

Collaborative Research Approaches to the Role of Wildlife in Zoonotic Disease Emergence

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Abstract Emerging infectious diseases are a key threat to public health and the majority are caused by zoonotic pathogens. Here we discuss new collaborative approaches to understanding the process of zoonotic disease emergence that link veterinary medicine, public health, and ecological approaches: conservation medicine and one health. We demonstrate how studies on the underlying drivers of disease emergence (bushmeat hunting, wildlife trade, and deforestation) can provide ways to model, predict, and ultimately prevent zoonotic disease emergence and spread.

1 Introduction

Emerging infectious diseases (EIDs) are a significant threat to global public health, and around 75% of these are caused by zoonotic pathogens (Taylor et al. 2001; Woolhouse and Gowtage-Sequeria 2005). Zoonotic emerging diseases cause significant mortality (e.g., HIV-1 and -2), threaten, or have caused pandemic spread (e.g., SARS coronavirus, Nipah virus, Avian influenza virus), or threaten global health due to high case fatality rates and no available vaccines or therapies (e.g., Ebola virus, Nipah virus, Hendra virus) (Chua et al. 2000; Guan et al. 2003; Hahn et al. 2000; Klenk 1999; Subbarao et al. 1998). The underlying causes of zoonotic disease emergence are often the same processes that threaten wildlife populations and are largely environmental (e.g., agricultural expansion), human behavioral (e.g., increased travel and trade), or demographic (e.g., migration into new regions) (Morens et al. 2004; Smolinski et al. 2003). These changes alter the contact rates among humans, wildlife, and domestic animals, and provide a bridge for pathogens to move into new host populations (Daszak et al. 2001). Zoonotic pathogens that move across this bridge are either microbes already established as infecting humans, or those with no prior ability but able to evolve and adapt to this new host (Daszak et al. 2000; Morse 1993b). In this review, we discuss strategies for investigating the process of disease emergence from wildlife. We highlight this process by providing examples of key emerging zoonoses and make a case for increased integration of wildlife biologists, epidemiologists, veterinarians, ecologists, microbiologists and others in dealing with the global threat of emerging zoonoses.

2 Local Spillover, Global Emergence

The dynamics of disease emergence from wildlife are complex, involve an array of anthropogenic factors, and a diverse assemblage of known and unknown viruses, fungi, bacteria, and other pathogens. Anthropogenic factors bring human and domestic animal populations into increasing contact with wildlife reservoirs of zoonotic pathogens. For example, in Malaysia, intensive management of pig production in farms located in fruit bat habitat led to the spillover of Nipah virus, a paramyxovirus for which these bats serve as a reservoirs (Chua et al. 2000). Similarly, logging routes carved into primary forest have provided easier access to hunters in search of animals to eat or sell. The trade in bushmeat, which brings wild animals from geographically disparate habitats

into contact with each other and with people, has led to the spillover of several important zoonotic viruses including HIV, Ebola, and SARS (Hahn et al. 2000; Karesh et al. 2005; Leroy et al. 2004; Li et al. 2005). As human populations continue to increase, so do these anthropogenic pressures on wildlife habitat and populations. The result is likely to be continued spillover of new zoonotic pathogens into human populations, and perhaps even an increase in spillover rates, reflecting increases in these anthropogenic drivers of emergence.

Each spillover event is not necessarily a threat to global health per se. The process of emergence of pandemic pathogens, such as HIV-1, occurs in a series of stages (Hahn et al. 2000; Wolfe et al. 2005a). First, there usually is a series of initial spillover events, only some of which result in virus replication in the new, human, host. In some cases, viral pathogens spill over into domestic animals before reaching humans (e.g., Nipah virus, SARS) (Chua et al. 2000; Li et al. 2005). The spillover process has been termed viral traffic (Morse 1993a) or viral chatter (Wolfe et al. 2004b) for viruses' and is the initial phase of invasion of a pathogen into a new population described by disease ecologists (Anderson and May 1986). The next stage is the persistence of new viral pathogens in the human population (Anderson and May 1986). This occurs only if the zoonotic pathogen is able to be transmitted successfully from person to person, a characteristic which may occur naturally (e.g., the recent small-scale persistence of Nipah virus in Bangladesh; Hsu et al. 2004). It may also be a product of evolution from an ancestral nonhuman animal virus to a human-adapted strain, such as occurred when SIV_{CPZ} entered the human population to become HIV-1 (Hahn et al. 2000) or the initial emergence of measles virus from a morbillivirus of domestic animals (Dobson and Carper 1996). Finally, the spread phase of emergence (Anderson and May 1986) occurs when local chains of transmission link into denser human populations or populations that are well connected through sex or through needle-sharing by intravenous drug users (HIV) or through increased travel (SARS).

Just as the pressures that foster spillover have increased, there has been a significant increase over the past few decades in international trade and travel, with a resulting increased potential for the last, pandemic phase of emergence. Between 1986 and 1999, the global GDP per capita increased by an average of around 2.5% p.a., while an index of global air travel increased by 5% p.a. (The Boeing Company 2000) (Fig. 1). Likewise, as the demand for air travel has doubled during this period, the number of kilometers of new routes developed has increased in direct proportion (The Boeing Company 2000). Air travel industry projections suggest that, during the next 20 years, the air travel share of GDP will rise steadily, with air traffic growing by 4.0% annually, two percentage points faster than global mean annual growth in GDP (The Boeing Company 2002). This expansion will represent a doubling of global air traffic that is

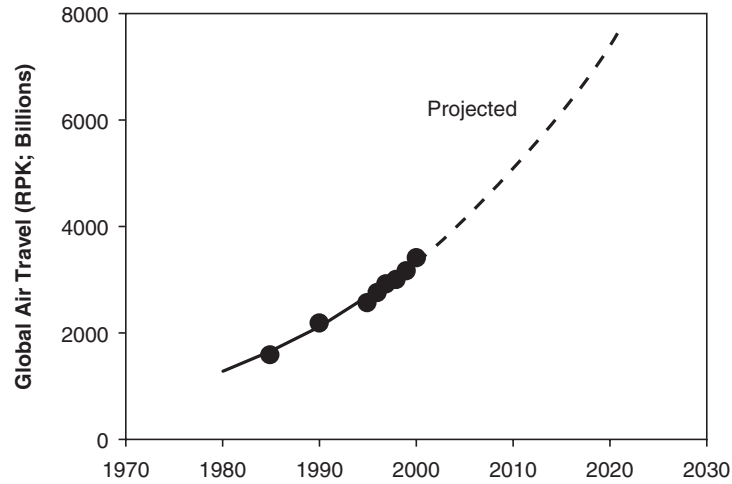


Fig. 1 Recent, and projected future, expansion of global air travel. Data are based on an index of air travel, revenue passenger kilometers (RPK), which describes the number of people traveling annually in relation to the number of kilometers traveled. (Data obtained from The Boeing Company, 2000)

unlikely to be mirrored by a similar expansion in disease surveillance budgets (particularly for wildlife EIDs). The impact of these trends on pathogen spread is likely to be significant, with a resulting growth in the ability of local spillover events to become pandemic outbreaks.

3 Fusing Ecology with Medical Sciences

Despite a large and growing literature on emerging zoonoses, there is still a dearth of research on the *process* of disease emergence. However, the association of disease emergence with anthropogenic environmental changes and demographic or human behavioral changes (Morse 1993b; Patz et al. 2004) may provide a fruitful way to examine this phenomenon (Aguirre et al. 2002; Daszak et al. 2000; Karesh and Cook 2005). For example, research that measures the rate of these anthropogenic or demographic changes and how they affect pathogen dynamics in wildlife would provide a way to assess the risk of spillover to people. Understanding relative or actual risks of spillover could provide

a tool to focus resources on high-risk regions (e.g., areas of recent deforestation) or high-risk behaviors (e.g., bushmeat hunting or agricultural changes). This may ultimately allow public health programs to predict and prevent zoonotic disease emergence.

The key to such approaches is a detailed, mechanistic understanding of the processes that drive disease emergence. Here we provide case-study examples in which ecologists have obtained a detailed understanding of the driver of an emergence event, and in which there have been varying degrees of collaboration between ecologists and medical scientists to study the process of disease emergence. These collaborations are especially fruitful areas of future research.

3.1 Bushmeat Hunting and Disease Emergence

In tropical forests, the building of roads to support logging or mining operations, or to connect villages and towns provides access to wildlife and is often associated with increased demand for, and access to, bushmeat. This process is thought to have led to spillover of simian immunodeficiency viruses and the emergence of HIV-1 and -2 (Hahn et al. 2000). Ebola hemorrhagic fever virus outbreaks in humans have repeatedly been linked to the handling of infected great apes (Leroy et al. 2004). With the expansion of human populations, there has been an increase in demand for bushmeat, particularly in locations where alternative sources of protein have been scarce (Bulte and Horan 2002; de Merode et al. 2004; Fa et al. 2003). It is therefore likely that the risk of future disease emergence through this process will also increase.

The process of deforestation, building of logging roads and expanding demand for bushmeat is complex, but there is a great deal of research that has quantified these factors. For example, researchers have analyzed the diversity of wildlife hunted, the weight of meat extracted from forests, its monetary and nutritional value, and the seasonal and interannual dynamics of hunting (Bulte and Horan 2002; de Merode et al. 2004; Fa et al. 2002a, 2002b). Anthropologists have studied how incentives for hunting wildlife vary from region to region. In Central and West Africa, hunters are often local village members hunting for subsistence or trade to local or regional markets (Wolfe et al. 2004a), whereas in other regions luxury, familiarity, medicinal value, tradition, prestige, taste preference, or subsistence drive the process (Wilkie et al. 2005). Ecologists have also measured the impact of hunting on the populations of some species (Bowen-Jones and Pendry 1999; Maisels et al. 2001; Plumptre et al. 1999). Combining these series of data would allow an assessment of how hunting increases as a logging road is built, and how this affects the dynamics of wildlife populations.

The final critical link of how these changes will affect the risk of pathogen spillover requires only three additional elements: measurements of background diversity of pathogens in hunted wildlife; assessment of whether these pathogens will be able to replicate in people; and measurement of the type of contact and rate of contact between hunted species and/or their meat, and people. Studies focused on these issues have already begun. For example, studies of exposure to nonhuman primate viruses in Cameroon bushmeat hunters have revealed new spillover events (Wolfe et al. 2005a, 2005b, 2005c). Studies of the patterns of spillover have identified those pathogen groups most likely to move from nonhuman to human hosts (Taylor et al. 2001; Woolhouse and Gowtage-Sequeria 2005). However, to truly fuse wildlife research with medical research on emerging disease will require a greater degree of collaboration among diverse disciplines. For example, few studies have used molecular techniques to survey hunted wildlife or other zoonotic reservoirs for novel pathogens, a study which would require collaboration among molecular biologists and wildlife biologists, and veterinarians. The wildlife mortality and monitoring network established in Central Africa is one example (Rouquet et al. 2005). Similarly, ecologists have used mathematical models to describe pathogen dynamics in wildlife (Dobson and Foufopoulos 2001; Hudson et al. 2002), but few studies have used these approaches to predict patterns of spillover from bushmeat. Expanding collaboration in the face of new zoonotic threats (e.g., H5N1 avian influenza) is likely to increase capacity to understand these complex processes.

3.2

Wildlife Trade and Disease Emergence

In 2002, SARS coronavirus emerged in humans in China (Drosten et al. 2003). The epidemiological risk factors of the first cases in Southeast China were proximity to live animal (wet) markets and working in the restaurant industry (Xu et al. 2004). Virus isolation and genome sequence data suggested a role for masked palm civets (*Paguma larvata*); however, infection seemed to be limited to those animals in the marketplace, as opposed to on farms or in the wild (Xu et al. 2004). Preliminary surveillance had suggested involvement of other species of small mammal traded for food in these markets; however, the natural reservoir for SARS-CoV remained unknown (Guan et al. 2003). Further work has demonstrated that *Rhinolophus* spp. bats are the wildlife reservoir of SARS-like coronaviruses, and it has been suggested that the trade in these animals for food initially led to spillover to other wet-market species and humans (Lau et al. 2005; Li et al. 2005). Bats, civets, and other mammals are traded in large numbers in Chinese wet

markets, but the origins of these animals are often many hundreds of miles from their point of sale. With an increasing demand for wild animal meat as China's economy grows, pathogen spillover from this wildlife trade is likely to be a continuing problem.

Wildlife trade also leads to the movement of animals over great distances and has caused the emergence of viruses in areas significantly outside their natural range (Karesh et al. 2005). For example, in 2003, Monkeypox emerged in the United States through the importation of Gambian giant rats from Africa (Sejvar et al. 2004). Pathogens may also be introduced into new regions in animals inadvertently carried with traded goods (Cook and Karesh 2005). West Nile virus emerged in the USA in 1999, with the first cluster of cases occurring in Queens, New York, close to a large international air and sea port (Lanciotti et al. 1999). However, it is unknown if this virus was introduced within birds shipped into New York for the pet trade or for livestock production, or whether it was carried within a mosquito in an airplane (Kilpatrick et al. 2004, 2006a). The highly pathogenic H5N1 strain of avian influenza has spread within Southeast Asia and Europe via the trade in poultry and via migrating birds, as well as through the trade in birds for pets (Kilpatrick et al. 2006c). A pair of H5N1-infected crested hawk eagles was confiscated by authorities at Brussels airport after being illegally smuggled into the country from Southeast Asia (Van Borm et al. 2005) and several mesias in a group of ornamental birds imported from Taiwan were found to be infected with the H5N1 virus while in quarantine in the UK (<http://www.defra.gov.uk/animalh/diseases/notifiable/disease/ai/pdf/ai-epidemrep111105.pdf>).

The model of collaboration between wildlife ecologists and medical scientists described in the bushmeat studies above suggests some simple but valuable strategies to predict and prevent zoonotic disease spillover and spread. For example, the spread of West Nile virus throughout the continental USA and into South America has led to concern over its potential spread to regions with endangered bird species that may be at risk of extinction by this pathogen. In Hawaii, over one-third of endemic bird species have been driven to extinction or endangered status by introduced avian malaria and pox (Van Riper et al. 1986). In the Galapagos islands, endemic Darwin's finches exist as separate species on individual islands, and are greatly threatened by disease introduction (Wikelski et al. 2004). Two recent studies have collated data on the average number of mosquitoes transported on airplanes and ships, the number and identity of migratory birds, pet birds and poultry imported onto these islands, and the number of people visiting these islands (Kilpatrick et al. 2004, 2006a). Using these data and simple mathematical models, it is possible to identify the most likely pathways of introduction of this zoonotic disease to the islands (mosquitoes carried by airplanes), and therefore to advise policy to reduce

the risk of pathogen introduction. This approach can easily be expanded using global data on wildlife trade to predict the risk of introduction of new or known zoonoses into new regions.

3.3

Urban Sprawl, Fragmentation, and Zoonotic Disease Emergence

Logging in tropical regions is paralleled by the process of urban sprawl in developed countries, and the removal of natural wildlife habitat. The impact of this process on wildlife diversity, ecology, and habitat quality has been studied extensively by ecologists (Johnson and Klemens 2005). The impact of this process on human health has also been well-studied, but largely regarding the impact of pollution and stress on human health and welfare. However, recent work by disease ecologists has shown a strong connection between urban sprawl, habitat fragmentation, the loss of biodiversity and increased risk of zoonotic disease spillover to people. Lyme disease emergence is facilitated by urban sprawl and associated fragmentation that reduce the diversity of mammal communities to a pair of highly competent reservoirs, the white-footed mouse (*Peromyscus leucopus*) and the eastern chipmunk (*Tamias striatus*) (LoGiudice et al. 2003). In the northeastern USA, the now endemic West Nile virus (WNV) is transmitted within a diverse assemblage of birds, mammals, and mosquitoes (Marra 2004). However, recent analyses of WNV dynamics across an urban-to-rural land use gradient has shown that the bulk of mosquitoes become infected by feeding on American robins (*Turdus migratorius*) (Kilpatrick et al. 2006b), a common suburban species. The risk of WNV infection at these sites is higher in urban and suburban habitat than in heavily forested habitat (A.M. Kilpatrick, unpublished observations).

4

A Call for Cross-disciplinary Collaboration

During the last few years, interest in the emergence of zoonotic diseases has grown. There has been a series of new programs developed by funding agencies in the USA, Europe, Canada, and Australia and national agencies working on public health and wildlife health in the USA, Canada, and Europe. Global organizations including the World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the Office Internationale des Epizooties (OIE), also known as the World Organization for Animal Health, have recently recognized the significance of wildlife as reservoirs for zoonotic diseases. Also, new journals have been published to deal with an increasing output of research

on emerging zoonotic diseases (e.g., *Vector-borne and Zoonotic Diseases*) and on ecological research in zoonotic emergence (e.g., *EcoHealth*).

The bulk of research on emerging zoonotic diseases in the USA and Europe continues to be concerned with developing new vaccines and drug therapies and surveillance in the human population. However, there might be more cost-effective and efficient ways of addressing this growing phenomenon. We have shown here that there is an increasing understanding of the ecological processes that underlie disease emergence from wildlife to people. We have highlighted examples of new, collaborative, and interdisciplinary approaches to emerging zoonotic diseases that are necessary to develop this new understanding into a focused surveillance and research approach that will ultimately allow for prediction and prevention of zoonotic disease spread. There has been a growing interest in such collaboration from veterinary researchers, through the new fields of “Conservation Medicine” (Aguirre et al. 2002) and “One Health” (Karesh and Cook 2005). There have also been calls for expansion of these initiatives from the National Research Council of the USA (Womack et al. 2005). However, there remains an urgent need to expand the connections and collaborations among veterinary researchers, microbiologists, public health researchers, and ecologists. We propose the following measures to encourage this approach:

1. Fostering collaboration among the disciplines. In particular, linking ecological approaches with laboratory advances in pathogen surveillance. This should be encouraged through education (undergraduate, postgraduate, and professional) and in research.
2. Encouraging studies to discover new pathogens in wildlife. This will provide a critical link toward predicting the risk of zoonotic disease spillover from wildlife. It will require the development of testing protocols and expansion of laboratory support in countries with high vertebrate biodiversity (those with a likely high biodiversity of potentially zoonotic agents).
3. Supporting studies that address the underlying drivers of emergence. Understanding how anthropogenic environmental changes and sociological or demographic factors affect the risk of disease emergence is likely to provide more cost-effective and ultimately more sustainable mechanisms to mitigate these threats.

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