The Significant but Understudied Impact of Pathogen Transmission from Humans to Animals

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OUTLINE

ABSTRACT

Zooanthroponotic pathogens, which are transmitted from humans to nonhuman animals, are an understudied aspect of global health, despite their potential to cause significant disease burden in wild and domestic animal populations and affect global economies. Some key human-borne pathogens that have been shown to infect animals and cause morbidity and mortality include measles virus (paramyxoviruses), influenza A virus (orthomyxoviruses), herpes simplex 1 virus (herpesviruses), protozoal and helminthic parasites, and bacteria such as methicillin-resistant *Staphylococcus aureus* and *Mycobacterium tuberculosis*. However, zooanthroponotic pathogens are most commonly reported in captive animals or domestic livestock with close human contact; there, the potential for economic loss and human reinfection is most apparent. There is also the potential for infection in wild animal populations, which may threaten endangered species and decrease biodiversity. The emergence and reemergence of human-borne pathogens in wildlife may also have negative consequences for human health if these pathogens cycle back into humans. Many of the anthropogenic drivers of zoonotic disease emergence also facilitate zooanthroponotic transmission. Increasing research to better understand the occurrence of and the potential for bidirectional pathogen transmission between humans and animals is essential for improving global health. ***Mt Sinai J Med 76:448–455, 2009.*** *© 2009 Mount Sinai School of Medicine*

Key Words: conservation, conservation medicine, H1N1 influenza A, herpesvirus, methicillin-resistant *Staphylococcus aureus*, paramyxovirus, primates, tuberculosis, zooanthroponoses, zoonoses.

> It is all one sickness, in the sense that our planet is suffering a systemic inflammation of *Homo sapiens*. The increasing frequency and increasing scope of zoonotic and zooanthroponotic infections should be seen in this light–as a pattern, a set of interconnected effects, reflecting causes that are largely of human doing. –David Quammen[1]

Zoonotic pathogens, which are transmitted from animals to humans, often infect persons in close contact with animals and have become an increasingly significant public health threat because of their potential to cause substantial and sometimes widespread disease in human populations.[2,3] Furthermore, the emergence of zoonotic pathogens can inflict substantial costs on national and global economies, leading to losses in trade and tourism and increased public health care costs (Figure 1).

Less frequently reported but constituting significant global health and potential economic issues, human-borne pathogens are transmitted to nonhuman animals. Such pathogens have, in the past, been

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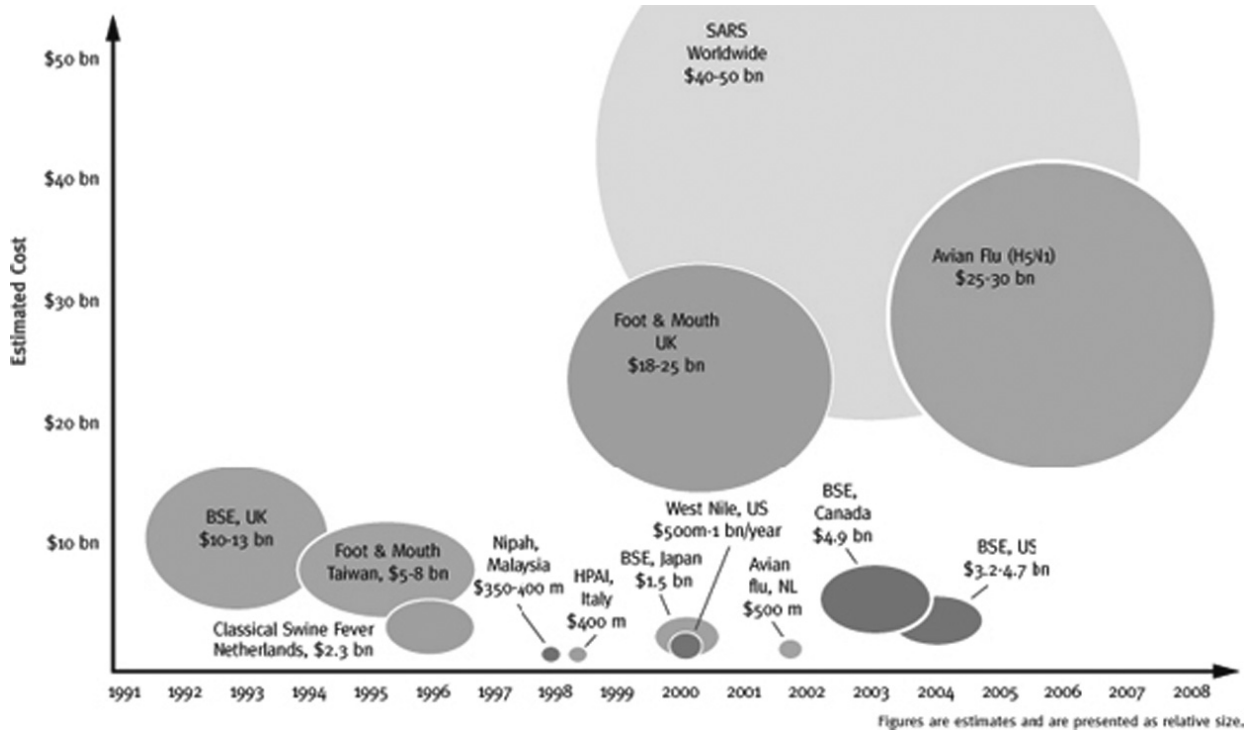

Fig 1. A chart showing the relative cost of recent outbreaks. Several of these outbreaks were due to zoonotic pathogens, including Nipah virus, SARS, West Nile virus, and avian influenza (H5N1). Figures include losses to tourism and trade and the cost of health care. **Abbreviations:** BSE, bovine spongiform encephalopathy; HPAI, highly pathogenic avian influenza; SARS, severe acute respiratory syndrome. Reprinted with permission from Bio-Era.[60].

Human-borne pathogens that are transmitted to nonhuman animals . . . (zooanthroponoses) not only present a health burden to many animal species but may cause damage to national or global economies and threaten wild animal populations. There also may be a risk of subsequent reinfection of humans if the pathogen is able to persist in animal populations.

termed *zooanthroponoses*[4] and not only present a health burden to many animal species but in some cases may cause damage to national or global economies and threaten wild animal populations.[5] There also may be a risk of subsequent reinfection of humans if the pathogen is able to persist in animal populations.

ZOOANTHROPONOTIC PATHOGENS

Zooanthroponotic pathogens include viruses, bacteria, and protozoal parasites and can be transmitted whenever humans come in contact with animals, whether those animals are wildlife, livestock, or zoo or laboratory animals. These pathogens may cause diseases with varying severity depending on the species infected. For example, increased human-primate interactions through activities such as ecotourism, research, and bushmeat hunting result in an increased risk of cross-species viral transmission.[6,7] Nonhuman primates, including chimpanzees (*Pan troglodytes*) and gorillas (*Gorilla gorilla* spp.), have been found to be susceptible to several pathogens carried by humans, including paramyxoviruses (eg, measles virus)[8] and intestinal bacteria,[7] which can be detrimental to the conservation of these endangered species.[9]

Domestic animals such as cattle, goats, and sheep can perpetuate cycles of infection in humans through the contamination of drinking water with human enteric pathogens.[10,11] *Cryptosporidium hominis* and *Giardia lamblia*, both human protozoal parasites, have been found in domestic cattle that

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have access to reclaimed wastewater.[12] The clinical presentation of common zooanthroponotic infections in animals is variable, and in some cases, such as herpes simplex virus 1 (HSV-1) or measles virus in primates, the disease is often rapidly fatal. Here we review some of the major groups of zooanthroponoses, the mechanisms of transmission, and the impact on animal and human health.

Measles Virus and Related Paramyxoviruses

Humans are the natural reservoir for measles virus. Human infection clinically presents with fever, maculopapular rash, and cough with coryza and conjunctivitis.[13] Another common sign of measles infection is Koplik's spots of the oral mucosa. The virus is transmitted via airborne droplets as well as direct contact with respiratory secretions of infected individuals.[13] The measles virus can infect any person who has not been exposed before or who has not been successfully immunized. Both New and Old World primates, including the great apes, which are all threatened with extinction, have also been shown to be susceptible to measles and other human-related paramyxovirus virus infections in the wild.[14,15] Great apes can become exposed to human viruses through close contact with tourists, researchers, or poachers.[15] Several outbreaks of respiratory illness were observed in chimpanzees at a research site in Côte d'Ivoire between 1999 and 2006.[14] Morbidity rates were 92%, and in 3 outbreaks that involved mortality, the rates were 13% on average (n = 110) and were as high as 19% (n = 32). Human metapneumovirus and human respiratory syncytial virus are both related to measles virus (family *Paramyxoviridae*) and are common respiratory illnesses in Africa.[16,17] Human metapneumovirus and human respiratory syncytial virus were found in some of the dead chimpanzees, and phylogenetic analyses indicated that these were of human origin.[14]

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Rhesus macaques (*Macaca mulatta*), which are often used as human models in biomedical research because of their physiological response to many human pathogens, have been shown to have a pathology similar to that of humans when infected with measles. In cases of natural infection in a wild setting and in cases of infection in a laboratory, they experience a progression of clinical signs very similar to those experienced by humans, including maculopapular rash, fever, conjunctivitis, and even Koplik's spots on mucosal membranes.[13,18] As with humans, macaques who recover from an initial measles infection will demonstrate immunity to measles virus.[18]

Measles infections in nonhuman primates may also have varied or more severe courses. In one experiment, it was found that infected marmosets (*Callithrix* spp.) lacked symptoms commonly found in humans and some nonhuman primates, such as rash, coryza, and conjunctivitis, and they exhibited a longer subclinical infectious period and a much higher mortality rate.[19] The lack of rash and the increased mortality among these animals have been attributed to a decrease in the immunological response to the measles virus.[19] A longer subclinical period may make infected marmosets more dangerous to susceptible humans.

In one outbreak that occurred among Japanese macaques (*Macaca fuscata*) in a Korean zoo, the source could not be identified, but it seemed that the monkeys were infected by aerosol from infected visitors.[20] Outbreaks of measles in primates have been shown to occur concurrently with human outbreaks of the same virus type.[20,21] In this case, the Japanese macaques suffered many secondary infections not normally seen in infected immunocompetent adult humans, and this indicated marked immunosuppression among infected primates.

Vaccination of wildlife or other animals at risk of exposure, where feasible, may be a beneficial strategy for preventing infection. Measles vaccine is highly effective in humans. One dose of live attenuated measles vaccine provides active immunity in 94% to 98% of susceptible persons, whereas a second dose will induce immunity levels of up to 99%.[13] Immunization with measles vaccine has been shown to be effective in some primate species,[19,22] and captive gorillas showed persistent immunity for up to 11 years post-inoculation. The potential for high mortality rates in endangered species may warrant immunization against measles in both captive and free-ranging populations that have high levels of contact with humans. Furthermore, improved regulation that limits contact between tourists and researchers and wild or laboratory primates may also

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reduce the risk of zooanthroponotic transmission of pathogens.[7]

Pandemic Influenza Virus (H1N1)

Wild birds are considered the natural reservoir for influenza A viruses (family *Orthomyxoviridae*) and have been shown to carry all hemagglutinin (H) and neuraminidase (N) subtypes.[23] Humans and other mammals, including pigs, are susceptible to infection with certain subtypes of influenza A virus, including pandemic strains of H1N1 (the etiological agent of both the 1918 Spanish flu and 2009 pandemic). Humans are susceptible to only 3 types of flu, H1N1, H1N2, and H2N3, all of which originated in birds but have become endemic to human populations and circulate globally. H5N1 remains an avian subtype to which people are highly susceptible, but it cannot easily transmit to other people. Pigs are unique in that they are susceptible to infection with both avian and human subtypes of influenza A; this allows them to act as mixing vessels for new strains via genetic reassortment.[24] Pigs are likely to have been infected with the pandemic H1N1 strain of 1918 by circulating human strains after the first wave of infection swept through the United States in 1918.[25] The pandemic in 1918 was the first instance of flu being described in pigs, and it spread widely throughout the United States, leading to recurrent outbreaks in pig populations and the name *swine flu*. H1N1 causes varying levels of morbidity in pigs, although it is rarely fatal. Strains of H1N1 have circulated in domestic swine herds in North America and Europe for decades since 1918, although in the1990s, H2N3 became the predominant strain in pigs in North America.[26–28]

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In 2009, a novel strain of H1N1 emerged in Veracruz, Mexico and quickly spread to the United States and more than 30 other countries via global travel networks, rapidly becoming a global pandemic.[27] Genomic sequencing of the 2009 pandemic H1N1 strain revealed that it was a novel strain that included genetic material with avian, swine, and human origins but that was not known to be circulating in swine herds.[29] The usual economic impact of H1N1 infection in swine herds is due to the high levels of morbidity, which include substantial weight loss and restriction on movement. However, H1N1 had a significant impact on the Mexican economy, which had an estimated $2.2 billion loss due to the closure of businesses and a drop in travel and tourism,[30] as well as a negative effect on the greater global economy because of the incorrect presumption that pigs were responsible for the human cases.[31,32] Additionally, the false perception that consuming pork could cause infection further affected the global swine trade.[33]

The only confirmed outbreak to date of the novel H1N1 strain in pigs occurred in a swine herd in Canada in March 2009. A laborer from the farm, who had recently traveled to Mexico, returned sick and may have introduced the H1N1 virus to the herd.[34] As the number of human cases increases globally, so too does the risk of additional instances of zooanthroponotic flu transmission, as was the case in 1918.

Herpes Simplex Virus 1

Herpes viruses as a group are associated with high mortality rates when exchange occurs between humans and nonhuman primates.[35–38] HSV-1 infection in humans is usually unapparent but may cause mild, recurrent oral and facial lesions.[13] More severe symptoms such as fever and malaise, keratoconjunctivitis, and pharyngotonsillitis are present in some 10% of primary infections, particularly in neonates and immunocompromised adults. Central nervous system involvement may also occur, although far less frequently. HSV-1 can be transmitted in the saliva of both symptomatic and asymptomatic humans. Humans are the natural reservoir for the HSV-1 virus, and 50% to 90% of adults worldwide have antibodies against it.

Although herpes simplex viruses cause relatively mild disease in immune-competent humans, they can be fatal when spread to many species of nonhuman primates, including gorillas (*Gorilla gorilla*), patas monkeys (*Erythrocebus patas*), colobus monkeys (*Colobus* spp.), marmosets (*Callithrix jacchus*),

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and white-handed gibbons (*Hylobates lar*).[35–38] Most animals infected with HSV-1 present with oral vesicles, as in human hosts, but the disease usually progresses to more severe sequelae, including conjunctivitis, meningoencephalitis, and death.[39] The most common outbreaks of HSV-1 in nonhumans have been described in zoo animals. In one such outbreak, 3 white-faced saki monkeys (*Pithecia pithecia)* in a zoo exhibit developed symptoms such as nasal discharge, anorexia, dehydration, fever, and seizures as well as oral ulcers.[40] All 3 died within 48 to 96 hours of the onset of the initial signs of disease. Necropsies revealed oral and esophageal lesions, liver lesions, and meningoencephalitis. The origin of the infection was thought to be visitors or a zookeeper. Researchers suspected that 1 monkey was initially infected, and then the virus quickly spread to the other 2 monkeys. The rapid transmission of HSV-1 to these monkeys and their death within 3 days suggest a very high susceptibility and illustrate the need for greater precautions to prevent zooanthroponotic infection in zoo settings.

Although HSV-1 causes acute fatal disease in a number of nonhuman primates, it does spare some species such as the macaque (*Macaca* spp.).[41] Researchers believe that the reason macaques are less susceptible to HSV-1 infection than other primates is that they are the natural host of another herpes simplex virus called herpes B virus, or cercopithecine−1.[41] Herpes B virus, like HSV-1 in nonhuman primates, causes acute fatal disease when people are infected. Although there have been substantial efforts toward research and prevention of herpes B in primate handlers in zoo and laboratory settings, recent studies of HSV-1 infection among captive animals remain scarce.[35–38]

Methicillin-Resistant *Staphylococcus aureus* and *Mycobacterium tuberculosis*

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacterial pathogen that has historically been the leading cause of hospital-based infections globally.[42] Recently, new strains of community-acquired MRSA have been identified and are an emerging public health threat and across the United States.[43] MRSA typically causes severe skin and soft tissue damage, and recently, community-acquired MRSA has also been identified as a cause of necrotizing pneumonia.[44] MRSA has been

MRSA has been reported in several livestock and companion animal species, and transmission between animals and between humans and animals has been described.

reported in several livestock and companion animal species, and transmission between animals and between humans and animals has been described.[45] Companion animals are vulnerable to hospital-acquired MRSA infections but may also acquire MRSA environmentally if living in a household with an infected person.[45] Long-term health care facilities have a high incidence of MRSA infection in their patients, who carry it from acute care facilities.[46] Interestingly, a recent study by Lefebvre *et al*.[47] showed that dogs that visited human health care facilities were more likely to become infected with MRSA than those that did not. These dogs were likely to have acquired the infection by licking patients or accepting treats from them. These dogs also moved from clinic to clinic, creating a potential opportunity to act as a vector for MRSA.

Humans are the natural reservoir for the bacterium *Mycobacterium tuberculosis*.[13] An infection from *M. tuberculosis* can have long periods of latency before proceeding to active tuberculosis (TB), which most commonly causes infiltrates and cavitations of the lungs, although extrapulmonary infections can be found in any tissue, including the lymph nodes, the central nervous system, kidneys, bones, and joints. Humans infected with TB may present initially with fever, fatigue, night sweats, and weight loss during the early period of infection and then with cough, chest pain, and hemoptysis as the disease progresses. TB can often be fatal, especially in immunocompromised hosts or when left untreated.[13]

Mycobacterium tuberculosis can also cause disease in a wide variety of animal species, including

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primates, elephants, Rocky Mountain goats, black rhinoceroses, and marine mammals.[48–50] As in humans, most animals develop pulmonary disease when infected with TB. Parrots present with skin and mucous membrane lesions.[51,52]

Anthropozoonotic transmission of *Mycobacterium tuberculosis* has been demonstrated in monkeys,[50,53] cattle,[54] parrots,[51,52] and elephants,[48] mostly in captive settings. Zoonotic transmission of TB has also been documented.[49] TB in animals can often be subclinical for longer periods of time in comparison with humans. Tuberculin tests, similar to those done in humans, can effectively detect subclinical disease in animals.[55] It has been suggested that humans may be at risk for TB infection when in contact with infected animals such as pet parrots; however, it is not known whether birds can reinfect humans.[52]

Anthropozoonotic transmission of Mycobacterium tuberculosis has been demonstrated in monkeys, cattle, parrots, and elephants, mostly in captive settings.

DISCUSSION

Zooanthroponoses negatively affect the health of livestock, companion animals, free-ranging wildlife, and zoo animals and can threaten populations of endangered species.[14] Zoonotic pathogens are responsible for 75% of emerging infectious diseases in humans, and outbreaks of zoonotic pathogens can have significant economic consequences globally (Figure 1).[56] Thus, it is not surprising that substantially more resources have been devoted to zoonotic disease research rather than zooanthroponotic disease research. One result of this, however, has been a lack of adequate surveillance in animals for human-borne pathogens, which may also have significant health and economic consequences.

Routine disease surveillance and diagnostic testing in animals are primarily reserved for large-scale livestock productions, for which there are economic incentives to maintain herd health, or for companion animals in countries in which owners are willing and able to pay for it. Infectious disease surveillance and control in wild animal populations have been much less common and typically occur in the context of a known zoonotic agent (eg, H5N1 and wild birds) or perhaps in endangered species. Unfortunately, the economic incentives for detecting and controlling infectious disease in wildlife are less obvious than in domestic animals, and in areas in which zooanthroponotic transmission is of high conservation importance (eg, in African countries with many of the great ape species), local wildlife authorities often do not have the necessary resources to identify etiological agents in an animal outbreak. Even though many zooanthroponotic infections occur in captive animals because of contact with researchers, trainers, and keepers, these pathogens may potentially emerge in free-living populations of the same or related species and have far-reaching detrimental effects on biodiversity and human health.[2] Furthermore, surveillance and control measures designed to prevent zooanthroponotic infections may also serve to protect human health by preventing spillback from animals to humans. In the case of flu, the infection of pigs with human influenza viruses has the additional risk of creating novel, potentially more virulent flu strains via genetic reassortment.[57]

The transmission of pathogens between humans and nonhuman species (in either direction) is driven by anthropogenic factors that increase contact between humans and animals.[2,58] These factors include agricultural expansion and intensification, global travel (tourism, business, and emigration), animal trade, and urbanization, all of which are likely to increase as the human population continues to grow.[3,58] Globally, regions with high biodiversity, human population density, and high levels of human-animal interaction are predicted to be most vulnerable to the emergence of zoonotic pathogens.[3] The same criteria are also likely to apply to zooanthroponotic pathogens.

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The health and economic impacts of zoonotic diseases are now more widely appreciated since the severe acute respiratory syndrome coronavirus and highly pathogenic avian influenza (H5N1) outbreaks (Figure 1). Although it is expected that there will continue to be a research focus on zoonotic pathogens, it would seem prudent to allocate more resources to screening wildlife and domestic animals for human pathogens and to studying the epidemiology of these pathogens as they cycle between humans and animals. Comprehensive scientific disciplines, such as conservation medicine, that recognize the links between human, animal, and ecosystem health, provide an effective approach to understanding the complex multidirectional exchange of pathogens among humans, wildlife, and domestic animals.[2,59] As the rate of emerging infectious diseases (in humans and animals) is likely to increase with an increase in anthropogenic pressures, it is important that we develop a better understanding of the potential for and occurrence of cross-species pathogen transmission in order to successfully protect human, animal, and ecosystem health.

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