xinjiang – are on the same level of the administrative hierarchy as “standard” provinces; all three categories are considered “provincial units,” but will be referred to as provinces in this paper for simplicity.

environmental interaction. This is reflected in the existence of distinct "macroregions" dating back several centuries (Cartier, 2002; Pomeranz, 1993; Skinner, 1977, 1985). As Spence (1982) observed, such historical "units in some cases coincid[e] with actual provinces… where combinations of economic and geographic factors gave rise to a kind of local cohesion." Provincial differences are central to understanding China's development; recent studies have examined a range of issues within the framework of interprovincial inequality, including migration (Taylor, 2011), water flows embodied in commodities trade (Dalin et al., 2014; Jiang et al., 2015b), energy and embodied carbon flows (Feng et al., 2013; Li et al., 2014; Qi et al., 2013). Additionally, as this paper will show, China's interprovincial differences have implications for the dispersal and persistence of pathogens (Hogerwerf et al., 2010).

Table 1

Development Indicators of Mainland Chinese Provincial Units, 2013.

Province	Area (km^2)	Population	Nominal GDP per capita	Urbanization (% population)	Human Development Index (2010)*
Beijing	16,411	20,693,000	¥93,213	86%	0.821
Tianjin	11,917	14,131,500	¥99,607	82%	0.795
Hebei	188,434	72,875,100	¥38,716	48%	0.691
Shanxi	156,711	36,108,300	¥34,813	53%	0.693
Inner Mongolia	1,155,092	24,898,500	¥67,498	59%	0.722

Liaoning	148,064	43,890,000	¥61,686	66%	0.740
Jilin	184,400	27,504,000	¥47,191	54%	0.715
Heilongjiang	452,645	38,340,000	¥37,509	57%	0.704
Shanghai	6,340	23,804,300	¥90,092	90%	0.814
Jiangsu	102,600	79,199,800	¥74,607	64%	0.748
Zhejiang	104,141	54,770,000	¥68,462	64%	0.744
Anhui	140,126	59,880,000	¥31,684	48%	0.660
Fujian	124,016	37,480,000	¥57,856	61%	0.714
Jiangxi	166,894	45,039,321	¥31,771	49%	0.662
Shandong	156,700	96,849,700	¥56,323	54%	0.721
Henan	165,536	94,060,000	¥34,174	44%	0.677
Hubei	185,888	57,790,000	¥42,613	55%	0.696
Hunan	211,855	66,389,300	¥36,763	48%	0.681
Guangdong	179,757	105,940,000	¥58,540	68%	0.730
Guangxi	237,558	46,820,000	¥30,588	45%	0.658
Hainan	35,354	8,865,500	¥35,317	53%	0.680
Chongqing	82,269	29,450,000	¥42,795	58%	0.689
Sichuan	485,000	80,762,000	¥32,454	45%	0.662
Guizhou	176,153	34,840,700	¥22,922	38%	0.598
Yunnan	383,194	46,590,000	¥25,083	40%	0.609
Tibet	1,228,400	3,076,200	¥26,068	24%	0.569
Shaanxi	205,800	37,530,900	¥42,692	51%	0.695
Gansu	454,000	25,775,500	¥24,296	40%	0.635
Qinghai	721,000	5,731,700	¥36,510	49%	0.638
Ningxia	66,000	6,471,900	¥39,420	52%	0.674

Xinjiang	1,664,897	22,327,800	¥37,181	44%	0.667

* HDI scores for Chinese provinces were only calculated for 2010; >0.800 = “very high human development”; 0.800 – 0.700 = “high human development”; 0.700 - 0.550 = “medium human development”

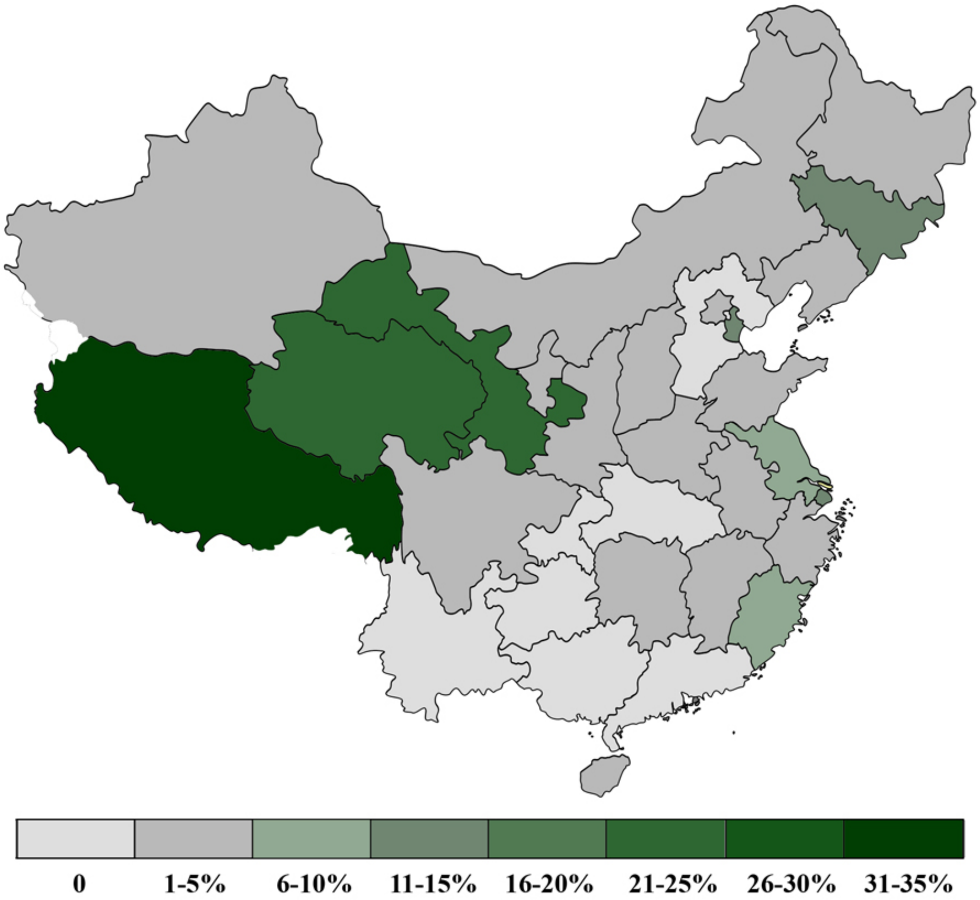
Sources: Chinese National Bureau of Statistics (2014); United Nations Development Program (2013)

Interspecies transmission of enzootic and zoonotic diseases is in large part driven by human activities that bring susceptible and infected animals into contact, especially at the interface between domesticated and wild systems (Daszak et al., 2000; Rahman et al., 2013). At the global scale, there is considerable evidence that the risk of emergence of enzootic and zoonotic pathogens is closely related to development status (Chan et al., 2013; Jones et al., 2008). Changes in land use associated with economic development bring both people and domesticated animals into closer contact with wild disease reservoirs. Amongst predisposing ecological conditions for the interspecies transmission of avian influenzas, the most frequently cited factors are the migration and behavior of wild birds. Migratory birds, particularly waterfowl, are argued to be responsible for both the long-distance (e.g., across Asia) and short-distance spread of avian influenza, infecting other wild bird populations as well as free-ranging poultry (Chen et al., 2005a; Gilbert and Pfeiffer, 2012; Prosser et al., 2011; Si et al., 2009). Several major bird migration routes traverse China, and the country is a major destination for wintering and breeding birds. Although economic development has taken a toll on biodiversity in China, the country’s wild bird populations have remained robust, stabilizing in numbers between 1970 and 2000 and increasing by over 40% since the turn of the millennium (Xie et al., 2015).

Lakes and wetland areas have been cited as points at which migrating waterfowl and domesticated ducks come into contact, leading to the spread of avian influenza (Fang et al., 2008; Martin et al., 2011; Si et al., 2013b; Si et al., 2010). Poyang Lake, the country's largest freshwater lake and an important habitat for migratory waterbirds, is a frequently cited example. A total of 310 species have been recorded in the area and it hosts approximately 1 million wintering birds (Ji et al., 2007). At the same time, extensive livestock farming surrounds the lake. Qinghai Lake, China's largest saltwater lake, is another important destination for migratory birds. In 2005, during the first major H5N1 outbreak among wild birds in the area, the population of bar-headed goose dropped by 5-10% (Kou et al., 2009). To assess the influence of wild migratory birds, I use the subset of Bird Life International-designated "Important Bird and Biodiversity Areas" (IBA) for congregatory and migratory waterbirds (see Figure 7). Both Poyang Lake and Qinghai Lake have been identified under this classification. Similar data were used in an earlier study of H5N1 spread at the national level in Europe (Kilpatrick et al., 2006).

Figure 7

The percentage of each province covered by “Important Bird and Biodiversity Areas” designated for migratory birds (Bird Life International).



Aside from lakes and wetlands, agroecosystems are also potentially implicated in disease emergence—the interspecies transmission of infectious epizootic and zoonotic diseases. The geographically uneven pattern of economic development has resulted in similarly uneven patterns of land-cover in China (Carter and Lohmar, 2002). More specifically, land-use changes are argued to have turned particular provinces into “agro-ecological niches” conducive to the establishment and persistence of H5N1 among both people and livestock (Hogerwerf et al., 2010; Wallace et al., 2010). Irrigated rice fields in China are at once habitats for wild birds, ducks, poultry and people, and consequently may increase the probability of interspecies influenza transmission. In particular, free-grazing ducks in rice-cropping areas have been argued to act as a conduit for H5N1 infections (Gilbert et al., 2008; Martin et al., 2011; Paul et al., 2010).

The relationship between economic development and the risk that novel diseases will spread among domesticated animals or people is less well understood (Alirol et al., 2011; McMichael, 2004; Wilcox et al., 2004). From an economic perspective, factors affecting spread risks include measures taken by people to alter either the probability of contact between infected and susceptible birds, or the probability that contact leads to infection (Perrings et al., 2014). These measures in turn depend on the value at risk (Perrings et al., 2014). Value at risk refers to potential losses, usually accounted for in monetary terms, caused by an outbreak or an epidemic. In the case of H5N1, this includes mass deaths of infected or culled poultry, or the medical costs and lost productivity from human cases (Qi et al., 204). Biosecurity and public health measures adopted to protect value at risk include both measures adopted in the production and distribution of domesticate animals, and the establishment of preventive and curative health institutions aimed at reducing both the likelihood and the impact of infection (Fabre and Rodwin, 2011; Gong et al., 2012).

There is some evidence that the growth of public health infrastructure in China has not kept pace with increasing infectious disease risks. For example, immunization of urban populations against common infections is increasing, but not at the rate of urban immigration (Gong et al., 2012). Nonetheless, since the first outbreaks of H5N1 and the

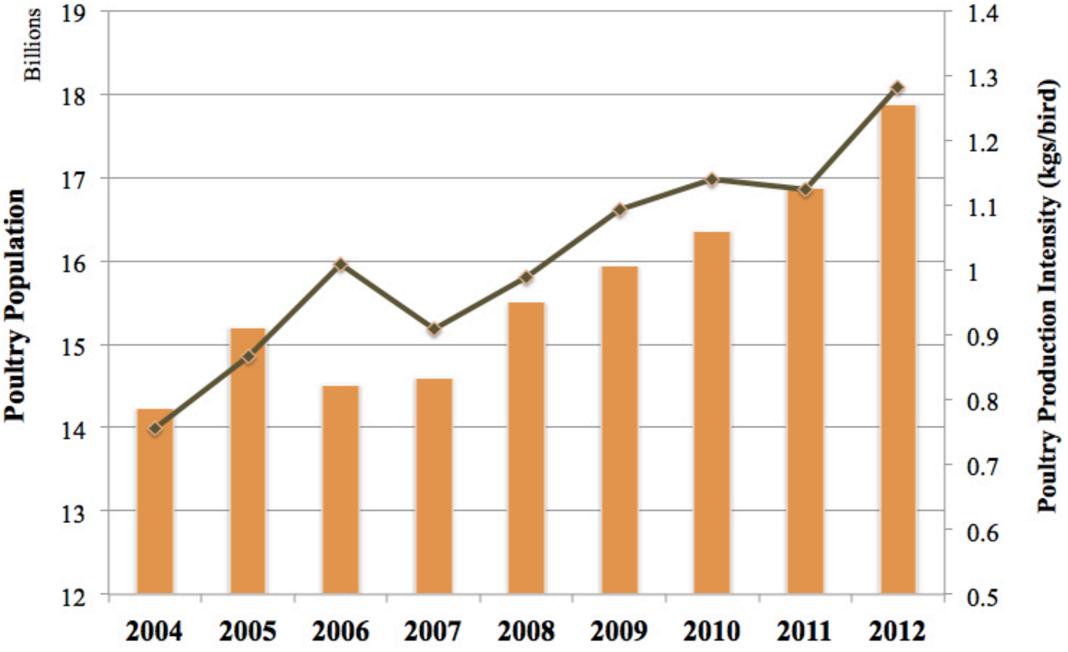
SARS epidemic, Chinese public health authorities have improved both their responsiveness and effectiveness (Wang et al., 2008). The Chinese Center for Disease Control and Prevention (CDC) has a network of institutes across all provinces to prevent and manage epidemics, along with an extensive internet-based surveillance system (Gong et al., 2012; Wang et al., 2008; Zhang and Atkinson, 2008). As of 2014, there were 3,490 CDC institutes in China (National Bureau of Statistics, 2015), implementing an infectious disease surveillance system that is the largest in the world (Gong et al., 2012; Li et al., 2012a).

At the national level, one proxy for value at risk from human disease is per-capita income, and the same measure can be used to signal interprovincial differences. Value at risk from animal diseases is more often measured by the value of trade that may be disrupted as a result of outbreaks. Internationally, the relationship between the growth of trade and travel and disease risk is well understood (Patz et al., 2004; Tatem et al., 2006). Nationally, the trade and travel at risk is harder to measure, but may be proxied by the growth of transport infrastructure such as air, road and rail networks, and of the vehicles that use them. The Pearl River Delta, where H5N1 was discovered, is a prime example: in 1990 there were only 16 km of expressways, but by 2020 there will be over 6,100 km (Hou and Li, 2011). Nationally, highways grew from 1.87 million km to 4.24 million km between 2004 and 2012. As with other indicators, however, road networks vary across provinces, with the more urbanized and affluent coastal provinces – e.g., Guangdong – having a more extensive infrastructure than the less urbanized and affluent inland provinces.

A measure of the local trade at risk from H5N1 outbreaks is given by size of the poultry sector, the growth of which is closely related to economic development. As incomes have grown in China, so has the demand for protein. This has led to the expansion and intensification of poultry production. Figure 8 shows that in the period covered by this study, poultry numbers grew at an average rate of 2.95% per year. Nor is the rate of growth slowing significantly. Over the coming decade, per-capita consumption of poultry is expected to grow by 2.4% annually (Westcott and Trostle, 2014). Economic development has been accompanied by the industry's modernization, with poultry farming becoming increasingly concentrated in industrial facilities where production is more standardized and mechanized (Pi et al., 2014). At the same time, backyard farming, which was likely the historical socio-ecological "engine" of avian influenza emergence and spread in China, has been on the wane (Cardona et al., 2009).

Figure 8

The annual population of poultry in mainland China from 2004 to 2012 (bars) and the changes in poultry production intensity – i.e., average weight of a bird – over the same period (line).



Sources: National Bureau of Statistics of China (NBS), 2005-2013. China Livestock Statistical Yearbooks. China Statistics Press, Beijing. URL: http://www.stats.gov.cn/.

3.3. Data and Methods

Our data comprise a balanced panel of provincial observations on a range of risk factors over the interval 2004-2012. The panel allowed us both to explore a range of risk factors, and to analyze the risk consequences of heterogeneity among provinces. The 2004-2012 timeframe was chosen for several reasons. First, 2004 was the year of a major outbreak of H5N1 on the Chinese mainland, likely constituting the re-emergence of the disease, since it is epidemiologically discontinuous from earlier outbreaks in the late 1990s. It was also one year after the end of the SARS epidemic, a watershed moment that prompted increased attention to infectious disease risks from policymakers and the general public. The endpoint of 2012 was chosen because it was the year before the emergence and rapid spread of H7N9 in China. This strain is epidemiologically distinct from H5N1, particularly in its effects on poultry and other bird species. The years 2004-2012, therefore, constitute a distinct period in which H5N1 was the primary avian influenza – if not the primary overall infectious disease – threat to livestock and people in China.

Our observations on disease outbreaks and risk factors at the provincial level derive from three primary sources: the United Nations' Food and Agricultural Organization (FAO), the World Organization for Animal Health (OIE) and China's National Bureau of Statistics (NBS). Most data on all environmental and socio-economic risk factors were taken from the annual statistical yearbooks published by the NBS, which provide data down to the provincial level. Poultry comprise all main domesticated bird species: chickens, ducks and geese. Currently, chickens account for 70 percent of meat production, while ducks and geese each account for about 15 percent (Bingsheng and Yijun, 2007). Data on poultry outbreaks and human cases were gathered from the Emergency Prevention System for Animal Health (EMPRES) reporting system, a joint project of the FAO and OIE (Welte and Teran, 2004). Data on important bird and biodiversity areas in China were taken from Bird Life International (Bird Life International, 2016). Many of these data were in turn subject to unit conversions for the sake of processing and interpretation, e.g., from hectares to square kilometers. Most factors used in the analyses were also converted into density or per-capita measurements.

Generalized linear models (GLM) have been frequently used in the study of avian influenza epidemiology (Gilbert and Pfeiffer, 2012). For instance, these models have been used to identify high-probability areas for influenza reassortment (Fuller et al., 2013), for predicting the spread of H5N1 (Fang et al., 2008; Gilbert et al., 2008; Hogerwerf et al., 2010; Martin et al., 2011; Si et al., 2013b; Si et al., 2010), and for predicting the spread of H7N9 (Fang et al., 2013; Zhu and Peterson, 2014). The value of GLMs in epidemiological problems is that they allow tests of the statistical relationships between a numerical or binary dependent variable of disease outbreaks or cases and a set of risk factors. I estimated three GLM models of H5N1 risk in China. The first was a multivariate regression model quantifying the impact on H5N1 poultry outbreaks from the following risk factors: land area, the percentage of land covered by rice paddy, the percentage of land covered by IBAs for congregatory and migratory birds, a proxy for poultry production intensity (the average weight of birds produced for market in the different provinces) and a proxy for interprovincial trade (the density of commercial trucks on highways in the provinces). Land area is a confounding variable. Rice paddy and IBAs are our two hypothesized environmental mixing zones between wild waterbirds and poultry.

To assess whether I needed to control for the time-invariant characteristics of provinces I conducted a Hausman/overdetermination test for correlation between provincial errors and the regressors, which indicated the equivalence between a random-effects panel analysis approach and a pooled OLS regression. I favored the random effects/OLS approach because it allowed me to take explicit account of the influence of interprovincial differences on the likelihood of H5N1 outbreaks. While there were potentially significant temporal changes in risk factors – particularly in poultry numbers and income – I am more directly concerned with how differences across provinces determine the heterogeneity of risk. Relatedly, a random effects model estimates the impact of important provincial risk factors that are invariant across our timeframe – in this case IBAs – instead of just controlling for them. Nonetheless, I report the results for fixed-effects models as well.

The first estimated model was a multivariate linear regression, estimated using robust standard errors to account for heteroskedasticity:

$$P_{it} = \alpha_0 + \alpha_1 x_{1it} + \alpha_2 x_{2it} + \alpha_3 x_{3it} + \ldots + u_i + \varepsilon_{it} \ , \tag{1}$$

in which P_{it} denotes the number of poultry outbreaks in province i at time t, x_{jit} is observations on risk factor j in province i at time t, and u_{it} and ε_{it} are 'between' and 'within' provincial errors respectively[2]. The second model estimated was focused more directly on risk. Using the same set of risk factors I estimated a negative binomial regression model, in order to calculate incidence rate ratios. While both Poisson and negative binomial models are candidates for analyzing risk using count data, I selected the negative binomial because the data for poultry outbreaks turned out to be

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[2] I also conducted a regression was clustered standard errors, grouped by regions – e.g., provinces along the Yangtze River were grouped together, while those in the northwest and northeast constituted separate regions. This was done to account for potentially unobserved influences from geophysical and economic correlation among adjoining provinces. However, the results, including both coefficient values and significance levels, were almost identical to those from the first model, so I chose not to report them.

overdispersed – i.e., the variance was much higher than the mean. For Y_{it} ~ Negative binomial (θ_{it},κ), the model took the form:

$$\theta_{it} = \exp\left[\alpha_0 + \alpha_1 x_{1it} + \alpha_2 x_{2it} + \alpha_3 x_{3it} + \ldots + u_i + \varepsilon_{it}\right] . \tag{2}$$

The third model focused on the linkage between human and poultry cases. Nearly every epidemiologically investigated human case in China identified exposure to infected poultry as the proximate reason for infection (Woo et al., 2006; Yu et al., 2007; Yu et al., 2014). To model this wild bird/environment-to-poultry-to-human sequence of infection, I employed a two-stage least squares (2SLS) regression approach. The epidemiological logic is similar to the study by Chen et al. (2013), which used 2SLS regression to model human mortality from exposure to airborne pollutants in major Chinese cities (Chen et al., 2013). The first stage estimated the relationship between poultry outbreaks and the same set of regressors as in model 1 (equation 1). The second stage was of the general form:

$$Y_{it} = \beta_0 + \beta_1 P_{it} + \beta_2 z_{1it} + \beta_3 z_{2it} + \ldots + \mu_i + \varepsilon_{it} \ , \tag{3}$$

where Y_{it} is the number of human cases, P_{it} is the number of poultry outbreaks and z_{jit} is observations on second-stage risk factor j in province i at time t. Independent risk factors in this stage were human population (confounding variable), percent urban population, per-capita GDP and the number of CDC institutes. These risk factors were chosen because of their direct impacts on human public health. An overidentification test was run, and the resultant Sargan-Hansen test statistic had a p-value of 0.371. This fails the five-percent significance test, meaning I fail to reject the null hypothesis of instrument validity, and implies that random effects regression is appropriate.

3.4. Results and Discussion

The results of all three models are reported in Table 2. In model 1, I found all five risk factors to be statistically significant at the 5% level: land area, the extent of rice cultivation, the extent of IBAs for migratory and congregatory waterbirds, poultry production intensity and commercial truck density on highways. Many of the results conformed to expectations. Risks were found to be increasing in land area. Larger provinces generally experienced more outbreaks. They were also increasing in the proxy for trade levels, commercial highway traffic density. A one-percent change in commercial truck density is associated with a 0.05 percent increase in H5N1 poultry outbreaks. This result is consistent with other studies of H5N1 in Asia that have identified transport infrastructure, and particularly highways, as sources of spread risk (Fang et al., 2008; Paul et al., 2010).

Table 2

Results for models of provincial-level risk factors of H5N1 poultry outbreaks and human cases in China, 2004-2012. Regressor coefficients, and incidence rate ratios for negative binomial regression, are reported, with significance levels indicated by asterisks.

Variables	Units	Poultry outbreaks (robust SEs)		Poultry outbreaks (Neg. Bin.)		Human cases (2SLS)	
		RE	FE	RE	FE	RE	FE
Area	km^2	1.07×10^{-6}**	omitted	1.00**	1.00**		
Rice paddy	%land area	0.0267**	-0.433	1.06**	1.03		
IBA, migratory	%land area	-0.0352**	omitted	0.957**	1.03		

Poultry production intensity (log)	kg/bird	-0.821**	-1.40*	0.212**	0.519		
Commercial trucks on highways	vehicles/km	0.0498**	0.149**	1.09*	1.44**		
Poultry outbreaks [†]	presence/ absence					0.746**	-0.0790
Population	persons					6.33×10^{-9}**	5.66×10^{-9}
GDP per capita	¥/person					-5.25×10^{-6}*	-3.78×10^{-6}
Urbanization (log)	%population					0.282	-1.18
CDC institutes	institutes					-0.00154*	-0.000293
	Observations	278	278	278	215	248	248
	Within R^2	0.0190	0.0378			0.0450	0.0439
	Between R^2	0.4709	0.0151			0.4664	0.0248
	Overall R^2	0.0822	0.0010			0.1071	0.0138
	Rho	0.0000	0.8421			0.0293	0.4935

* statistically significant at the 10% level

** statistically significant at the 5% level

[†] Instrumented on area, poultry production intensity, rice paddy coverage, IBA for migratory birds and commercial truck density

Average poultry weight, a proxy for the intensification of poultry production, was found to have a negative effect. The industrialization of poultry production is an ongoing trend in China, and is progressively reducing the share of small-scale, backyard and other traditional forms of farming. Large-scale and mechanized production, while not without environmental and public health risks (Leibler et al., 2009), is more insulated from the wildlife-livestock interface of disease transmission – i.e., wild birds carrying influenza are less likely to come into contact with and thereby infect poultry in factory farms. Additionally, the modernization of production also allows it to be more effectively regulated, and Chinese authorities have taken steps in recent years to improve health safety in poultry production and marketing. The improvements in technology and management that have accompanied the industrialization of the poultry industry, for which poultry production intensification is a proxy, therefore are likely to have a mitigating effect on avian influenza risks (Pi et al., 2014).

The two habitat variables – percent rice cover and percent IBA for congregatory and migratory birds – were both hypothesized to be positively correlated with H5N1 outbreaks in poultry. The literature suggests that flooded rice paddies on the one hand, and lakes and wetlands on the other, are both mixing zones in which wild and domesticated birds can come into contact with each other and exchange pathogens. I had accordingly expected both to be positively correlated with outbreaks in poultry. As expected, the proportion of land under rice cultivation was positively correlated with H5N1 outbreaks in poultry. This is in line with the conclusions of earlier studies, as well as with basic intuition. As a ready habitat for both wild birds and free-ranging poultry, rice paddy is likely to facilitate infections between wild and domesticated birds.

What was not expected is that I found the proportion of land covered by IBAs to be negatively correlated with H5N1 outbreaks in poultry. This ran counter to expectations and conflicts with much of the literature. There may nevertheless be a sound ecological rationale. The mere presence of surface water and wetlands, as habitat for pathogen-carrying birds, should enhance the likelihood of an outbreak. However, as the size of a lake or wetland increases, the likelihood that wild birds make contact with domesticated birds or that contacts result in infection appears to decrease. Fang et al. (2008) found that smaller water and wetland habitats caused birds to congregate in greater density, increasing contact and the probability of transmission (Fang et al., 2008). More surface area dilutes waterfowl density, thereby decreasing opportunities for transmission. Additionally, lakes and wetland areas – "natural" habitats – may also offer an alternative to paddy, where free-ranging poultry are often prevalent. This segregation effect may be strengthened if the natural habitats are protected, as the majority of the IBAs in China are. The prohibition of agriculture in or near protected lakes and wetlands lowers the likelihood of mixing between wild and domesticated birds.

One potential point of interest – or concern – when comparing the results from random-effects regression with those from fixed-effects regression (aside from the fact that predictor variables were more statistically significant across the random-effects models), is that the coefficient on rice paddy was significant and positive for the former but negative and insignificant for the later. This appears counterintuitive, but the results are similar to those of Baltagi and Pinnoi (1995), a panel analysis of the economic output of U.S. states regressed on a set of state-specific variables (Baltagi and Pinnoi, 1995). The authors found the same coefficient sign change for the variable public investment, and concluded that this was due to the difference between the short- and long-run effects of the variable, with fixed effects capturing the former and random effects capturing the latter. Additionally, the low Rho value for random-effects regression, which measures the amount of variance due to inter-panel differences, points to random effects as being the more appropriate model.

Our second model was a negative binomial regression of H5N1 poultry outbreaks on the same set of risk factors as in model 1. The regression coefficients had the same signs as in the previous model, and again all five variables were statistically significant, with four at the 5% threshold and one at the 10% threshold. Incidence rate ratios (IRRs) are reported instead of coefficients in Table 2. An IRR measures relative risk, and can be interpreted as the factor change in H5N1 outbreaks resulting from a one-unit increase of the associated risk factor, holding all other factors constant. Therefore, the results indicate that a one-percent increase in rice paddy cover increases the number of poultry outbreaks by 6%, while the same increase in IBA cover lowers outbreaks by 4.3%. As a proxy for production intensity, a one-unit increase in the log-transformed value of average poultry weight (i.e., doubling the value) lowers the number of outbreaks by 79%. As a proxy for trade, increasing the density of commercial trucks by one vehicle per kilometer of highway increases poultry outbreaks by 9%.

In the third, 2SLS, model, I analyzed the risk factors for human infections (results also in Table 2). In this case I treated the presence or absence of H5N1 in poultry as an endogenous variable, and the independent variables analyzed in models 1 and 2 as instruments. I found that H5N1 outbreaks in poultry, instrumented on the same set of explanatory factors as in the first and second models, was statistically significant at the 5% level. This is as expected, fits both with epidemiological intuition and with existing medical case studies of human H5N1 infections (Yu et al., 2007). By implication, the risk factors that determine the likelihood of outbreaks in poultry also determine the likelihood of human infections.

Of the four second-stage independent variables, three were statistically significant: population size at the 5% level, and per-capita GDP and the number of CDC institutes at the 10% level. More people mean a larger pool of potential infections, and thus had a significant positive effect on human cases as expected. Per-capita income was selected as a proxy for value at risk. I expected this to be negatively correlated with H5N1 infections, since greater value at risk generates a stronger incentive to undertake preventive biosecurity measures. Our findings on the relationship between CDC institutes and H5N1 infections in people suggests that biosecurity measures have a significant role to play in mitigating human infections. Since the SARS crisis and the initial outbreaks of H5N1, policymakers have invested considerable attention and resources to improving CDC effectiveness (Gong et al., 2012; Li et al., 2012b; Wang et al., 2008). Additionally, Chinese public health authorities have expanded international collaboration to raise domestic standards, and have, for instance, sent CDC staff to receive training from the WHO and the U.S. Center for Disease Control (Tong et al., 2015). However, Chinese infectious disease management still has several weaknesses, including a lack of training for health workers in poorer areas and a low per-capita level of funding compared to international standards (Tong et al., 2015). Greater investment in public health infrastructure and management may help mitigate human infections from avian influenza.

Finally, caveats should be made about the data. As Hogerwerf et al. (2010) observe, H5N1 circulation among poultry may be partly undetected (Hogerwerf et al., 2010), and there is likely to be underreporting for both poultry and human infections. This may be particularly true for rural areas, where interactions at the human-livestock-wild bird interface are acute, but where infections are less likely to be diagnosed and reported to relevant agencies (as mentioned above, public health management in poorer areas of China often suffer from a lack of funding and training). Certainly, the ratio of reported human cases to the poultry outbreaks appears disproportionately low (41:118).

Furthermore, the discreteness of poultry outbreaks may not be clear-cut. The numbers of birds “at risk” and the numbers infected vary from 48 to 581,000 and from 2 to 82,000, respectively. Multiple outbreaks have also been reported at the same location, or adjacent locations, and on the same date. The extent to which these are separate incidents or are part of a larger, continuous outbreak may be blurred by observation and reporting error, which is difficult, if not impossible, to recognize and rectify after the fact. Nonetheless, this dataset offers one of the best available tabulations of H5N1 infections; and the models presented represent, at the very least, a reasonable approximation of a complex epidemiological, ecological and economic phenomenon.

3.5. Conclusions

Returning to the conservation question I posed at the outset, our findings have two broad implications for the effect on avian influenza risk of bird habitat. First, since the correlation between outbreaks and rice paddy is positive, H5N1 risk may be treated as amongst the external costs of the use of paddy as habitat for domesticated birds. The marginal external disease costs of paddy are positive. This is due to the fact that paddy enables close enough contact between domesticated and migratory waterfowl so that the presence of infected birds poses a risk to susceptible birds. Management of domesticated birds to reduce contact with wild birds in paddy would address this risk.

The second, unexpected, finding is that the correlation between outbreaks and IBAs is negative, implying that the marginal infectious disease cost of IBAs is negative. . An increase in the area covered by IBAs for migratory and congregatory waterbirds, other things being equal, is associated with a reduction in the risk of H5N1 outbreaks in poultry. While the exact mechanisms behind this result are beyond the scope of this study (they are being explored in another, finer-grained study by the authors), the implication is that an increase in (protected) natural lakes and wetlands on flyways does not threaten the health of poultry populations (and consequently the livestock industry). At the margin, there are no disease costs to offset against the conservation benefits of such areas.

Our results on the relation between economic development and infectious disease risks are less unexpected. While growth in trade and transport volumes, and the concentration of people in urban areas are both risk-increasing, the improved biosanitary conditions that come with agricultural intensification, and the investment in public health facilities, are risk-reducing. They are associated with a reduction in the risk of infectious disease outbreaks amongst animals and people alike. Per capita income growth is closely associated with trade growth, and hence with the disease risks from trade, but it is also associated with many changes that have positive implications for human and animal health. The modernization variables in our set are all negatively correlated with disease risk.

CHAPTER 4

BIODIVERSITY CONSERVATION, MIGRATORY BIRDS, AND AVIAN INFLUENZA RISKS

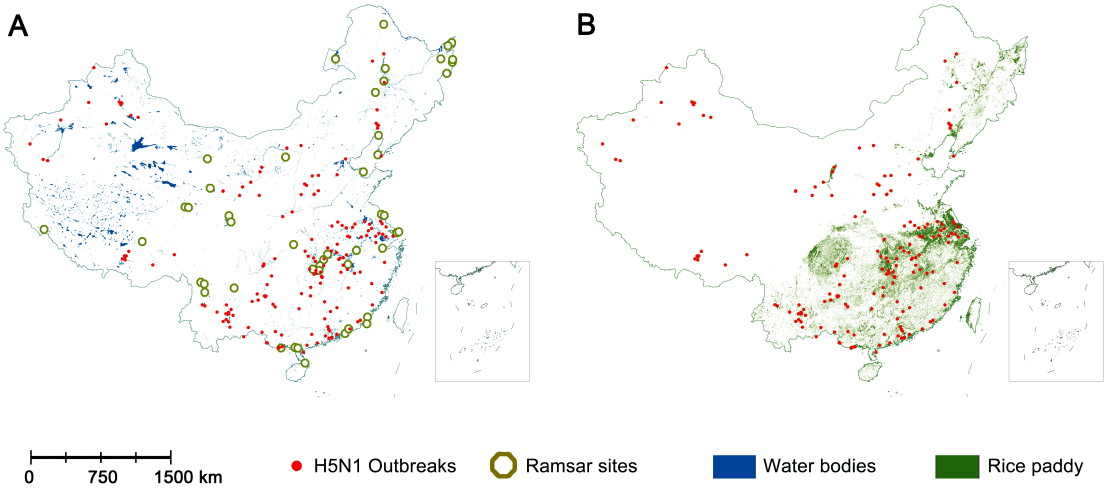
4.1. Introduction

There is a general perception that the preservation of intact ecosystems should reduce the prevalence of infectious diseases (Keesing et al., 2010; Kilpatrick et al., 2017b; Wood et al., 2017). Among the mechanisms most frequently cited are zooprophylaxis, by which protected species divert vectors from humans, and the dilution effect, by which the increased diversity of protected species lowers the probability and scale of an epidemic by distributing pathogen transmission across species with greater or lesser propensity to transmit infection (Ostfeld, 2009). However, the evidence suggests that these effects apply in rather limited circumstances (Randolph and Dobson, 2012). A major driver of the emergence and spread of zoonotic and epizootic diseases is transmission between infected wildlife and susceptible livestock, or vice versa—disease transmission from domesticated reservoirs to sympatric wildlife being a particular concern in conservation biology (Daszak et al., 2000). Globally, wildlife species richness is a strong predictor of emerging zoonotic disease events (Jones et al., 2008; Olival et al., 2017). A large number of zoonotic and epizootic diseases have been transmitted at the interface between managed landscapes and wildlands, including: Nipah (Pulliam et al., 2011); SARS (Wang and Eaton, 2007; Wang et al., 2006); Ebola and Marburg (Wood et al., 2012); bovine tuberculosis; paratuberculosis; avian tuberculosis (Gortázar et al., 2006); and avian influenza (Li et al., 2004).

Taking the case of highly pathogenic avian influenza (HPAI) H5N1, I consider how outbreaks are related to the distribution of more or less protected waterbird habitat in China. Migrating waterbirds are known to spread H5N1 across and beyond China (Keawcharoen et al., 2008; Kilpatrick et al., 2006; Kou et al., 2009; Liu et al., 2005; Olsen et al., 2006; Tian et al., 2015). China is traversed by three important flyways: the East Asia–Australasia flyway covers most of the country, while the East Asia-East Africa flyway affects the northwestern, and the Central Asia flyway stretches over the western, parts of the country (Olsen et al., 2006). China also has abundant natural and man-made wetland and lake habitats suitable for wintering and breeding migratory waterbirds (Figure 9). Opportunities for wild and domestic birds to come into contact in these habitats differs substantially. In more densely populated areas, unprotected lakes, wetlands and paddy fields all provide opportunities for wild waterbirds to come into contact with free-ranging poultry such as chickens, ducks, and geese, which are common in rural areas across the country. In recent decades, rising consumer demand and the scrapping of restrictions on rural husbandry have contributed to the rapid growth of poultry production in China, a large portion of which involves small-scale producers implementing few biosecurity measures (Conan et al., 2012; USDA Foreign Agricultural Service, 2017).

Figure 9

The distributions of HPAI H5N1 poultry outbreaks in relation to lakes and wetlands, Ramsar sites, and rice paddy in mainland China. A. Outbreak locations and unprotected wetlands and lakes and Ramsar sites. B. Outbreak locations and rice paddy land cover.



Yet, not all such waterbodies seem to be equally at risk – even those near rural areas with large poultry populations. Consider Poyang Lake—the country's largest freshwater lake. A 2006 census recorded 50 million ducks, geese, and chickens with approximately one million wintering wild birds around the lake (Xiao et al., 2010). While Poyang has been identified as a potential avian influenza hotspot (Prosser et al., 2013), the incidence of H5N1 poultry outbreaks in the neighborhood of the lake has been much lower than expected from prior risk assessments. Between 2004 and 2017, Jiangxi province, the northern and middle sections of which are dominated by the Poyang Lake watershed, recorded only 6 out of 201 H5N1 poultry outbreaks in China. Many other natural waterbird habitats turn out to be only weakly related to H5N1 poultry outbreaks in China (Takekawa et al., 2010).

Why? One possible explanation lies in the quality of protection offered by these habitats. A Ramsar Convention-designated “Wetland of International Importance especially as Waterfowl Habitat,” Poyang Lake has been a focus of major conservation efforts. The Poyang Lake Nature Reserve was established in 1983, and since 2009, the national government has expanded the area in which livestock husbandry, agricultural activity, and other forms of development are restricted. This has had the dual effect of reducing contact between domestic and wild birds while protecting wintering and breeding birds. In a decadal survey of the Poyang Lake area, Wu et al. (2014) found waterbird numbers and diversity to be increasing in protected wetland habitats relative to farmlands and unprotected waterbodies (Wu et al., 2014). This is consistent with evidence elsewhere that migratory waterbirds prefer protected, natural lakes and wetlands to human-dominated landscapes such as farmlands (Beatty et al., 2014; Li et al., 2013). Both effects have potentially important epidemiological implications.

In this study I used a case control approach to analyze the location of H5N1 poultry outbreaks relative to waterbird habitats characterized by different rates of contact between wild and domestic birds, whilst controlling for general biosecurity levels. I focused on the period January 1, 2004 to September 1, 2017. The highest rates of contact between domesticated and wild fowl were assumed to occur in paddy fields or unprotected water bodies. The lowest rates of contact occur in water bodies protected by buffer zones from which domestic birds are excluded. Our proxy for the existence of effective buffer zones is Ramsar status (Figure 9). Our proxy for general biosecurity levels is a measure of development, per-capita gross domestic product (GDP).

4.2. Data and Methods

Data sources: The timeframe of this analysis was from January 2004 to September 2017, during which time there were 201 H5N1 poultry outbreaks in China. Data on H5N1 poultry outbreaks in China, including locations and dates of observations, were taken from the Emergency Prevention System for Animal Health (EMPRES), a joint project of the FAO and OIE (Welte and Teran, 2004). Land cover data, including for rice paddy and water bodies, came from the Institute of Geography at the Chinese Academy of Sciences and the Center for Human-Environment Systems Sustainability at Beijing Normal University. Spatially explicit data for Ramsar sites were taken from the official database of the Ramsar convention (http://www.ramsar.org/): during the study period there were 48 Ramsar sites, corresponding to important large water bodies and their associated wetlands. Data on per-capita income were taken from the databases and statistical yearbooks published by the National Bureau of Statistics of China (National Bureau of Statistics, 2016). Data varied in availability and quality across prefectures. Where there were gaps in prefectural economic data, the missing values were extrapolated as a linear time series trend from data for previous or latter years, or substituted with the contemporary provincial-level values.

Case-control approach: I used a case-control approach, in which the spatial locations of all H5N1 poultry outbreaks in the study period were treated as the population of cases, and a set of randomly selected uninfected locations was treated as the population of controls (at a ratio of 5 controls per case). Case-control research design is a comparative, population-level analysis of disease risk factors. It produces odds-ratios that are a measure of relative risk, and are particularly sound when used to assess diseases with a low incidence rate – what is known as the "rare disease assumption" (Greenland and Thomas, 1982; Schulz and Grimes, 2002). Although not without potential shortcomings, particularly with respect to selection biases, the relative flexibility in data requirements and efficiency of use has made the method widely used in epidemiology (Breslow, 1996; Grimes and Schulz, 2005). Applications range from non-communicative pathologies, such as mental health disorders and cancer, to a wide range of infectious diseases (Jha et al., 2008; O'Donnell et al., 2016; Yusuf et al., 2004). In particular, its value was shown in the early research into the causes of the AIDS epidemic (Schulz and Grimes, 2002).

Avian influenza, whether in terms of poultry or human cases, has a low incidence rate given the sizes of the susceptible populations, and thus meets the "rare disease assumption" underlying the validity of a case-control research design. Additionally, in the absence of a population roster from which to select a set of controls, random-digit dialing can be undertaken (Grimes and Schulz, 2005). In this study, I implemented the approach through random selection of locations over the study area. Other studies of environmental risk factors in avian influenza and other diseases at large scales have similarly identified cases by outbreak coordinates or administrative units, and controls by random selection of uninfected locations (the randomness producing a representative sample). This was, for example, the approach taken by Fang et al. (2008) and Fang et al. (2013) in their respective analyses of the environmental drivers of H5N1 and H7N9 in

China.   Both studies used a ratio of 5 controls for every 1 case, as this study has also done.

GIS analysis and data management: The land cover raster dataset and the Ramsar wetland dataset were inputted into the GIS software package ArcMap 10.4 to calculate the values of the explanatory variables. The resolution of the dataset was 1000 meters, and the reference year was 2010.   Each outbreak (case) was placed on the land-cover map based on the reported coordinates of the location in which it was first observed. The locations of the controls were generated using a random points generator algorithm in ArcMap, and distributed across the map of China. I randomly generated a population of controls using two other methods, the uses of which did not lead to regression results significantly different from the ones reported here. These additional results, and descriptions of the methods used to produce them, can be found in the Appendix.

Proximity to nearest Ramsar site (of which there were 48 in the study period) values was calculated as the shortest direct distance to the edge of the wetland. The Ramsar site identified also had to be contemporary to the outbreak (i.e., the site had to have acceded to the convention the year before the outbreak). Proximity to nearest large water body – i.e., those larger than 1 square kilometer – values were also calculated as the shortest direct distance to the edge of the water body. For the rice paddy variable, each outbreak was given a 20-km radius buffer zone, and the area in that buffer zone covered by rice paddy was estimated. The per-capita income value associated with each outbreak was the officially reported value for the prefecture in which the outbreak was observed, for the year of occurrence.

Statistical analysis: The data generated by the GIS analysis were used to estimate a set of multivariate logistic regression models. The general form of the models was:

$$\Pr(y_i = 1) = \frac{\exp(\theta_i)}{\exp(\theta_i) + 1}, \tag{4}$$

$$\theta_i = \alpha_0 + \sum_j^4 X_{ij}\beta_j + \varepsilon_i, \tag{5}$$

where $\Pr(y_i=1)$ is the likelihood of a H5N1 poultry outbreak at location i ($y_i=0$ in the absence of an outbreak), α_0 is the intercept, ε is the error term, and X_i are the risk factors at location i: the proximity of the outbreak to the nearest Ramsar-designated wetland; the proximity of the outbreak to the nearest large water body; the amount of rice paddy land cover within a 20-kim radius buffer of the point of outbreak; the per-capita income of the prefecture in which the outbreak occurred (a proxy for the effectiveness of public health and biosecurity measures).

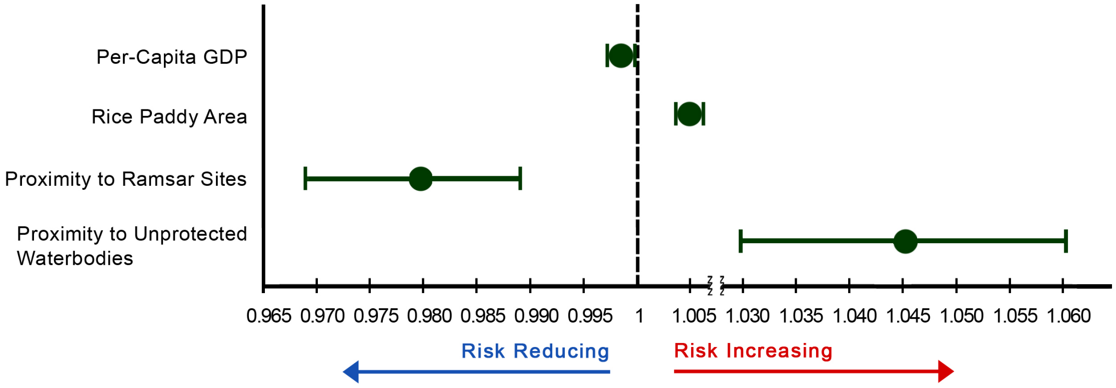
General linear models of this kind are frequently used in epidemiological studies of avian influenza, including for H5N1 in wild birds and poultry (Fang et al., 2008; Fang et al., 2013; Si et al., 2013a; Si et al., 2010). This study extends the analysis by focusing explicitly on the epidemiological effect of protected areas, which the existing literature has ignored. The dependent variable used across all models was the presence or absence of a H5N1 poultry outbreak. Explanatory variables across all models were: the proximity of the outbreak to the nearest Ramsar-designated wetland; the proximity of the outbreak to the nearest large water body; the amount of rice paddy land cover within a 20-kim radius buffer of the point of outbreak; the per-capita income of the prefecture in which the outbreak occurred (a proxy for the effectiveness of public health and biosecurity measures). The proximity measures were calculated as normalized indices of 100, based on the formula: ((maximum distance – location distance)/maximum-distance)*100. A value of 100 represents maximal proximity – e.g., the location of the outbreak is within the Ramsar site, while a value of 0 represents maximal distance away.

4.3. Results

Our results are summarized in Figure 10, and in the Appendix (which includes results from alternative statistical models). All risk factors in our analysis had high levels of statistical significance – below the 0.1% p-value threshold. I found that proximity to a Ramsar site was associated with a reduced risk of an H5N1 poultry outbreak. Conversely, proximity to a large unprotected water body and the density of rice paddy were both associated with an increased risk of an outbreak. While reliable data on wild and domestic bird abundance in these different habitats do not exist, it is known that rice paddy indicates the presence of free-ranging poultry in most areas. Domestic waterbirds such as ducks and geese are often raised in rice paddy—a traditional rearing method that has been encouraged by agricultural policy in many provinces. Rice paddy is therefore also a proxy for “at-risk” domestic birds.

Figure 10

The relative risks of different environmental and socioeconomic factors in HPAI H5N1 poultry outbreaks. The odds-ratios and 95% confidence intervals are shown for each risk factor.



While I did not have direct measures of biosecurity, I found that the higher the per-capita GDP of a given area, the lower the likelihood of an outbreak. Higher income levels mean more resources for conservation and public health, as well as higher standards for the implementation of regulations. This is consistent with results reported in our earlier provincial-level analysis of H5N1 in China. It reflects a "modernization effect" (Wu and Perrings, 2017a).

4.4. Discussion

This study hypothesizes that protection has two main epidemiological effects. The first is that the segregation of wild birds and poultry, through restrictions on agriculture and animal husbandry at the boundaries of protected areas, reduces contact between infected wild and susceptible domestic birds. In China, Ramsar sites have been accorded a high priority for protection, given their status as key elements of a long-standing international convention (Jiang et al., 2015a; Wang et al., 2012). A central feature of the protection of Ramsar sites has been the exclusion of agricultural activity, including the production of poultry.

The second effect is that diversion of migratory wild birds away from farmlands—particularly from paddy fields where mixing between poultry and wild waterbirds is most common—reduces the abundance of infected wild waterbirds in agricultural areas. Since migratory waterbirds prefer natural lakes and wetlands to human-dominated ones, farmlands in China benefit from the same "buffer effect" that has seen wild birds displaced to natural refugia across the world (Beatty et al., 2014; Gill et al., 2001).

The relation between income and H5N1 outbreak risk reflects a number of different things. Biosecurity in this context covers both the way that poultry is produced, and the way that migratory waterbird habitat is protected. In the absence of direct measures of biosecurity, I took per-capita income as a proxy for the general quality of public health infrastructure, environmental protection, and biosecurity in livestock production and distribution (Hennessy and Wang, 2012). At the same time, higher income could also mean greater consumption of poultry, and therefore increase risk. However, our results suggest that on balance more affluent areas in China had lower risk, suggesting they had better biosecurity and more resources to enforce the protection of habitats and therefore the separation of wild birds and poultry. This is consistent with global evidence that more affluent, better-governed countries are more effective at enforcing protected areas and implementing waterbird conservation (Amano et al., 2018)

These results have important implications for the role that conservation can play in human and animal health. It has become increasingly evident that existing strategies to prevent avian influenza outbreaks have not been sufficient. Disease risk mitigation has relied heavily on poultry vaccination and the monitoring and management of poultry supply chains. However, in China as elsewhere, it is often impractical to implement such measures at a sufficiently large scale and for long enough to contain disease risks. Furthermore, undetected pathogen spread can occur even among vaccinated flocks (Poetri et al., 2014). And while vaccination may offer protection against circulating strains, it provides no guarantee against the novel influenzas that are still emerging at the nexus of wild birds, poultry, and people.

Policies that lower the probability of wild bird-poultry transmission could be a useful complement to efforts at vaccinating high-risk flocks, as well as to efforts to control outbreaks after they occur. Our findings suggest that protecting wetlands and lakes – the most important migratory waterbird habitat – is an effective means of doing so. China is in the process of establishing a national park system to standardize and improve habitat protection across the country. Current protected areas in China are relatively successful at protecting avian species (Xu et al., 2017), but greater protection of wetland habitats is still need to secure the long-term ecological prospects of waterbirds in the country (Yang et al., 2017; Zhang et al., 2017). Further expansion and consolidation of the country's protected areas could improve disease risk mitigation at the wild bird-poultry interface.

Avian influenza is a complex epidemiological phenomenon. Despite a growing body of research, there is still an incomplete understanding of its many processes, particularly with respect to the role of avian ecology (Yasue et al., 2006). While I found a strong relationship between habitat protection and H5N1 risk in the largest country infected by the disease, I have yet to test and quantify the mechanisms involved in this relationship. Nonetheless, what makes the "conservation-as-biosecurity" effect identified in this study potentially important for policy is that disease risk mitigation strategies that target the environmental drivers of contact between infected wildlife and susceptible livestock may be more cost effective in the long run than strategies that take contact as given (Pike et al., 2014). Concern about avian influenza could undermine public willingness to pay for migratory bird conservation(Brouwer et al., 2008). Therefore, providing scientific evidence for avian conservation as a means of preventing avian influenza could help turn a potential conflict between two meaningful objectives into a "win-win" solution that advances both.

CHAPTER 5

THE LIVE POULTRY TRADE, MIGRATORY BIRDS, AND THE INTERNATIONAL SPREAD OF H5N1

5.1. Introduction

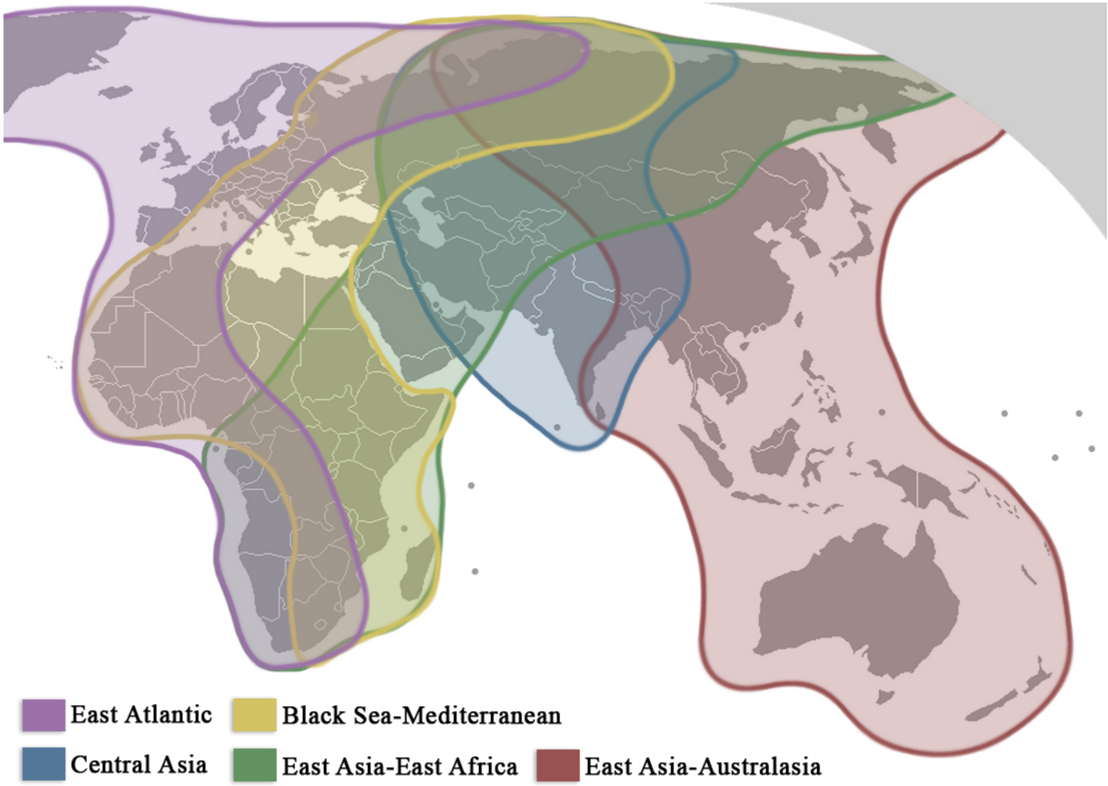
In recent decades, the world economy has been characterized by increasing interconnectedness. This process of “globalization” has included the rapid growth of international trade. While recognized as being essential for economic growth, trade networks have also facilitated the negative externality of pathogen dispersal, as many infectious diseases are borne by commercially traded animals and animal products (Levin and D'Antonio, 2003; Manuja et al., 2014; Pavlin et al., 2009; Perrings, 2010, 2016). These dynamics have been highlighted by recent epidemics of animal-borne pathogens such as foot-and-mouth disease or avian influenza – the focus of this study.

Much of the existing literature on trade-related disease risks has explored the links between disease outbreaks, international trade and travel patterns, and attendant economic and regulatory structures. The likelihood of a pathogen moving from one location to another is frequently taken to be a function of the destination’s environmental suitability and its distance from the origin, as well as the biosecurity measures undertaken at both locations (Hufnagel et al., 2004; Kimball, 2016; Tatem et al., 2006). Much international trade is conducted under the auspices of regional agreements, usually involving geographically proximate countries. Regional trade blocs differ in socioeconomic and regulatory characteristics as well as environmental conditions. This makes regional trade blocs an important topic of epidemiological research (Otte et al., 2004). For instance, analysis of highly pathogenic avian influenza H5N1 (henceforth H5N1) in east and southeast Asia found significant phylogenetic clustering, indicating high frequency circulation among adjacent countries (Wallace and Fitch, 2008; Wallace et al., 2007).

Another important pathway for the regional, as well as global, spread of avian influenza is bird migration. Large migratory corridors crisscross Africa and the Eurasian landmass (Figure 11), which are the principal areas of H5N1 infections. Migratory waterbirds alight in wetlands, lakes, and nearby agricultural lands for wintering and breeding, in the process sharing habitats with domestic fowl such as ducks and chicken. By means of physical mixing and environmental pollution, wild birds can transmit avian influenza to poultry, which in turn become the primary source of human infections (Kilpatrick et al., 2006).

Figure 11

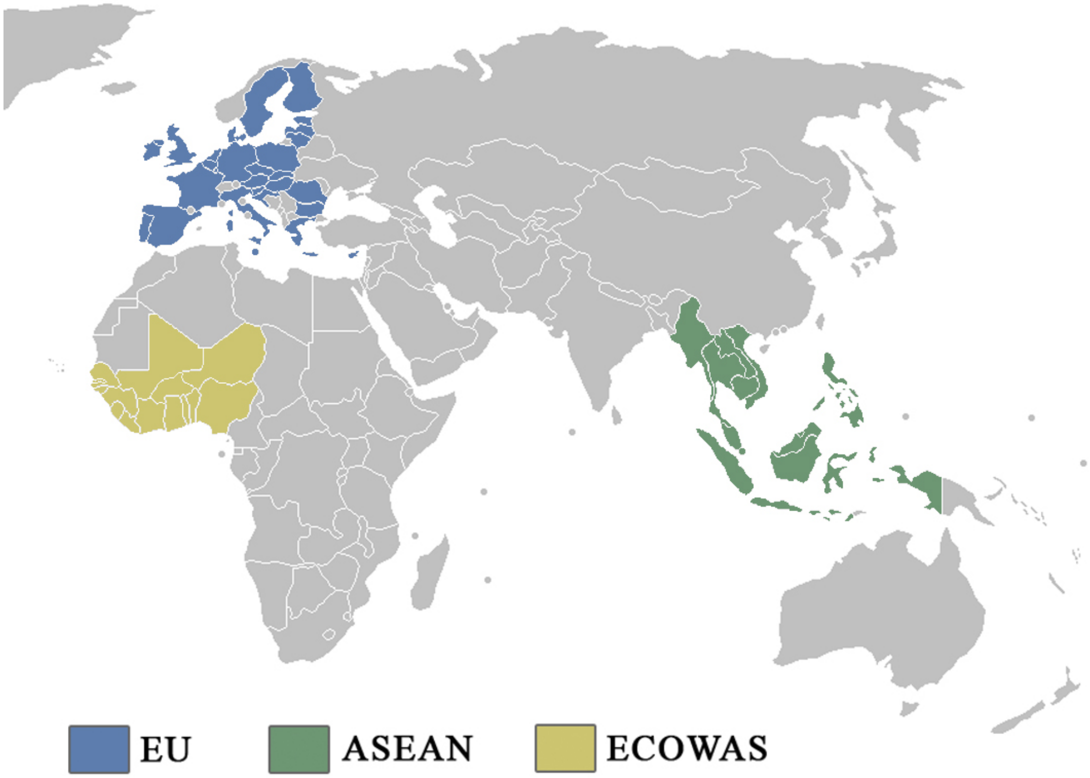
The major migratory bird flyways that cover Africa, Europe, and Asia.



In this study, I focus on the three regions of the world where the H5N1 epidemic has been most intense (as indicated by numbers of outbreaks) and extensive (as represented by contiguousness of infected countries): Europe, West Africa, and Southeast Asia. These regions also happen to be framed, respectively, by three regional trade blocs: the European Union (EU), the Economic Community of West Africa (ECOWAS), and the Association of Southeast Asian Nations (ASEAN) (Figure 12). The relative contributions to H5N1 spread by the two aforementioned pathways are quantified using a set of relevant indicators and proxy variables. Additionally, this study explores how socioeconomic and environmental differences between these three regions may account for contrasting impacts from different risk factors. There is unlikely to be a "one-size-fits-all" solution to the control of avian influenza risks, applicable in every epidemic location. The development of effective policy responses needs to take these differences into account.

Figure 12

The three trade blocs heavily impacted by avian influenza under study: the European Union (EU), the Economic Community of West Africa (ECOWAS), and the Association of Southeast Asian Nations (ASEAN).



5.2. Methodology

The conceptual model underpinning the statistical analysis in this study is based on a socio-ecological, or coupled human-environmental, systems approach. Kilpatrick et al. (2006) explored the relative risks posed by migratory birds and trade in the spread of H5N1 in the early years of the global epidemic. This dual-pathways approach also provides the basis of our conceptual framework, but with an additional decade of data on both outbreaks and risk factors. There is a large and growing literature on the relationship between trade and the spread of infectious diseases. Studies have identified a strongly positive relationship between the opening of new markets and the introduction of a range of animal and plant diseases, and between growing trade volumes and the probability that these diseases will establish and spread (Cassey et al., 2004; Dalmazzone, 2000; Dehnen-Schmutz et al., 2010; Drew, 2011; Fèvre et al., 2006; Karesh et al., 2005; Karesh et al., 2012; Li et al., 2005; Pavlin et al., 2009; Rweyemamu and Astudillo, 2002; Semmens et al., 2004; Smith et al., 2009; Tatem, 2009; Tatem et al., 2006; Vila and Pujadas, 2001; Xu et al., 2004). In terms of trade-related risks, I focus on the imports of live poultry as the primary source of trade-related avian influenza risk. Other poultry products, such as packaged meat and eggs, pose significantly lower risk of transmission. Although avian influenza can persistent in frozen meat, contact with that meat is unlikely to cause infection (Cobb, 2011b). Furthermore, HPAIs are lethal to egg embryo (Cobb, 2011a).

With respect to wild bird migration as a pathway for H5N1 spread, I use habitat types as proxies for the presence and scale of migratory bird populations, and their likelihood of mixing with domestic birds or polluting shared environments. In particular, I use lakes, wetlands, and agricultural areas as habitat proxies because they have been consistently identified as wintering and breeding grounds for migratory birds and as places where these wild species may have a high likelihood of coming into contact with free-ranging poultry, especially if these habitats are unprotected; these ecological dynamics have been found in all three of the regions analyzed in this study (Bragstad et al., 2007; Cecchi et al., 2008; Ducatez et al., 2006; Gaidet et al., 2007; Gilbert et al., 2008; Park and Glass, 2007; Si et al., 2010; Tian et al., 2015).

5.2.1. Data

Data on trade in live poultry were obtained from the United Nations' Comtrade Database (comtrade.un.org) and resourcetrade.earth, a project of the Royal Institute of International Affairs (www.chathamhouse.org). Country-level statistics on socioeconomic and agro-ecological conditions were taken from the United Nations' Food and Agriculture Organization (www.fao.org/faostat/en/) and the World Bank (data.worldbank.org). The indicator for wild bird habitat used in this study was the set of "Important Bird and Biodiversity Areas" (IBAs) for "migratory and congregatory waterbirds" identified by BirdLife International (datazone.birdlife.org). In their 2006 analysis H5N1 spread, (Kilpatrick et al., 2006) also identified IBAs as a proxy for migratory birds and the infection risks they pose. Data on the annual biosecurity measures targeting avian influenza undertaken by each country was gathered from the World Organisation for Animal Health (OIE) (www.oie.int). Data for 2016 was missing for certain variables; in these cases, the gap was filled by extrapolating the missing data as a linear trend of the preceding 11 years, for the sake of simplicity. Additionally, in any given year, there were

1 to 4 countries that did not provide a report of biosecurity measures to the OIE; I assume that this indicates an absence of action, and the dataset records these cases as zeroes. Finally, while data on the population of live chickens were available for all countries, those on live duck and other poultry populations were only reported for a fraction of the countries. Therefore, I used live chickens as a proxy for live poultry more generally, and assume that agricultural land – where free-ranging chickens, ducks, and geese are commonly raised in all three regions – also acts as a relevant proxy for susceptible poultry.

5.2.2. Statistical Analysis

In this study, I used multiple linear regression models over an unbalanced panel dataset (the membership of the EU changed over the timeframe). Generalized linear models (GLM), of which linear regression is a subclass, are frequently used in economics, epidemiology, and ecology. In the study of avian influenzas, for instance, such models have been used to predict the spread of H5N1 (Fang et al., 2008; Martin et al., 2011; Si et al., 2013b) and H7N9 (Fang et al., 2013; Gilbert et al., 2014; Zhu and Peterson, 2014) as a function of myriad environmental factors. GLMs are "general" because they can incorporate more than one predictor variable and "linear" because the response variable is expressed as a linear function of those predictors. As Hogerwerf et al. (2010), who used multiple linear regression to analyze the agro-ecological drivers of H5N1 persistence, notes, GLMs are well suited to epidemiological studies because of their flexibility regarding data type, simplicity of application to different diseases (and hence familiarity and reproducibility by other researchers), and frequency of use in both the natural and social sciences (which promotes interdisciplinary investigations).

The response variables in all models were a log transformation of the number of H5N1 poultry outbreaks in a given country in a given year. The log transformation was applied to account for the wide disparities in the numbers of the outbreaks across countries (e.g., in 2010, Indonesia recorded 1206 outbreaks while Romania, the only EU country to be infected that year, had only two). In addition to reflecting the differing directions and intensities of risk factors, this wide range could also be due to under-reporting, which could be widespread for H5N1 at the international level (Hogerwerf et al., 2010). Differences in reporting conventions may also play a role, as a series of outbreaks in a given country could be reported separately but be treated as a single event in another. The predictor variables fall into five categories: confounding, modernization, agro-ecological, trade, and biosecurity. I developed three types of regression models. The first uses the confounding, agro-ecological, and modernization variables as predictors. The second incorporates the trade variables and the third further adds the biosecurity measures, which are dummy variables (e.g., presence/absence).

Each model type was run for all regions together and for each region separately. The first model specification (Model 1) included as predictors: land area, human population, per-capita GDP in purchasing power terms, agricultural area, wild bird habitat area, and live chicken population. The second specification (Model 2) includes these above predictors in addition to intra-regional trade bloc and extra-bloc imports of live poultry. The third specification (Model 3) includes all these along with the biosecurity measures: border precautions, general surveillance, vaccination prohibition, and wild disease reservoir management. These are categories of OIE-reported biosecurity measures taken against avian influenza. The general form of the estimated models was:

$$y_{it} = \beta_0 + \sum_{j=1}^{6} X_{jit}\beta_j + \sum_{k=1}^{2} Z_{kit}\beta_k + \sum_{s=1}^{4} U_{sit}\beta_s + u_i + \varepsilon_{it} \ , \qquad (6)$$

where y_{it} denotes the number of poultry outbreaks in country i in year t, X includes the predictors for Model 1, Z includes the additional predictors for Model 2, U includes the additional predictors for Model 3, and u_{it} and e_{it} are the "between" and "within" errors respectively.

To account for heteroskedasticity, the models used robust standard errors. Although both random effects and fixed effects were used, Hausman tests conducted at the all-regions level indicated that random effects were more appropriate, as the *p*-values exceeded the 5% threshold below which fixed-effects regression is conventionally considered necessary. Fixed effects are often preferred, particularly in economic analysis, because they better elucidate the impacts of predictors that change over time, and therefore produce less biased coefficient estimates by omitting time-invariant characteristics. However, this omission may mean that the important causes of differences between individuals – countries in this case – are underestimated. Many factors that influence the likelihood and number of outbreaks in a given country are not likely to change significantly over the course of several years, or even a decade. In our dataset, for example, the amount of land covered by wild bird habitat is time-variant, and others, such as agricultural land and even per-capita GDP for many countries, experienced relatively modest variations over the timeframe of the study. In this case, and as the Hausman diagnostics indicate, random effects are more appropriate. Nonetheless, I estimated both random- and fixed-effects models, in order to more comprehensively capture the international as well as inter-temporal dynamics of H5N1 spread. Finally, since the data used in this analysis are reported annually, and H5N1 has been a fast-moving epidemic, particularly among poultry, I did not use a lag structure in our statistical analysis. In other words, I assumed that the outbreaks in a given year were independent of the conditions and biosecurity measures of the previous year.

5.3. Results

Regressions results from all models, including both random and fixed effects, are reported in Tables 3-6. At the all-regions level, the results for the random- and fixed-effects models were very similar, with the same set of predictor variables being statistically significant (i.e., *p*-values below the 5% or 10%) and the same direction of impact on the response variable. This set of predictors was human population (positive direction), per-capita GDP (negative direction), intra-trade bloc live poultry imports (negative direction), extra-trade bloc live poultry imports (positive direction), and the biosecurity measure of surveillance (negative direction). Additionally, although the coefficient values for the same predictor differed between the two effects type, all pairs were within the same order of magnitude. The only exception to this consistency was the migratory waterbird habitat variable, percent of land area covered by IBAs for migratory and congregatory waterbirds: it was statistically significant and negative (i.e., had a mitigating impact on H5N1 poultry outbreaks) for the fixed-effects model but was not significant for the random-effects model. The R-squared for the random-effects model was significantly higher than that for the fixed-effects model (0.451 vs. 0.0181), and the former's "between R-squared" value was particularly high (0.682). Between R-squared measures the variation among individuals in a panel dataset (as opposed to "within R-squared," which measures the variation of an individual over time). As the individuals in this dataset are countries, a high between R-square value means the model has explained, to a relatively high degree, why the incidence of outbreaks differed across countries.

Table 3

Results for regression models of agro-ecological, trade-related, and biosecurity factors of H5N1 poultry outbreaks across all member countries of the Association of Southeast Asian Nations (ASEAN), the Economic Community of West African States (ECOWAS), and the European Union (EU) from 2005-2016. Regressor coefficients are reported; statistically-significant factors are marked by asterisks.

Variables	Units	Model 1		Model 2		Model 3	
		Random Effects	Fixed Effects	Random Effects	Fixed Effects	Random Effects	Fixed Effects
Population	# people	1.32×10^{-8} **	4.51×10^{-8} **	1.35×10^{-8} **	4.47×10^{-8} **	1.36×10^{-8} **	4.51×10^{-8} **
Area	km^2	-4.18×10^{-7}	-0.0000225	-4.31×10^{-7}	-8.41×10^{-6}	-4.01×10^{-7}	-2.94×10^{-6}
Agricultural land	% land area	-0.00769	-0.0106	-0.00736	-0.00691	-0.00777	-0.00923
Live chickens	1000 birds	1.30×10^{-6}	4.75×10^{-7}	1.28×10^{-6}	5.42×10^{-7}	1.25×10^{-6}	4.22×10^{-7}
IBA for waterbirds	% land area	-0.000132	-0.176	-0.000107	-0.164 *	-0.000140	-0.154 **
Per-capita GDP	current international	-9.74×10^{-6} **	-0.0000171 **	-8.37×10^{-6} **	-0.0000138 **	-8.05×10^{-6} **	-0.0000108 *

	$						
Intra-bloc live poultry imports	kg			-5.84×10^{-6} **	-4.82×10^{-6} **	-5.10×10^{-6} **	-3.14×10^{-6} **
Extra-bloc live poultry imports	kg			0.00179 **	0.00189 **	0.00177 **	0.00184 **
Border precautions	presence/ absence					0.125	0.196
General surveillance	presence/ absence					-0.299 *	-0.370 *
Vaccination prohibited	presence/ absence					0.0506	0.122
Wild reservoirs management	presence/ absence					0.153	0.175
Observations		621	621	621	621	621	621
Within R^2		0.0319	0.0410	0.0683	0.0785	0.0964	0.1082
Between R^2		0.6930	0.0114	0.6982	0.0072	0.6819	0.0277
Overall R^2		0.4319	0.0063	0.4500	0.0049	0.4507	0.0181
Rho		0.2930	0.9978	0.3070	0.9974	0.3293	0.9971

** statistically significant at the 5% level

* statistically significant at the 10% level

Table 4

Results for regression models of agro-ecological, trade-related, and biosecurity factors of H5N1 poultry outbreaks across member countries of the Association of Southeast Asian Nations (ASEAN) from 2005-2016. Regressor coefficients are reported; statistically-significant factors are marked by asterisks.

Variables	Units	Model 1	Model 2	Model 3

		Random Effects	Fixed Effects	Random Effects	Fixed Effects	Random Effects	Fixed Effects
Population	# people	$6.20\text{x}10^{-8}$ **	$1.92\text{x}10^{-7}$	$8.96\text{x}10^{-8}$ **	$1.65\text{x}10^{-7}$	$1.13\text{x}10^{-8}$	1.83x10-7
Area	km^{2}	$-5.96\text{x}10^{-6}$ *	0.00353 **	$-8.29\text{x}10^{-6}$	0.00417 **	$-1.13\text{x}10^{-6}$	0.00445 **
Agricultural land	% land area	-0.174 **	-0.647 **	-0.244 **	-0.549 **	-0.0467 **	-0.593 **
Live chickens	1000 birds	$9.85\text{x}10^{-7}$	$-1.02\text{x}10^{-6}$	$4.08\text{x}10^{-7}$	$-4.59\text{x}10^{-7}$	$1.69\text{x}10^{-6}$	-1.18x10-6
IBA for waterbirds	% land area	-0.0290	0.322	-0.0577	0.190	-0.0122	0.380
Per-capita GDP	current international $	-0.0000522 *	$-7.25\text{x}10^{-6}$	-0.0000447 *	$-8.48\text{x}10^{-6}$	-0.0000317 **	-8.33x10-7
Intra-bloc live poultry imports	kg			$-4.86\text{x}10^{-6}$	$1.00\text{x}10^{-6}$	-0.0000108	0.0000112
Extra-bloc live poultry imports	kg			0.00212 **	0.00171 **	0.00222 **	0.00187 **
Border precautions	presence/ absence					0.398	1.23 **
General surveillance	presence/ absence					-0.625	-0.606 *
Vaccination prohibited	presence/ absence					-1.00 *	-0.267
Wild reservoirs management	presence/ absence					0.881 **	-0.533 *
Observations		120	120	120	120	120	120
Within R^{2}		0.1626	0.3038	0.2596	0.3472	0.2036	0.4759
Between R^{2}		0.4346	0.5503	0.2800	0.5504	0.8057	0.5503
Overall R^{2}		0.3252	0.3674	0.2346	0.3674	0.5921	0.3674
Rho		0.7242	1.000	0.8798	1.000	0.0000	1.000

** statistically significant at the 5% level

* statistically significant at the 10% level

Table 5

Results for regression models of agro-ecological, trade-related, and biosecurity factors of H5N1 poultry outbreaks across all member countries of the Economic Community of West African States (ECOWAS) from 2005-2016. Regressor coefficients are reported; statistically-significant factors are marked by asterisks.

Variables	Units	Model 1		Model 2		Model 3	
		Random Effects	Fixed Effects	Random Effects	Fixed Effects	Random Effects	Fixed Effects
Population	# people	$6.05\text{x}10^{-9}$	$3.85\text{x}10^{-8}$ **	$7.34\text{x}10^{-9}$	$4.21\text{x}10^{-8}$ **	$1.82\text{x}10^{-9}$	1.95x10-8 *
Area	km^2	$1.30\text{x}10^{-8}$	0	$-1.40\text{x}10^{-8}$	0	$-3.50\text{x}10^{-8}$	0
Agricultural land	% land area	0.00247	0.00434	0.00233	0.00907	-0.00461	0.00626
Live chickens	1000 birds	$2.02\text{x}10^{-7}$	0.0000112	$-3.24\text{x}10^{-7}$	0.0000113	$3.12\text{x}10^{-6}$	9.58x10-6
IBA for waterbirds	% land area	-0.00744 *	0	-0.00646	0	-0.0119 **	0
Per-capita GDP	current international $	0.000198 *	0.0000887	0.000173	0.000172	0.000290 **	0.000303
Intra-bloc live poultry imports	kg			0.0122 **	0.0124 **	0.0138 **	0.0107 **
Extra-bloc live poultry imports	kg			-0.000638	-0.000990 **	-0.000895 *	-0.000815

Border precautions	presence/ absence					-0.552 **	-0.741
General surveillance	presence/ absence					0.103	0.0430
Vaccination prohibited	presence/ absence					0.476 **	0.540
Wild reservoirs management	presence/ absence					0.477 **	0.266
Observations		180	180	180	180	180	180
Within R^2		0.0477	0.0582	0.0603	0.0782	0.1506	0.1722
Between R^2		0.8843	0.8672	0.8895	0.8733	0.8752	0.8314
Overall R^2		0.2492	0.2354	0.2648	0.2420	0.3303	0.2786
Rho		0.0000	0.7844	0.0000	0.8101	0.0000	0.6304

** statistically significant at the 5% level

* statistically significant at the 10% level

Table 6

Results for regression models of agro-ecological, trade-related, and biosecurity factors of H5N1 poultry outbreaks across all member countries of the European Union (EU) from 2005-2016. Regressor coefficients are reported; statistically-significant factors are marked by asterisks.

Variables	Units	Model 1		Model 2		Model 3	
		Random Effects	Fixed Effects	Random Effects	Fixed Effects	Random Effects	Fixed Effects
Population	# people	$6.34x10^{-9}$ **	$1.37x10^{-7}$	$9.46x10^{-9}$ *	$1.09x10^{-7}$	$1.07x10^{-8}$ **	1.29x10-7
Area	km^2	$3.88x10^{-7}$	-0.0000108	$2.65x10^{-7}$	$-8.15x10^{-6}$	$2.79x10^{-7}$	-0.0000149
Agricultural land	% land area	0.00333 *	0.0410 **	0.00293	0.0395 *	0.00311	0.0399

Live chickens	1000 birds	-2.47x10^{-6} **	-8.66x10^{-6} *	-2.98x10^{-6} **	-8.03x10^{-6}	-3.51x10^{-6} **	-8.58x10-6
IBA for waterbirds	% land area	0.0000163	-0.109 **	4.30x10^{-6}	-0.115 **	0.000116	-0.103 **
Per-capita GDP	current international $	-1.74x10^{-6}	-9.03x10^{-6} *	-1.51x10^{-6}	-7.34x10^{-6}	-3.04x10^{-7}	-9.52x10-6 *
Intra-bloc live poultry imports	kg			-2.82x10^{-6}	-3.42x10^{-6} **	-3.34x10^{-6} *	-2.22x10-6
Extra-bloc live poultry imports	kg			-0.00413	-0.00517	-0.00471	-0.00459
Border precautions	presence/ absence					0.0377	-0.116
General surveillance	presence/ absence					-0.0476	-0.0706
Vaccination prohibited	presence/ absence					0.107 **	0.188 **
Wild reservoirs management	presence/ absence					0.0657	0.0812
Observations		321	321	321	321	321	321
Within R^2		0.0835	0.1134	0.0986	0.1319	0.0970	0.1552
Between R^2		0.3471	0.0384	0.2584	0.0319	0.3218	0.0271
Overall R^2		0.0682	0.0051	0.0858	0.0043	0.1075	0.0038
Rho		0.0079	0.9992	0.0045	0.9993	0.0187	0.9992

** statistically significant at the 5% level

* statistically significant at the 10% level

There were differences across trade regions. In the random-effects model, ECOWAS diverged from all-regions conditions and from ASEAN with respect to per-capita GDP and extra-bloc imports: while the two predictors were, respectively, risk-decreasing and risk-increasing at the all-regions level and in ASEAN, they had the opposite impacts in ECOWAS. Furthermore, ECOWAS differed from the all-regions level and from the EU in terms of intra-bloc imports: while this was risk-decreasing for the former two, it was risk-increasing for ECOWAS. Finally, there were predictors that were statistically insignificant at the all-regions level but had a significant effect within different regions. For ASEAN, agricultural land cover was a mitigating factor for outbreaks while wild disease reservoir management showed a strong positive correlation with outbreaks. For ECOWAS, wild waterbird habitats and border precautions had a mitigating effect on outbreaks while vaccination prohibition and wild reservoir management had a positive effect. In the EU, the population of live chickens had a strong negative correlation with outbreaks, while vaccination prohibition, similar to the case with ECOWAS, was positively correlated.

5.4. Discussion

Among the predictors, per-capita GDP perhaps captures the broadest array of underlying mechanisms. Generally, it is a measure of modernization. Its mitigating effect on outbreaks is consistent with the evidence that industrial livestock production may protect poultry from contact with disease-carrying wild birds. Unlike traditional methods of free-range or "backyard" husbandry, factory production minimizes the likelihood of poultry intermingling with wild birds or being exposed to environmental pathogen pollution. At the same time, industrial livestock production – for all its epidemiological, ecological, and ethical problems – allows for more timely and widespread disease surveillance and vaccination, and for the implementation of regulations more broadly (Hennessy and Wang, 2012).

However, the positive correlation of per-capita GDP and poultry outbreaks for ECOWAS suggests that this “modernization effect” is not a linear relationship, and that other mechanisms may also be at play. To test this, I ran the all-regions, all-predictors regression model with a quadratic term, per-capita GDP-squared (Table 7). Both per-capita GDP and per-capita GDP-squared were statistically significant, and had opposite signs. This indicates an environmental Kuznets Curve (EKC)-type relationship between affluence and avian influenza risk, with ECOWAS (a low-income region) on the ascending slope, ASEAN (a middle-income region) at the top of the curve, and EU (a high-income region) on the descending slope. At low levels of economic development, increasing affluence may mean greater production and consumption of livestock, an important source of protein. This is coupled with lower levels of regulation and biosecurity, as a greater share of poultry husbandry is done traditionally. At high levels of economic development, in addition to more modern livestock production methods, protein demand may already have saturated. This means higher income will not necessarily reflect greater poultry numbers, much less of the highly-susceptible, free-ranging kind.

Table 7

Results for regression models of agro-ecological, trade-related, and biosecurity factors of H5N1 poultry outbreaks across all member countries of the Association of Southeast Asian Nations (ASEAN), the Economic Community of West African States (ECOWAS), and the European Union (EU) from 2005-2016, with the additional quadratic term for per-capita GDP. Regressor coefficients are reported; statistically-significant factors are marked by asterisks.

Variables	Units	Random Effects	Fixed Effects
Population	# people	1.39×10^{-8} **	4.77×10^{-8} **
Area	km^2	-5.03×10^{-7}	-6.07×10^{-6}
Agricultural land	% land area	-0.00770	-0.00866
Live chickens	1000 birds	1.33×10^{-6}	5.50×10^{-7}
IBA for waterbirds	% land area	0.000148	-0.0317
Per-capita GDP	current international $	-0.0000278 **	-0.0000469 **
Per-capita GDP-squared	-	2.52×10^{-10} **	3.39×10^{-10} **
Intra-bloc live poultry imports	kg	-4.65×10^{-6} **	-2.54×10^{-6} *
Extra-bloc live poultry imports	kg	0.00171 **	0.00177 **
Border precautions	presence/ absence	0.164	0.204
General	presence/	-0.298 *	-0.345 *

surveillance	absence		
Vaccination prohibited	presence/ absence	0.109	0.143
Wild reservoirs management	presence/ absence	0.182 *	0.195 *
Observations		621	621
Within R^2		0.1006	0.1137
Between R^2		0.7080	0.0728
Overall R^2		0.4684	0.0516
Rho		0.3210	0.9474

** statistically significant at the 5% level

* statistically significant at the 10% level

Extra-trade bloc live poultry imports may be a significant source of avian influenza risk because they do not meet to the sanitary and phytosanitary standards embedded in many free-trade agreements. The EU's common market and the ASEAN free trade regime in particular have long-standing and standardized protocols, in accordance with the World Trade Organization's Agreement on the Application of Sanitary and Phytosanitary Measures. Other studies have come to similar conclusions. For instance, a study found that intra-EU imports of live poultry to Spain did not pose a significant threat of avian influenza introduction (Sanchez-Vizcaino et al., 2010), while another of Vietnam found that extra-ASEAN imports of live poultry increased the risk of introduction (Desvaux et al., 2016). That intra-bloc live poultry imports are risk-mitigating may, correspondingly, be a reflection of a "substitution effect" in which imports of safer intra-bloc poultry crowds out riskier extra-bloc imports. ECOWAS is the exception, inverting the dynamics – extra-ECOWAS imports are risk-mitigating while intra-bloc imports are risk-increasing. This is likely due to poor internal biosecurity, such as lax standards and inconsistent execution of inspections. In this case, imports from more biosecure countries could be risk reducing. At the same time, it could also be due to low regulatory standards within the ECOWAS trade bloc (Hughes et al., 2008), as harmonized sanitary and phytosanitary standards for its 15 member states were only adopted in 2010. Even then, progress has been slow: as of 2017, most ECOWAS states had yet to submit legislation for international certification (Bachabi et al., 2017).

Of the biosecurity measures, only surveillance was significant at the all-regions level. General vigilance to poultry production and trade, as well as of wild waterbirds, is likely to reduce outbreaks. The symptoms of H5N1 are acute and can be conspicuous among poultry, especially compared to low pathogenic avian influenzas such as H7N9. The divergent impacts of the other biosecurity measures across regions may be a reflection of regional disparities or post-hoc implementation (i.e., measures are undertaken after an outbreak has already occurred in the country). This may be especially true for vaccination prohibition, which has a positive correlation to outbreaks for ECOWAS and EU. In addition to signaling a lack of appropriate vaccination, such prohibition is associated with livestock culling, which is a post-outbreak measure. For poultry, vaccination is often prohibited because the practice makes it difficult to distinguish infected from vaccinated flocks, hobbling the efficiency of culling (Callahan, 2009). The management of wild disease reservoirs can differ widely across countries, but techniques include: vaccination; treatment of infections with drugs; fencing off infected populations; draining, flooding, or burning the environment; population translocation; reproduction reduction; and culling (World Organization for Animal Health, 2010). As with vaccination prohibition, many of these measures may be post-hoc, therefore not reflecting the efficacy of preventative management.

In their survey of the international spread of H5N1, Kilpatrick et al. (2006) found that transmission into Europe more likely to be caused by wild birds, into Southeast Asia by the poultry trade, and into Africa by a more even balance of both. Our results suggest that after introduction into these regions, inter-country spread had differing dynamics. While regional trade facilitated H5N1 spread among West African countries, trade among members of their respective free trade agreements did not increase cross-border transmission in Europe and Southeast Asia. In these latter two areas, greater risk was posed by out-of-region poultry imports. Kilpatrick et al. (2006) do not make the distinction between intra-regional trade and international trade more broadly, but in the decade since their analysis, the continued spread of H5N1 points to it as being an important factor, particularly in the context of relevant biosecurity measures.

5.5. Conclusion

In recent decades, avian influenzas have emerged as a major threat to human and animal health across the world. In particular, HPAI H5N1, which was first isolated in 1996, has been the most widespread and among the most devastating in terms of livestock and human mortality. It has inflicted severe losses to poultry stocks as well as caused hundreds of human deaths. Even today, as other avian influenzas have become epidemic, H5N1 remains in circulation among wildlife and livestock. Identifying and quantifying the mechanisms of its international spread can help lay the groundwork for prediction and mitigation, and may also provide an instructive framework for the management of other avian influenzas.

In this study, I identified key risk factors for H5N1 spread among countries, particularly as facilitated or mitigated by regional trade and biosecurity measures. Differing agro-ecological and socioeconomic conditions across the trade regions were shown to influence epidemic dynamics in different ways, with certain factors being risk-enhancing or risk-decreasing in one region but having the opposite effect, or no significant effect, in another. In policy terms, there is no one-size-fits-all solution to preventing avian influenza outbreaks. The particular conditions, including those related to the trade agreements and associated regulatory standards, of a given region need to be carefully considered. But overall, biosecurity measures are potentially effective at controlling H5N1 risks, and should be undertaken as a means to forestall spread – in general, mitigation of epidemics is significantly more cost-efficient than suppression (Pike et al., 2014). On-farm and other forms of domestic biosecurity may be more important than trade-related measures, but where the protection of trade pathways is weak, the risk of avian influenza spread is clearly higher.

CHAPTER 6

CONTROLLING AVIAN INFLUENZA RISKS IN CHINA: A REVIEW OF POLICIES AT THE LOCAL, NATIONAL, AND GLOBAL LEVELS

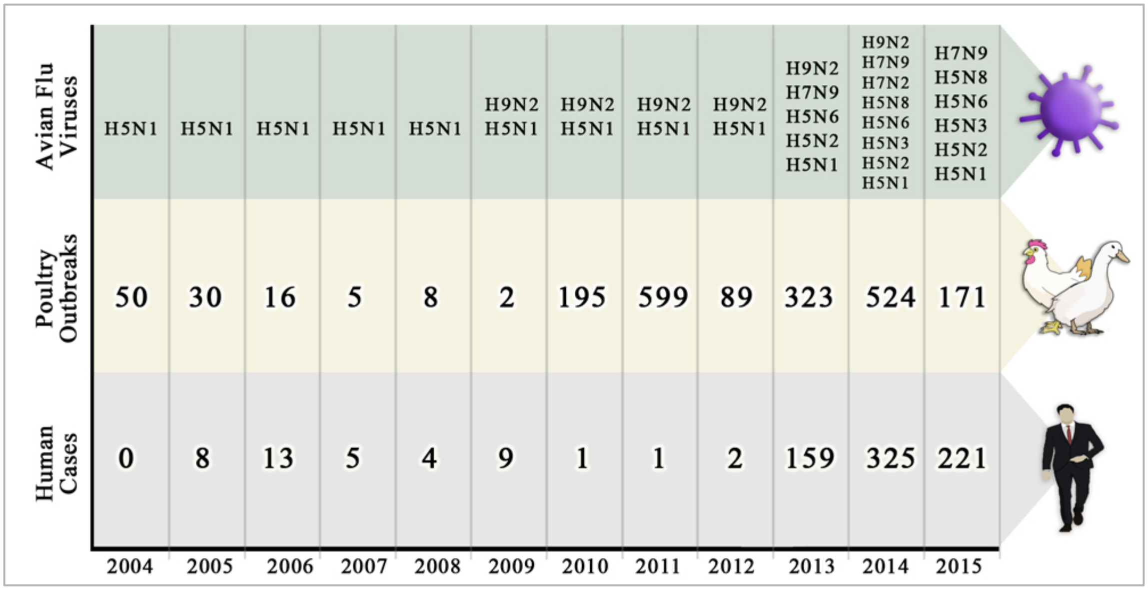
6.1. Introduction

Over the past two decades, avian influenzas have become a major concern for livestock and public health across the world. Outbreaks among poultry have increased globally, with consistently high mortality rates. Between 1999 and 2003, poultry fatality from H5N1 exceeded 50 million birds in the European Union (Capua and Marangon, 2006), and during the 2003-2004 Asian epidemic, Vietnam lost 44 million birds, or roughly 17.5% of the country's total stock, while Thailand lost 29 million birds, or 14.5% of the national total. Outbreaks cause mass die-offs or prompt mass slaughter to stem disease spread. For instance, the 1997 H5N1 outbreak in Hong Kong led to the culling of 1.3 million poultry. In the winter of 2016-2017, 1.67 million Japanese chickens were culled over fears of H5N6 (Reuters, 2018). The ramifications of such outbreaks and the measures they prompt can extend beyond narrowly agricultural concerns. In the winter of 2017-2018, fears of an H5N8 epidemic prompted mass culling in Iran, leading to a major spike in the prices of poultry meat and eggs – important dietary staples for a Muslim-majority population. This precipitous inflation coincided with broader economic difficulties and helped spark nation-wide protests (Vahdat and Gambrell, 2018).

Although far fewer, human infections have also been characterized by high mortality rates, with the majority of cases being in Asia. Given the convergence of risk factors within its borders, along with its vast geographic, economic, and demographic scale, China in particular has been a country of concern – in the words of Davis (2005), it has been the world's "cradle of influenza" (see Figure 13). Both highly pathogenic H5N1 and H7N9 influenzas emerged in China and have since spread across the country and beyond. These two strains have been the most lethal to people of all contemporary avian influenzas. To date there have been 45 confirmed human cases of H5N1 in China, with a mortality rate of 67%. The H7N9 epidemic, which emerged in Shanghai in 2013, has infected 681 people and killed 270. Although differing in certain aspects of virology and ecology, the two influenzas share important epidemiological features. Their ready transmissibility between wild and domesticated birds, and between infected poultry and people, are among the most important (Lai et al., 2016; Li et al., 2015).

Figure 13

Timeline of avian influenza poultry outbreaks and human cases in China, with the strains involved each year, 2004-2015.



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Avian Flu Viruses	H5N1	H5N1	H5N1	H5N1	H5N1	H9N2 H5N1	H9N2 H5N1	H9N2 H5N1	H9N2 H5N1	H9N2 H7N9 H5N6 H5N2 H5N1	H9N2 H7N9 H7N2 H5N8 H5N6 H5N3 H5N2 H5N1	H7N9 H5N8 H5N6 H5N3 H5N2 H5N1
Poultry Outbreaks	50	30	16	5	8	2	195	599	89	323	524	171
Human Cases	0	8	13	5	4	9	1	1	2	159	325	221

* Poultry outbreaks, particularly from H9N2 and H7N9, may be over-reported: e.g., many reported outbreaks occur at the same location on the same day or within a few days of each other, therefore may be different manifestations of a continuous outbreak as opposed to being discrete events.

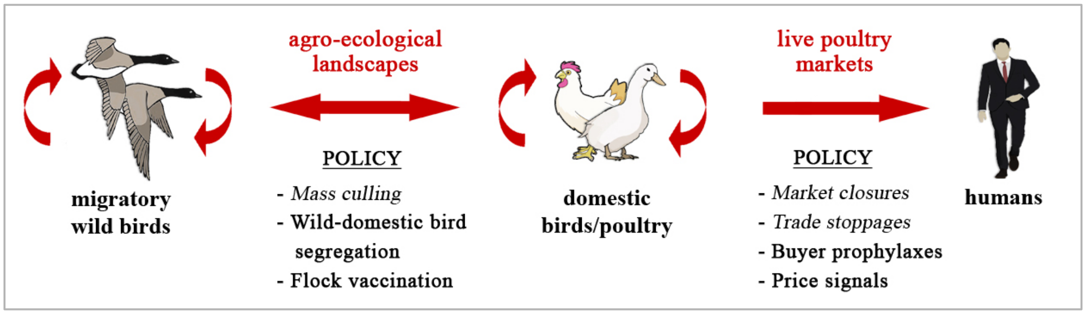
Source: The Emergency Prevention System for Animal Health (http://empres-i.fao.org/eipws3g/).

China is traversed by several important migratory bird pathways, which are conduits of avian influenza spread. Rice paddies also cover large sections of the country, providing habitats for both wild birds and free-ranging poultry. This population overlap can facilitate interspecies influenza transmission (Gilbert et al., 2008; Martin et al., 2011; Paul et al., 2010). Additionally, China has seen large increases in both wild bird and poultry numbers, the latter stimulated by rising consumer demand – per-capita consumption of poultry has risen from 1 kg to 9 kg over the past three decades (Pi et al., 2014). With rising poultry consumption, chickens, ducks, and other domestic bird species can act as an intermediary for human infection. Once established within the poultry trade, avian influenzas can spread rapidly to China's numerous live poultry markets (LPMs), as has been demonstrated by the H7N9 epidemic (Gilbert et al., 2014). And despite being "unique epicenters" of human infections, LPMs have been, and for the foreseeable future will remain, a major source of poultry sales in China (Pi et al., 2014; Webster, 2004; Woo et al., 2006).

In China, efforts to control avian influenza risks have been both ad hoc and post hoc. Against a background of rising zoonotic risks, policies should be anticipatory, aiming to avoid outbreaks rather than merely respond to them (Castillo-Chavez et al., 2015; Pike et al., 2014). The present approach of managing avian influenza risks in China has been characterized by: (a) mass culling, with wholesale slaughter of entire flocks, often prompted only by the suspicion of infection; (b) attempts at widespread vaccination, the implementation of which has been insufficient and the potency of which is confined to circulating strains; (c) abrupt trade restrictions and market closures that can threaten livelihoods and abrade traditional values. Such policies are unsustainable in the long run (Gao, 2014). Policies should instead emphasize preventative management in the landscapes that serve as mixing zones for wild and domesticated birds on the one hand, and the LPMs that serve as the primary venues of human exposure on the other. Mitigation at these two points is integral to controlling avian influenza risks in China (see Figure 14).

Figure 14

Pathways of avian influenza transmission among migratory birds, poultry, and people, including environments of frequent infection, and common (italics) and potential policies.

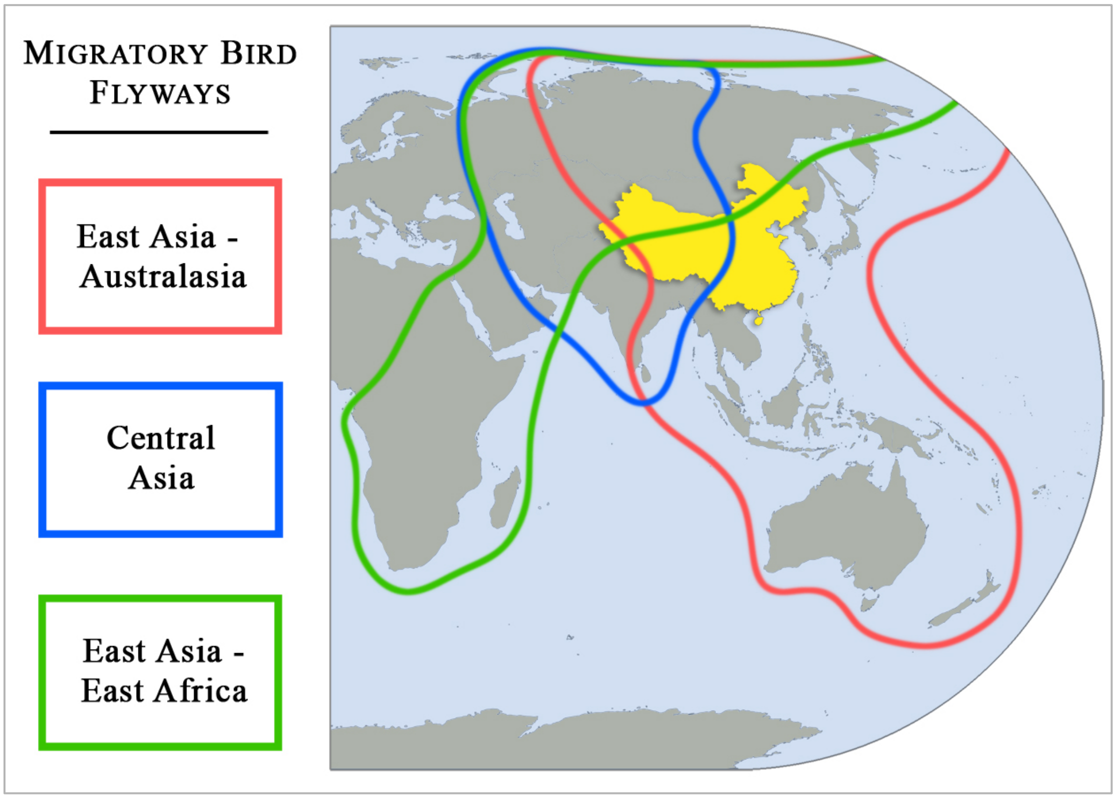


6.2. Infected Landscapes: The Wild Bird-Poultry Interface

China's biodiversity has declined steeply in recent decades. The major exception has been the avian population, which stabilized between 1970 and 2000 and has since increased by over 40% (Xie et al., 2015). Three major migration corridors extend across China: the East Asia-Australasia, Central Asia, and East Asia-East Africa flyways (see Figure 15). These flyways bring wild birds into landscapes populated by livestock, including free-ranging poultry. This has significant epidemiological implications. In Asia, migratory waterfowl are responsible for both the long- and short-distance spread of avian influenza, and is likely the principal, non-anthropogenic means by which the disease enters China (Chen et al., 2005a; Gilbert et al., 2010; Peterson et al., 2007; Si et al., 2009; Takekawa et al., 2010; Tian et al., 2015). Given the length of these flyways, migratory birds pass over numerous and sizeable reservoirs of potential infection (e.g., both wild and domesticated bird populations) in a number of countries before finally arriving in China.

Figure 15

The three major migratory bird flyways that traverse China: East Asia-Australasia, Central Asia, and East Africa-East Asia.



Additionally, several of China's largest lakes and wetland areas are located along these migratory corridors, such as Poyang Lake and Qinghai Lake. These large water bodies and their wetlands are important habitats for wintering and breeding birds, and thus potential hotspots for avian influenza outbreaks ((Martin et al., 2011; Takekawa et al., 2010; Tian et al., 2015). In general, areas with water and consistent NDVI values – that is, high seasonal consistency in vegetation cover – tend to be more susceptible to the spread of avian influenza (Williams and Peterson, 2009; Zhu and Peterson, 2014). Along these lines, rice paddy is another high-risk type of land cover. Multi-cropped rice fields are prevalent throughout China, especially in the lake- and river-strewn southern provinces. Free-ranging domestic ducks are widely raised in such landscapes (it is a traditional method of husbandry and has also been encouraged by agricultural policy), which when flooded also attract wild waterfowl (Gilbert et al., 2008; Muzaffar et al., 2010). Managing wild-domesticated bird interactions in such "mixing-zone" landscapes is therefore crucial to mitigating avian influenza risks, as this is the initial point of "spillover" into chains of transmission that could ultimately lead to human infections.

6.2.1. Habitat Protection and Interspecies Segregation

Although many aquatic and vegetated habitats attract pathogen-carrying birds, the landscapes of highest concern are those in which large numbers of wild and domesticated birds coexist. Poyang Lake, for instance, has been frequently identified as a high-risk area because it is surrounded by rice cultivation and rural settlements: a 2006 census of the area recorded 50 million ducks, geese, and chickens, coupled with a wintering population of approximately one million wild birds (Xiao et al., 2010). Many of China's large freshwater lakes – including Poyang, Dongting, and Taihu, the top three, and their extensive networks of tributaries and wetlands – are located in rice-producing regions. The cropping systems along the middle stretches of the Yangtze River in particular are intensive, having been actively promoted by government policies in recent decades (Torbick et al., 2011). Between 2002 and 2010, 90% of all sown areas around Poyang Lake were for rice, which accounted for 95% of all cereal production in the region.

In these and similar landscapes across China, rice production and poultry farming are coupled. There is often a synchronization of the duck production cycle and the arrival of migratory birds in places like Poyang and Dongting. This brings together hundreds-of-thousands of wild birds with even larger numbers of juvenile poultry (which are most susceptible to avian influenza infection) (Cappelle et al., 2014). In areas where wild birds and free-ranging poultry coexist, the movement patterns of the latter bring the two populations into close enough contact for pathogen transmission (Prosser et al., 2015). More generally, agricultural development increases infectious disease risks for livestock and people, in large part by amplifying interspecies interactions at the "wildlife-livestock-human interface" (Jones et al., 2008). As Patz et al. (2004) have argued, the encroachment of wildlife habitats from agriculture exacerbates the risk of novel pathogens entering livestock and human populations.

In the middle Yangtze River basin alone, there are 159 recorded species of waterbirds, at least half of which are migratory (Wang, 2004). An extensive 2004 census of waterbird populations in the entire lower Yantgze floodplain – which includes Poyang, Dongting, and several other important lakes and wetlands – identified the region as a critical area for avian conservation (Barter et al., 2005). By contrast, Qinghai Lake is located in a sparsely populated landscape and is largely devoid of poultry production, and consequently has been of much lower concern (Cappelle et al., 2014; Prosser et al., 2013). Therefore, *a priori*, lakes and wetlands that attract significant numbers of migratory waterbirds, and which are nestled within extensively farmed and settled landscapes, are the highest risk areas for poultry outbreaks (Prosser et al., 2013).

However, the recorded poultry outbreaks of avian influenza around such "hotspots" do not always match *a priori* risk assessments. Although rice cultivation has been highly correlated with H5N1 poultry outbreaks in China, natural waterfowl habitats such as lakes and wetlands have not (Takekawa et al., 2010). Careful study of the connections between poultry production and disease ecology suggests a potential explanation: the protection of wild birds and their habitats mitigate avian influenza risks by segregating them from poultry populations; this may be called the "Conservation-as-Biosecurity Effect" (CBE). The scientific rationale for CBE comes from landscape epidemiology, which integrates concepts from disease ecology with those from landscape ecology (Meentemeyer et al., 2012; Reisen, 2010).

Migratory birds and poultry can exchange pathogens when in close proximity, through physical contact or environmental pollution. Protecting natural avian habitats therefore becomes a kind of *de facto* quarantine of the former. In the terminology of landscape epidemiology, effective protection of wild bird habitats can reduce or eliminate the "nidus of infection," in which interspecies transmission occurs (Reisen, 2010). Although the concept was initially developed with reference to vector-borne diseases, they can be instructively applied to avian influenza as well (Cumming, 2010; Cumming et al., 2015). Our understanding of avian behavioral ecology seems to support this conclusion. Empirical studies of migratory waterfowl in the US and China have found that they prefer natural wetlands to anthropogenic landscapes, and protected habitats to non-protected ones (Beatty et al., 2014; Li et al., 2013; Wu et al., 2014). Recent analysis of "Important Bird and Biodiversity Areas" for migratory waterbirds in China (catalogued by Bird Life International) has shown that habitat protection may have a mitigating effect on H5N1 outbreaks among poultry (Wu and Perrings, 2017b).

In China, avian conservation efforts have largely focused on the preservation and restoration of lakes and wetlands, which have come under stress from land use changes, especially for agriculture and urbanization. Since the turn of the century, there has been extensive ecological restoration of such landscapes, returning farmland to wild land. Additionally, human settlements have also been relocated. All these measures have improved the quality for migratory bird habitat (Fang et al., 2006; Sun et al., 2015). Among the many migratory bird habitats set aside for protection include large sections of both the Poyang and Dongting ecosystems. Both have been classified as “Wetlands of International Importance” under the Ramsar Convention, and reserve areas with the specific aim of avian conservation have been set up.

The Poyang Lake Nature Reserve (PLNR) was established in 1983, covering 22,400 hectares in the northwestern part of the lake system. In 2012, the government designated the 5,180 km^2 of Poyang Lake proper and its surrounding wetlands as a “core protection zone,” where ecological preservation and restoration are given highest priority. There is also an auxiliary zone around this core where only limited development can occur (Wang and Li, 2012). By strictly debarring human activity, including poultry husbandry, from the primary lake and wetland habitats, this zoning scheme is likely to diminish contact, and therefore pathogen transmission, between wild birds and poultry. However, to fully quantify the extent of CBE in China and elsewhere, as well as the general and particular conditions under which it occurs, more site-specific studies are needed.

6.2.2. Vaccination and Industry Modernization

Despite best efforts at the segregation of wild and domesticated birds, widespread husbandry of free-ranging poultry will persist in China for the foreseeable future.

Notwithstanding the country's rapid urbanization, China's rural population stands at approximately 600 million people; by 2030, that figure will decline markedly, but is still likely stand at around 400 million (National Bureau of Statistics, 2017; Peng, 2011b). Furthermore, an emerging civic ethos and policy momentum towards conservation will improve the ecological prospects of avian species in China (Ma et al., 2013; Wong, 2005; Yang and Calhoun, 2007). The extent to which this will translate into improved habitat protection – e.g., of the Ramsar Convention quality – is unclear, but it means that large numbers of migratory birds will continue to arrive in China. Given the practical difficulties of preventing mixing between wild birds and poultry, other preventative measures should be, and in certain cases have already been, taken. However, collaboration between organizations and officials charged with conservation and those from public health have been conspicuously lacking.

Currently, the most efficient means of addressing an outbreak after the fact is mass culling of infected and exposed poultry. But such policies have become increasingly ineffective and uneconomical given the diversity and frequency of HPAI outbreaks (Peyre et al., 2009). Furthermore, wholesale animal slaughter conflicts with bioethical and other humane values, creating social frictions that may delay or even forestall effective action. Therefore, in managing avian influenza risks, as in managing risks from forest fires, lake pollution, or fishery collapse, mitigation is more economically efficient than adaptation (Castillo-Chavez et al., 2015; Pike et al., 2014). The risk of an undesirable event, from an economic perspective, is the probability of its occurrence multiplied by its cost. The aim of poultry flock vaccination, which has become an important prophylaxis in the poultry industry, is to lower occurrence probability (similar to the aim of wild bird-poultry segregation).

Like all other epidemic control measures, vaccination is not a comprehensive solution, with efficacy varying geographically and across different HPAI strains. Nonetheless, when applied with sufficient consistency and scope, it can mitigate the spread of avian influenza among poultry flocks (Swayne, 2006). The existing empirical and theoretical literatures suggest a general epidemiological relationship between HPAI spread and vaccination, and therefore guidelines for implementation. In principle, vaccination, aims to reduce the pathogen reproduction value (R_0) below 1, the threshold beyond which an infection precipitates an epidemic. As Anderson and May (1985) showed, based on first epidemiological principles, the corresponding vaccination level should be $1-1/R_0$. Quantifying the transmission rate of H5N1 among poultry flocks during the 2004 Thailand epidemic, Tiensin et al. (2007) found that a critical proportion of the susceptible poultry flock (80%) needs to be vaccinated to eliminate the virus. For areas where backyard poultry farming is particularly high, the study concluded that critical proportion needs to be even higher, but a value has not been specified empirically.

According to van der Goot et al. (2005), an experimental study of vaccination's effect on H7N7 transmission among poultry, "Vaccination is able to reduce the transmission level to such an extent that a major outbreak is prevented… We conclude that vaccination of poultry can be an effective tool to prevent the spread of highly pathogenic AI viruses." This conclusion is reinforced by other studies of avian influenza vaccines, notably for H5N1. For instance, Hong Kong launched a large-scale poultry vaccination campaign in 2002. Although there have still been HPAI infections among poultry and people, the campaign has been considered a success given the high number of risk factors favoring outbreaks in the city – e.g., its location directly along a major migratory bird flyway; its adjacency to mainland China and the high volume of poultry imports therefrom; and a subtropical climate conducive to viral persistence (Capua, 2014; Ellis et al., 2005). In one of the few studies of poultry vaccination in China, a farm-level survey around the putatively high-risk Poyang Lake area found that poultry vaccination decreased the likelihood of infection from avian influenza and a number of other poultry diseases (Jiang et al., 2014).

Nonetheless, given the large size of poultry populations across Asian countries and the high costs of implementation across a variety of livestock production methods, national-level immunity is difficult, if not impossible, to achieve in the region (Hinrichs and Otte, 2012). Large-scale vaccination is often hampered by the practical difficulties of implementation. The efficacy of avian influenza vaccines has been influenced by myriad genetic, ecological, and administrative factors (Capua, 2014; Capua and Marangon, 2006; Peyre et al., 2009). It has also been found that "silent", or undetected, spread of avian influenza can occur even among vaccinated flocks (Poetri et al., 2014). And more generally, vaccination doesn't guard against viral mutations and novel strains. The costs of continual, widespread vaccination against both existing and recently emergent avian influenzas are likely to be prohibitively high.

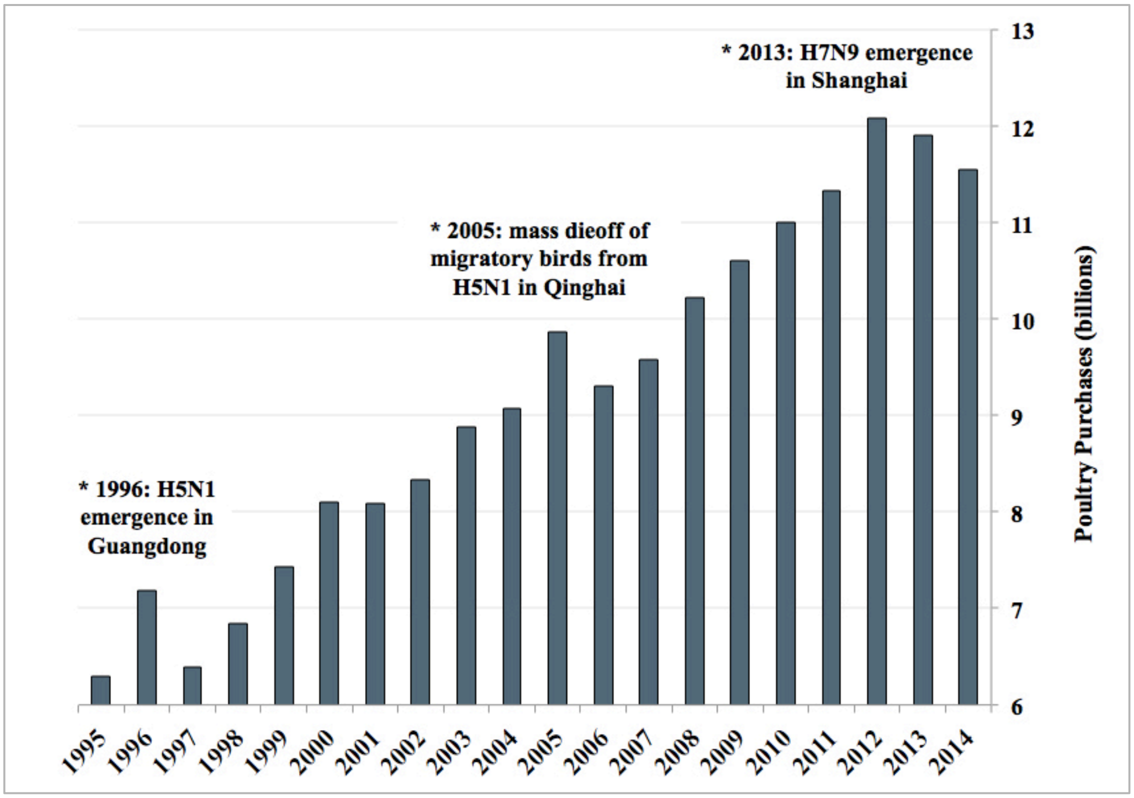
In recent years, China has greatly improved its institutions and regulations overseeing livestock health. This has included improving surveillance, passing a series of laws outlining the necessary steps to contain outbreaks upon discovery, and developing a system of veterinary support extending down to the county level (Wei et al., 2015).

Despite these improvements, biosecurity is still underfunded compared to developed-country standards (Tong et al., 2015). Additionally, biosecurity in China's livestock sector often suffers from administrative problems such as lack of accountability, inadequate instructional capacity, and low professional standards (Wei et al., 2015). These problems may be particularly acute in poorer inland areas, where rural poultry production is the least modernized.

One way in which biosecurity against avian influenza may have improved is as an indirect consequence of poultry industry modernization. The shift towards the industrial production of livestock in China will likely improve biosecurity in the long run (Wei et al., 2015). For instance, more modern production methods can make it easier to implement and enforce sanitary regulations, including vaccination, and to carry out surveillance. Factory production also helps insulate poultry populations from contact with wild birds. The consumption of poultry meat has grown significantly in recent decades (Figure 16). To cope with rising demand, the proportion of backyard husbandry – the traditional socio-ecological "engine" of avian influenza in China (Cardona et al., 2009) – has declined as a share of production, giving way to factory-style farming. This trend will likely continue into the foreseeable future (Pi et al., 2014). This modernization, measured by the proxy of production intensity – i.e., average bird weight – has been found to be a mitigating factor of H5N1 poultry outbreaks at the provincial level (Wu and Perrings, 2017b). Indeed, due to increasing returns to scale, the industrialization of livestock production could go hand-in-hand with increased biosecurity (Hennessy and Wang, 2012).

Figure 16

Total annual poultry sales in China, 2004-2015.



Source: The National Bureau of Statistics of China (2015).

Nonetheless, industrial poultry production generates its own epidemiological risks (not to mention ethical concerns), perhaps most notably by creating extremely high population densities, rapid throughput of animals, and other acute ecological conditions (Leibler et al., 2009). In the equation of risk, occurrence probability (i.e., exposure to infection) may consequently be lower due to the screening of susceptible poultry from wild birds; but the value-at-risk (e.g., a much larger population of poultry) is higher. Industry modernization by itself is not sufficient as a means of disease risk mitigation; it needs to be coupled with rigorous biosecurity regulations and professional standards of operation.

6.3. Live Poultry Markets: The Human-Poultry Interface

So far, H5N1 and H7N9 have not achieved sustained person-to-person transmissibility. Exposure to diseased poultry has been the primary pathway of human infection in China, with the risk highest in LPMs (Gilbert et al., 2014; He et al., 2014; Webster, 2004; Woo et al., 2006; Yu et al., 2014). Factors that make Chinese LPMs "unique epicenters of transmission" include the diversity of marketed animals, high densities of people and animals, carryover of animals day-to-day, daily introduction of new animals, constant traffic of people, and potentially unhygienic conditions (e.g., large amounts of blood and excreta) (Webster, 2004; Woo et al., 2006). Connected by trade, LPMs are also nodes in a trade network that greatly expands the geographic scope of avian influenza spread (Fournié et al., 2013; Gilbert et al., 2014; Magalhaes et al., 2012).

Despite their role in the emergence and spread of avian influenza, LPMs remain an important part of China's cultural and commercial life (Gao, 2014; Goldman et al., 1999; Woo et al., 2006). As recently as 2010, more than a decade after the emergence of H5N1, 77% of China's poultry were still sold in LPMs (Pi et al., 2014). LPMs owe their preeminence to, *inter alia*, culinary culture (e.g., a strong preference for fresh ingredients, including meat), lower prices (or the perception thereof), more engaging service, product variety, and opportunities for social engagement (Goldman et al., 1999). In China, the market share of LPMs will decline with continued economic modernization, but by 2020 they will likely still constitute the largest source of poultry sales (Pi et al., 2014).

Consequently, LPMs are expected to remain a significant source of avian influenza risks for the foreseeable future (Gilbert et al., 2014; Webster, 2004; Woo et al., 2006; Yu et al., 2007; Yu et al., 2014).

6.3.1. The Live Poultry Trade and Supply-Side Management

The mitigation of avian influenza risks in China's LPMs has focused on the supply side: targeting poultry supply chains and improving monitoring, vaccination, and other biosecurity practices during delivery and vending. For instance, ducks have been banned from Shanghai's LPMs since 2004 in an attempt to mitigate H5N1 outbreaks. However, this did not prevent the emergence and rapid spread from Shanghai of H7N9 less than a decade later. In that metropolis of approximately 25 million people (ranked in per-capita GDP terms as the most affluent province in China), approximately 120 million of 190 million chickens sold annually were purchased in LPMs (Pi et al., 2014). In China as a whole, the further spread of H7N9 will most likely occur in urban LPMs (Gilbert et al., 2014).

Post-outbreak management has also focused on the supply side. For instance, responses to successive H5N1 outbreaks in Hong Kong, where the disease first came to international attention, have included: the elimination of aquatic birds, and then selling them chilled; screening poultry truckloads for immunity; removal of quail, a known wild carrier of the disease, from markets; the implementation of cleaning days every month in which every market is emptied and cleaned; use of inactivated vaccines on Hong Kong poultry farms (Webster, 2004). In 2013, after the initial H7N9 outbreak in Shanghai, local authorities closed all 464 LPMs in the city, subjected them to cleaning and disinfection, and interdicted live poultry imports from adjacent provinces (He et al., 2014; Yu et al., 2014). These policies were effective in arresting the proximate forces of disease spread. The 2013 H7N9 containment efforts in the Yangtze River Delta (YRD) prevented further human infections for the duration of their enforcement. Controlling for environmental factors – namely humidity and seasonality – market and trade closures were shown to be the most effective means of containing spread (cases were reported in neighboring areas that did not implement such measures) (Yu et al., 2014). Similarly, in Hong Kong, closures and cleanings reduced the spectrum of influenza strains compared to those circulating in the LPMs of mainland China (Webster, 2004).

However, such ad-hoc and post-hoc measures are costly and complex, entailing surveillance, monitoring, reporting, closures, interdictions, and disinfections. The implementation of such measures is also complicated by governance structures. As evidenced by the responses to H5N1 and H7N9, implementing policies throughout poultry supply chains and containing outbreaks usually involves numerous administrative jurisdictions (e.g., counties, prefectures, and provinces) as well as various ministries (e.g., for agriculture, public health, and commerce). Furthermore, due to their abruptness and heavy-handedness, market closures and trade restrictions may result in high costs to the local economy, the abrasion of cultural sensibilities, and social discontent provoked by prohibitions on communal and commercial activity.

And perhaps most significantly, this strategy has not been successful at attenuating the underlying drivers of risk. For instance, shortly after the stringent regulations in the YRD were lifted in early 2014, a new human infection was confirmed and the region’s LPMs had to be shut down once again (He et al., 2014). Conventional supply-side policies are important –including reactive measures to contain spread after an outbreak. However, to be sustainable in the long term, these measures must be supplemented by policies that address the demand side, particularly factors relating to the behavior of participants in the live poultry markets and trade. These are the primary drivers of human exposure, and therefore of infection risk.

6.3.2. Behavioral Dynamics and Demand-Side Policies

Demand-side policies should be based on an understanding of how LPM epidemiology is influenced by the behavior of vendors and consumers. Their choices affect the quantities of poultry bought and sold, interactions with live poultry at the market, and the levels of biosecurity undertaken, including prophylaxes and hygiene – in sum, the likelihood of exposure to infection. Following an outbreak, the aggregate effect of individual decisions largely determines the epidemic's trajectory (Fenichel et al., 2011; Perrings et al., 2014). A systematic understanding of consumer and vendor choices in LPMs capacitates more cost-effective and less heavy-handed forms of intervention. These include the use of market instruments to deter risky behavior, thereby more closely aligning private decision-making with public welfare (Morin et al., 2015).

Studies suggest that the risks of avian influenza exposure in LPMs tend to be underestimated by consumers and vendors alike (Fielding et al., 2005). For instance, traditional but risky practices such as blowing on cloacae to assay the health of live poultry can still be observed among LPM customers in China (Woo et al., 2006). And even among workers who handle poultry daily, lack of knowledge often leads to inadequate levels of prophylaxis (Kim et al., 2011). It follows that demand-side risk management should use information to discourage unsafe behaviors and promote beneficial ones. Fortunately, there is evidence that increased awareness of avian influenza risks prompts behavioral changes in Chinese LPMs that reduce disease exposure, such as not buying live poultry, avoiding markets during outbreaks (i.e., selective distancing), and wearing masks in (Kuo et al., 2011; Lau et al., 2008; Liao et al., 2009).

Mitigating the risks of food-borne pathogens is a general public health challenge. In the case of pathogens with animal-to-human, but not human-to-human, transmissibility, the principles of demand-side management for avian influenzas are similar to those for salmonella, another poultry-borne zoonosis of long-standing international concern. To control salmonella exposure, the USDA outlined procedures for the handling of raw poultry, including the labeling of raw poultry to indicate that they must be fully cooked to ensure safe consumption (White et al., 1997; White et al., 2007). Explicitly identifying the potential health risks of poultry and attendant safe-handling practices could also lower human exposure to avian influenza. When it comes to foods that are naturally pathogen-prone such as poultry, even small changes among vendors and consumers could significantly reduce the incidence of infection (Griffth and Redmond, 2005).

That said, for all their social functions LPMs are still markets: venues for commercial transactions where economic logic remains central. Economically speaking, if the price of a product increases, the quantity demanded falls. This offers another way to appeal to the agency of discriminating individuals, creating opportunities for less intrusive and less costly, and ultimately more sustainable, policies. Consumers may not always be equipped with adequate information about the riskiness of live poultry in certain markets, but if the risk is embodied in prices, the information is communicated and will likely be acted upon with the consumer switching to safer alternatives (e.g., frozen poultry or other types of meat). Applying this logic to the control of avian influenza could yield new options for successful intervention (Zilberman et al., 2012). For instance, in a survey of consumer attitudes and preferences in China, Jin and Mu (2012) found that there was a significant premium associated with avian influenza in poultry purchases, and that consumers were willing to pay for traceability labeling to ensure product safety.

Relatedly, prompted by costly epidemics in the 1950s and ‘80s, Sweden developed what is arguably the world’s most successful *Salmonella* control program. In addition to standard supply-side quality control measures, it also developed an incentive structure that includes insurance schemes to compensate for potential losses in the event of outbreaks; this has encouraged voluntary participation by producers, which, by the 1990s, approached industry-wide adoption (Altekruse et al., 1993). Under such conditions, the costs of indemnification would be internalized by suppliers, which are then reflected in market prices. To address avian influenza risks, a corollary policy would be to subsidize producers of frozen poultry, thereby lowering the price of their products and thereby offering a more economical substitute for LPM poultry.

The design and implementation of such demand-side policies require new analytical frameworks, especially with an anticipatory/preventative dimension. The existing literature on the role of LPMs in avian influenza epidemics is dominated by medical studies. More social, and especially behavioral, models are needed to clarify the drivers of avian influenza epidemics, and to inform timely interventions (Janes et al., 2012). Traditional epidemiological models abstract from how decision-makers weigh benefits, expected costs, and perceived risk, as well as from feedbacks between behaviors and the risk environment. Models that incorporate dynamics in which parameters are not exogenous but endogenous, changing iteratively based on the choices of reactive individuals, can enhance predictive power and thereby improve the efficacy of disease control (Fenichel et al., 2011; Perrings et al., 2014). Such behavioral models and their policy extensions require more research into the social ecology of LPMs, including ethnographic data to inform the parameters of behavioral models (Janes et al., 2012; Kapan et al., 2006). There are already such efforts underway in China, notably with USAID's Emerging Pandemic Threats program (PREDICT).

6.4. Conclusion

As we mark the centenary of the influenza pandemic of 1918-1919, in which upwards of a quarter of the world's population was infected and 100 million people died (Lemon et al., 2005; Taubenberger and Morens, 2006), we should be mindful that many of its underlying risk factors still exist, and in a more populated and interconnected world. Indeed, that particular virus has left an long-lasting epidemiological legacy: it remained in circulation and contributed genes to other epidemic and pandemic influenzas over the past century (Morens et al., 2009). Furthermore, it is believed to have been an avian-borne virus that "jumped" directly into an immunologically naïve human population (Taubenberger et al., 2005). Although widely referred to as the "Spanish Flu," recent analyses have pointed to China as the actual origin of the pandemic (as it was for the other two 20th Century influenza pandemics, of 1957 and 1968) (Langford, 2005). Mitigating the risks of a fourth influenza pandemic from China is an urgent challenge for global public health.

The fact that avian influenzas have yet to acquire sustained human-to-human transmissibility makes the task of management simpler, but also more urgent. Greater efforts need to be made to mitigate the risks posed by avian influenza at the wild bird-poultry and poultry-human interfaces. Once an avian influenza such as H5N1 or H7N9 achieves sustained interpersonal transmission, it will likely precipitate a global pandemic. As this review has shown, the conventional strategies of culling and vaccination should be supplemented by policies that segregate wild and domesticated birds in their common habitats, which has the positive side effect of avian conservation (and vice versa). Additionally, traditional supply-side management of LPMs should be reinforced by demand-side policies focusing on market behavior, which would also be less disruptive than many existing measures. With the emergence of new avian influenzas and the continued infections of poultry and people showing no signs of abatement, the time for effective action is dwindling.

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APPENDIX A

THE RESULTS OF THE REGRESSION MODELS IN CHAPTER 4

Table 8

Results for models of risk factors of H5N1 poultry outbreaks in China, from January 1, 2004 to September 20, 2017. Odds ratios and p-levels are reported (the latter in parentheses). All are significant at the 1 per cent level. Controls were generated at a ratio of 5 for each 1 case, distributed randomly over the map without reference to administrative boundaries. Results from columns (a), (b) and (c) differed because of different values for rice paddy area radius. The variables “Proximity to nearest unprotected large water body” and “Proximity to nearest Ramsar wetland” were unit-less because they were normalized (see Methods section).

Variables	Units	H5N1 Poultry Outbreaks (a)	(b)	(c)
Proximity to nearest unprotected large water body	-	1.0051 (0.000)	1.0455 (0.000)	1.0418 (0.000)
Proximity to nearest Ramsar wetland	-	0.98326 (0.001)	0.97906 (0.000)	0.97633 (0.000)
Rice paddy area				
within 10-km radius zone	km^2	1.0163 (0.000)		
within 20-km radius zone	km^2		1.0052 (0.000)	
within 50-km radius zone	km^2			1.0010 (0.000)
Per-capita GDP	¥	0.99999 (0.000)	0.99999 (0.000)	0.99998 (0.000)
Observations		1206	1206	1206
Pseudo R^2		0.1940	0.2205	0.2293

Table 9

Results for models of risk factors of H5N1 poultry outbreaks in China, from January 1, 2004 to September 20, 2017. Odds ratios and p-levels are reported (the latter in parentheses). All are significant at the 1 per cent level. Controls were generated at a ratio of 5 for each prefecture, regardless of the size of the prefecture, to account for geographically uneven distribution of population. Results from columns (a), (b) and (c) differed because of different values for rice paddy area radius. The variables "Proximity to nearest unprotected large water body" and "Proximity to nearest Ramsar wetland" were unit-less because they were normalized (see Methods section).

Variables	Units	H5N1 Poultry Outbreaks		
		(a)	(b)	(c)
Proximity to nearest unprotected large water body	-	1.0777 (0.000)	1.0735 (0.000)	1.0715 (0.000)
Proximity to nearest Ramsar wetland	-	0.97168 (0.000)	0.96936 (0.000)	0.96834 (0.000)
Rice paddy area				
within 10-km radius zone	km^2	1.0065 (0.000)		
within 20-km radius zone	km^2		1.0022 (0.000)	
within 50-km radius zone	km^2			1.0004 (0.000)
Per-capita GDP	¥	0.99998 (0.000)	0.99998 (0.000)	0.99998 (0.000)
Observations		1356	1356	1356
Pseudo R^2		0.1476	0.1571	0.1571

Table 10

Results for models of risk factors of H5N1 poultry outbreaks in China, from January 1, 2004 to September 20, 2017. Odds ratios and p-levels are reported (the latter in parentheses). All are significant at the 1 per cent level. Controls were generated at a ratio of 5 for each case within a given province; the controls were then randomly distributed within the boundaries of the province. There were five mainland provinces without reported cases during the study period: Hainan, Sichuan, Heilongjiang, Beijing, and Shandong. Results from columns (a), (b) and (c) differed because of different values for rice paddy area radius. The variables "Proximity to nearest unprotected large water body" and "Proximity to nearest Ramsar wetland" were unit-less because they were normalized (see Methods section).

Variables	Units	H5N1 Poultry Outbreaks		
		(a)	(b)	(c)
Proximity to nearest unprotected large water body	-	1.0563 (0.000)	1.0546 (0.000)	1.0551 (0.000)
Proximity to nearest Ramsar wetland	-	0.98474 (0.002)	0.98333 (0.001)	0.98370 (0.002)
Rice paddy area				
within 10-km radius zone	km^2	1.0041 (0.003)		
within 20-km radius zone	km^2		1.0013 (0.001)	
within 50-km radius zone	km^2			1.0002 (0.004)

Per-capita GDP	¥	0.99999 (0.000)	0.99999 (0.000)	0.99999 (0.000)
Observations		1206	1206	1206
Pseudo R^2		0.0861	0.0883	0.0856