CHAPTER 8

Emerging Diseases from Animals

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In December 2013, an outbreak of the deadly Ebola virus began in a small village in southern Guinea, the first outbreak of the Zaire Ebola strain in West Africa. Within a year's time, the outbreak, which was not officially noticed by health authorities until March 2014, had led to approximately 18,000 known human cases and 6,300 deaths, posing an unprecedented challenge to global public health. Air travel helped the disease leap from West Africa to other continents, including North America and Europe.[1]

Despite global attention and response, 12 months into the outbreak the initial source of human infection still had not been identified. Prior Ebola outbreaks in humans, as well as a concurrent outbreak in the Democratic Republic of the Congo beginning in August 2014, have been linked to the hunting or handling of wild animals, with subsequent transmission among humans. Certain bat species are the suspected natural source for the virus and are thought to harbor it without signs of disease. Researchers have detected Ebola infection and mortality in wild chimpanzees, gorillas, and duiker antelopes, and evidence from human outbreaks suggests that these species have served as brief hosts for potential human infection when hunted or handled. Studies suggest that Ebola is causing severe declines in great ape populations—particularly critically endangered wild lowland gorillas—making it as much a threat to biodiversity as it is to human health.[2]

Around the same time that the Ebola outbreak was spreading through West Africa, a human case of a different disease, caused by another pathogen in the same family of viruses, emerged in Uganda. The infected patient experienced symptoms including fever, abdominal pain, vomiting, and diarrhea and ultimately died a few weeks into the illness, caused by the Marburg virus. While the source of this particular outbreak was not known, past human cases of Marburg originated from contact with certain species of cave-dwelling bats that serve as the natural carriers of the virus.[3]

Ebola and Marburg viruses are just two examples of an emerging but

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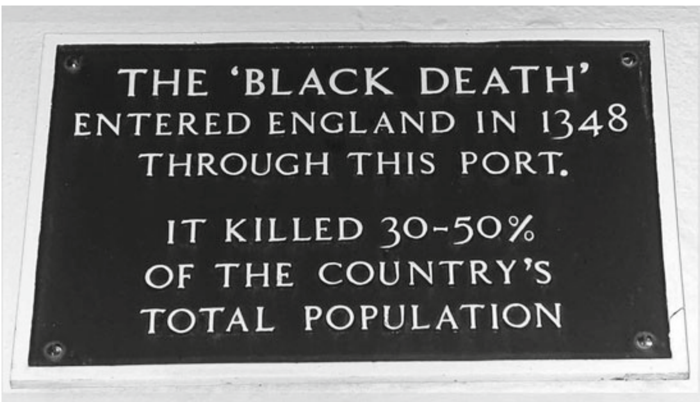
largely overlooked trend: the spread of infectious disease from animals to humans. The emergence of such "zoonoses," responsible for a growing number of disease outbreaks that have sickened or killed millions, is facilitated by the human disruption of natural ecological conditions, which has allowed for increased human-animal contact. Despite the extensive public health response to these emerging infectious diseases, the focus has been on reactive rather than preventive efforts. But new strategies for dealing with these threats offer the possibility that such diseases need not be a threat and a scourge, and that humans once again can learn to live in balance with the natural ecology that supports us.

Pandemics of Animal Origin: A Growing Threat

For millennia, humans have been stricken, sometimes seriously so, by pathogens originating in animals. Many diseases that are commonly known to be transmitted among people, such as measles and (formerly) smallpox, evolved from microbes living in wildlife. And many of history's most devastating pandemics have animal origins, including the Justinian Plague (541–542 AD), the Black Death (Europe, 1347), yellow fever (South America, sixteenth century), and the global flu outbreak of 1918—as well as modern pandemics such as HIV/AIDS, severe acute respiratory syndrome (SARS) in 2003, and the highly pathogenic H5N1 (avian) flu.



Mark A. Wilson

Portal of entry: commemorative plaque in Weymouth, England.

Today, diseases of animal origin account for about two-thirds of human infectious diseases, causing about a billion cases of human illness and millions of deaths each year, and racking up hundreds of billions of dollars in economic damage over the past two decades. Most known zoonoses are "endemic," meaning that they tend to be confined to a particular region. These endemic infections—such as rabies or trypanosomiasis (sleeping sickness, transmitted by the tsetse fly)—typically pass from animals to people with little or no subsequent person-to-person transmission.[4]

But when an endemic zoonosis crosses into a new geographical area or host species, or evolves new traits (such as drug resistance)—or when a novel pathogen is transmitted to humans for the first time and causes an outbreak—it becomes an "emerging" zoonosis. Emerging zoonoses from wildlife account for most of the emerging infectious diseases identified in people in the past 70 years. Their spread typically is facilitated by human activities, including changes in land use, population growth, alterations in behavior or social structure, international travel or trade, microbial adaptation to drug or vaccine use or to a new host species, and breakdown in public health infrastructure. These activities give zoonoses tremendous range: with more than 1 billion international travelers every year, as well as the extensive international trade of wildlife, infected individuals could potentially spread zoonotic diseases anywhere in the world.[5]

In the past few decades, accelerating global changes have led to the emergence of a striking number of newly described zoonoses, including hantavirus pulmonary syndrome (a respiratory disease contracted from infected rodents), monkeypox (similar to smallpox, and transmitted from a variety of animals), SARS (a pneumonia spread by small mammals), and simian immunodeficiency virus (the animal precursor to HIV). Some of these zoonoses, such as HIV, have become established as serious diseases that now pass from person to person without repeated animal-to-human transmission.

Ecology of Disease

Like any infection, zoonoses emerge when a chain of infection is activated—a process whereby the pathogen or infectious agent passes from the reservoir host in which it naturally occurs, or from an intermediate host species, to a susceptible host and is ultimately pathogenic to humans. For infection to occur, all six elements of the chain of infection must be present, from the disease-causing agent, to the mode of transmission, to the susceptible host. (See Box 8–1.) In its simplest form, this chain is straightforward—but any of the elements can present complications.[6]

Consider a case where an animal species, such as a small rodent, can be a reservoir host (carrying the infectious agent), but it also can host ticks (a vector for spread of infection of some pathogens)—thus complicating and potentially increasing the opportunities for dissemination. White-footed mice are a natural reservoir of the bacteria that cause Lyme disease and can spread the bacteria to ticks that feed on the mice, enabling the infection to spread to other species that the ticks feed on, including humans. Some zoonoses can have several reservoirs or intermediate host species, each of which might have a different role in a pathogen's emergence. The Nipah virus, which lives in fruit bat reservoir hosts in Malaysia, also became established in domestic pig populations in the 1990s, amplifying viral transmission and leading to a large human outbreak in 1998–99 that killed 100 people and led to the slaughter of more than a million pigs as a control measure.[7]

Human activities can change the ecologies underlying the chain of infection of zoonoses, such as when these activities alter the size of the host

Box 8–1. The Chain of Infection

Development of an infection has six components:

Agent of disease. The disease-causing organism, or pathogen, which can take the form of a bacteria, virus, fungus, or parasite.

Reservoir. The species—human, animal, or insect—in which the pathogen naturally resides. Pathogens can live in a reservoir for long periods without emerging to cause an epidemic. Reservoir hosts may not be seriously harmed by the pathogen.

Portal of exit. The path by which a pathogen leaves its reservoir or host. Examples include the respiratory tract, urinary tract, rectum, and cuts or lesions in skin.

Mode of transmission. The way a pathogen spreads from its reservoir host to the susceptible host. This can occur directly, via skin-to-skin contact or sexual relations, or through the spread of droplets from coughing or sneezing. It also can occur indirectly, as when organisms are carried on airborne particles, when intermediate objects such as handkerchiefs or bedding are the vehicle of transmission, or when mosquitoes, ticks, and other vectors carry the pathogen.

Portal of entry. The place a pathogen enters a susceptible host. The mouth and nose are common portals of entry. Others include the skin (for hookworm), mucous membranes (for influenza or syphilis), and blood (for hepatitis B and HIV).

Susceptible host. Some host species can acquire the pathogen but do not naturally carry it, and may be affected or unaffected by it, potentially transmitting it to other species or populations or serving as a dead-end for transmission.

Importantly, human activities can facilitate the transmission of a pathogen at any of these six places—by, for example, enabling contact between reservoir and host species or inducing genetic selection for virulent strains that are more likely to be pathogenic to humans. Conversely, human intervention around any of the six components can stop the spread of an infectious disease.

Source: See endnote 6.

population. Reducing the population of a preferred animal host, such as a large, hoofed animal, can cause a transmitter, such as a mosquito, to shift its feeding patterns to humans, leading to a disease outbreak. After cattle imported from Asia introduced a viral disease known as rinderpest, or "cattle plague," to Africa, both cattle and wildebeest populations in Africa declined rapidly and tsetse flies switched to feeding on people, causing a large epidemic of sleeping sickness.[8]

Sometimes, a naturally occurring or environmental change can lead to a change in the size of host populations, increasing the risk of transmission to humans. El Niño events in 1991–92 and 1997–98 led to the appearance of human hantavirus cases in the southwestern United States, via an ecological cascade: increased precipitation caused vegetation growth, which supported increased populations and densities of rodents, which, in turn, facilitated hantavirus infections in rodents. These changes increased the risk of infection in people.[9]

Ecological principles also apply to the dynamics of pathogens within individual hosts. Pathogen populations living within an infected host grow and evolve according to the same competitive principles that govern the growth of plants or animals living freely outside a host. This competition between pathogens and other microbes within a host, in addition to molecular factors and the mode of transmission, can determine how great a threat the pathogen poses to human health. Shifting the diet of beef cattle before slaughter, for example, creates new environmental conditions within the gut of the animal that can increase the population of human pathogens, such as the foodborne bacterium *E coli* that can result in illness and even death.[10]

The community of commensal (or co-existing) bacteria—such as the "good bacteria" in the gut that help with the digestive process—also plays an important part in combating pathogens. Disruption of this community through changes in diet or through the use of antimicrobial remedies can allow the growth of other organisms, some of which might be pathogenic. This disruption may explain some of the increased risk of zoonotic infections for salmonella, for example. The vital role played by commensal bacteria underscores the importance of studying the full microbial community within a host, and not just pathogens.[11]

Livestock and Wild Animals

People eat a wide range of animals, both farm raised and wild, and many of these can harbor bacteria, viruses, or parasites that can be transmitted to humans. This makes the production, processing, and consumption of livestock, as well as the hunting, preparation, and consumption of wild meat, potential paths of disease transmission.[12]

As human societies develop, each era of livestock revolution presents new health challenges and new opportunities for the emergence of zoonotic pathogens. Pathogens found in livestock production processes have caused repeated outbreaks of bovine tuberculosis, brucellosis, salmonellosis, and other illnesses that result from new cultural and farming practices. Livestock production practices that can create challenges for animal health include high stocking rates, mixing of species, prophylactic use of antimicrobials for growth promotion, and poor implementation of disease surveillance and control measures. These practices often are found in areas where the veterinary infrastructure is weak and where the public-private partnerships, policies, and capacities to support and strengthen it are insufficient.[13]

Meanwhile, livestock raising in concentrated feeding operations (or factory farms), a common practice in industrial countries and increasingly in developing countries, may heighten the risk of dissemination of animal diseases to humans. Intensification offers economies of scale, but it also can contribute to the spread of disease by increasing the density of potential host populations, raising contact rates among animals, reducing genetic

EPA

Concentrated feeding of hogs in the United States.

diversity within populations, and prioritizing species that are good at converting feed over those with higher disease resistance. The highly pathogenic H5N1 bird flu, which killed hundreds of people in Asia in the early 2000s, likely evolved into such a virulent strain because of high rates of mixing among flocks, and it spread because of marketing practices and the contamination of bird-raising environments. Hundreds of millions of birds were killed by the flu or had to be killed to prevent its spread.[14]

In addition, methods of slaughtering and processing animals; storing, packing, and transporting products; and preparing foods in the home can facilitate outbreaks of foodborne diseases. Incomplete cooking of pigs and wild boars can lead to trichinosis and cysticercosis, the latter afflicting 50 million people annually (often subsistence farmers in developing countries) and resulting in epilepsy and even death. Echinococcosis, caused by the larval stages of a tapeworm that is transmitted via hoofed animal hosts, is spread through the ingestion of inadequately prepared food, affecting 200,000 people every year and costing more than $4 billion annually for treatment and control. Other notable parasites transmitted through inadequate food processing and preparation include trematodes (liver, lung, and intestinal tapeworms), a neglected disease group that poses a serious threat to public health and economic prosperity in Southeast Asia.[15]

Globally, people consume far fewer wildlife products than they do livestock, but the human demand for wild meat is not inconsequential: in central African countries alone, people eat an estimated 1 million tons of wild meat annually. Human contact with animals through the hunting, preparation, and consumption of wild animals has led to the transmission of deadly diseases such as HIV/AIDS (linked to the butchering of hunted chimpanzee), SARS (which emerged in wildlife markets and among restaurant workers in southern China), and Ebola. In each case, the organisms or pathogens exploited new opportunities that resulted from changes in human behavior.[16]

Land-Use Change

Large-scale changes in land use contribute to the spread of many zoonoses, by affecting biodiversity and the relations between animal reservoirs and other animal hosts or vectors, people, and pathogens. Land modification can lead to changes in vegetation patterns, microclimates, human contact with animals (both domestic and wild), and the abundance, distribution, and demographics of vector and host species, all of which are critical factors in disease ecology.

In the region surrounding the town of Lyme, Connecticut, a repeated cycle of deforestation, reforestation, and habitat fragmentation changed the dynamics of predator-prey populations and led to the emergence and spread of Lyme disease, now the most common vectorborne illness in the United States. The mobility of ticks and other carriers has enabled the disease's observed northward and westward spread over the past decade. Similarly, the origin of human alveolar echinococcosis, a disease associated with a tapeworm that often resides in small mammals (especially rodents), has been traced to Tibet, where overgrazing and degradation of pastures increased the population densities of small mammals, which served as intermediate hosts for the disease and passed it to humans.[17]

Many tropical regions are emerging disease hotspots, rich in diversity of both wildlife and microbes—many of which have not yet been encountered by people. The opening up of tropical forests for plantation development and extractive industries such as mining, logging, and oil and gas may increase the risk of zoonotic disease by changing the composition of habitats and vector communities, altering the distribution of wild and domestic animal populations, and increasing exposure to pathogens through increased human-animal contact. Among the infectious diseases associated with changes in tropical land use are Chagas disease, leishmaniasis, and yellow fever—all of which are life-threatening illnesses spread via infected insects.[18]

Human contact with wildlife is increasing on a large scale through road building, the establishment of settlements, and the rising mobility of people, as well as through the extractive processes themselves. In areas where such changes take place, the hunting, consumption, and trade of wildlife for food often rises. If a site is poorly managed, the growing human population can strain existing infrastructure, leading to overcrowding, poor sanitary conditions, improper waste disposal, and a lack of potable water. All of these changes increase the risk of cross-species transmission of pathogens, resulting in zoonotic disease. Recent human immigrants to an area may not have immunity to zoonotic diseases that are endemic to that area, making them particularly susceptible to infection.[19]

Although extractive industry companies often do assessments of the environmental and social impacts of their activities, these studies rarely include principles of disease ecology because standard operating procedures in developing countries and specific laws or regulations often do not require the assessment of health risks at a community level. And although some assessments do include zoonotic disease from domestic animals in their guidelines, few adequately address the full range of potential zoonotic pathogens, especially from wildlife.[20]

Resistance to Antimicrobial Drugs

Injudicious use of antibiotics and other antimicrobial remedies in animals can leave people vulnerable to the spread of infectious disease. The most direct mechanism for the evolution of antimicrobial-resistant infectious diseases in people is the use of antibiotics in treating human infections. But the widespread use of antimicrobial drugs in livestock production—both to prevent disease and to promote animal growth—has led to worries about this being another possible route for emerging antibiotic resistance in people. Not only may genetic selection pressures from antimicrobial use lead to development of resistant strains, potentially posing food security risks and zoonotic disease risks for livestock handlers, but antimicrobial exposure may also occur via the food chain as well as through environmental dispersion (e.g., through manure, runoff, etc.).[21]

From an ecological perspective, antimicrobial resistance is a natural occurrence. Genes conferring resistance probably originated as an evolutionary response to antimicrobial compounds that bacteria, fungi, and plants living freely in the environment produced to protect themselves from infection or competition. The early antibiotics used in human medicine all were derived from natural bacterial and fungal sources. Over time, use of these compounds resulted in selection for resistance in bacteria, and horizontal transfer allowed these genes to spread rapidly through microbial populations and communities. Today, antimicrobial resistance is emerging based on these same evolutionary principles, with microbial populations adapting through competition and selection. But because the use of antimicrobial agents in people is far more widespread now than it was when these drugs were developed, the potential for emergence of resistance is likely much more rapid.[22]

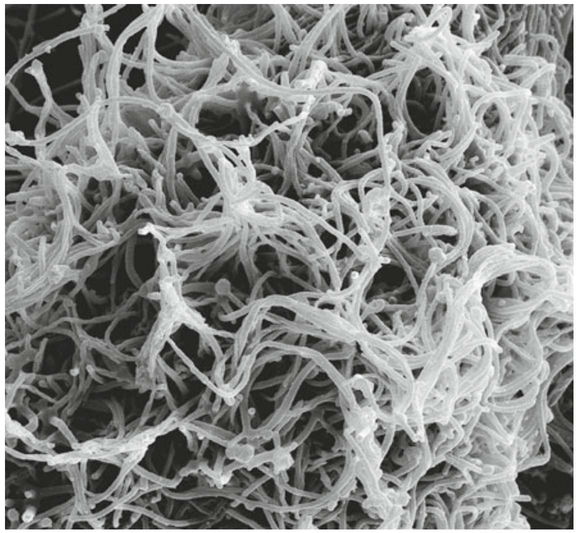
The common practice of administering antimicrobials to livestock may be contributing to this trend. Increased intensification of livestock production over the past half century has created dense host populations that readily transmit disease. In response, agricultural industries introduced a range of antimicrobial drugs to combat the spread of infection among closely confined animals. In addition to being used prophylactically, some of these antibiotics are used in animal feed to enhance growth rates, improve feeding efficiencies, and decrease the animals' waste output.[23]

The question of whether antibiotic use in agriculture has exacerbated drug resistance in people is widely debated. Farm workers who were exposed to antibiotics through their jobs showed an increased prevalence of resistant bacteria in their gut, and studies have reported instances of farm animals containing resistant pathogens of relevance to human medicine—including a strain of *Staphylococcus aureus* that is resistant to methicillin, a first-line antibiotic once commonly used to prevent Staph infections. It is possible, however, that these bacteria were passed to the animals from people.

Antimicrobial-resistant pathogens may be transmitted from livestock to people in several ways, including food consumption, direct contact with treated animals, waste management, use of manure as fertilizer, fecal contamination of runoff, and relocation or migration of animals. Additionally, some 30–90 percent of veterinary antibiotics are excreted after being administered to livestock—mostly in an unmetabolized form—providing a route for dissemination and potentially exposure in the environment.[24]

Combating Zoonoses

The recent re-emergence of Ebola in the Democratic Republic of the Congo, as well as the ongoing challenge of the HIV/AIDS pandemic, are sober reminders of the serious threat that zoonotic pathogens pose to human well-being. These global health challenges are also a reminder that traditional approaches to identifying potential new human pathogens—such as tracing back to the host source of a human disease once it has emerged—may be of limited effectiveness in preventing ongoing human transmission. (Such approaches probably would not, for example, have identified simian immunodeficiency virus, the forerunner to HIV/AIDS, as a potential risk to humans.) Thus, bold new approaches to the prevention of zoonoses are needed.[25]


NIAID

Scanning electron micrograph of filamentous Ebola virus particles budding from an infected cell.

Understanding the ecology of zoonotic diseases is a complex challenge. It requires knowledge of animal and human medicine, ecology, sociology, microbial ecology, and evolution, as well as of the underlying dynamics that increase the transmission of pathogens in humans, wildlife, and livestock. The so-called One Health perspective, which considers this wider web of interactions and dynamics, incorporates a critical understanding of how the environment is changing, and how these changes, in turn, affect microbial dynamics. Because of the wide range of disciplines involved, preventing and responding to zoonotic diseases requires a multidisciplinary effort, with collaboration among ministries of health, environment, and agriculture; within and across governments; and with intergovernmental agencies involved in health, trade, food production, and the environment.[26]

As one key to a multisectoral approach to zoonosis prevention, ecologists and clinicians need to collaborate in early-detection and control programs. Combining ecological science and real-time clinical data could improve the accuracy of mathematical models, the design of prospective and retrospective studies, and the outcomes of field studies seeking to identify key risk factors. In addition, great value would accrue if public health scientists (who use epidemiological techniques and rely on human case data) collaborated closely with disease ecologists (who often work with wildlife or livestock data) to model risk in human beings. Such disease ecology approaches might be useful not only in containing an established outbreak, but also in predicting the emergence and spread of new zoonoses. Understanding the relationship between environmental changes; the dynamics of wildlife, domestic animal, and human populations; and the dynamics of their microbes can be used to forecast the risk of human infection from zoonoses.[27]

Frequently, the dynamics of pathogens in the non-human reservoirs of a zoonosis (apes, mosquitoes, mice, etc.) determine the risk of outbreak in people. This risk can vary with geography, the season, or across multiyear cycles, and is influenced by changes in land use, weather, climate, and the environment. Knowing the dynamics of zoonotic pathogens in their wildlife reservoirs could help in creating an early-warning system to alert authorities of the risk of an outbreak in livestock or people. In the case of Rift Valley fever, the density of vegetation correlates with breeding sites for the mosquito vectors, and satellite monitoring of this density has been used to forecast cases of the disease in people and to predict the need for vaccines. Such approaches can be refined and developed, and eventually used to predict the risk of future disease emergence.[28]

Other ways to further global disease prevention capacity and efforts include implementing the World Health Organization's International Health Regulations, which make it easier to report a broad range of human disease events, and supporting implementation of the World Organisation for Animal Health's international standards for animal health, which require the reporting of animal diseases, including zoonoses. Improving veterinary services in many low-income and middle-income countries can help to expand awareness of zoonotic diseases, the ability to detect and prevent them in animals (including wildlife), and the ability to quantify and report their occurrences. Because of the high economic costs of zoonotic diseases to both commerce and society, it could prove more cost effective to try to prevent and control these diseases by integrating science-based control strategies in animals, rather than seeking to control the illnesses in people alone.[29]

Because approximately three-quarters of recently emerging diseases in humans have originated in wildlife, an early step in preventive efforts should be to identify the diverse pathogens that wildlife harbor, as well as the characteristics that make them risks to human health. Researchers estimate that detecting 85 percent of the viral diversity in mammals would cost around $1.4 billion, or $140 million per year over 10 years. This is a small fraction of the cost of an emerging disease event (the 2003 SARS outbreak, for example, cost the global economy an estimated $30 billion-plus). The public health community can use the information gained from this effort to better identify emerging disease threats and to take measures to prevent outbreaks in both humans and other species that we depend on for nutrition, other resources, and ecosystem functions. Routine disease surveillance of animals also may help with early detection of health risks to humans.[30]

Sarahtz

Selling bush meat at Makenene market, Cameroon.

New avenues of research are needed to understand the complex ecology of antimicrobial resistance and foodborne zoonoses, including how the microbiomes of both humans and the animals that we interact with work, and what causes zoonotic microbes to proliferate. The effects of antibiotic use in livestock are not well understood, but involving physicians, veterinarians, and ecologists in the design and interpretation of studies could advance our understanding of this area. Standardized data collection, long-term monitoring, and risk assessments are needed to better understand the development of multidrug resistance and multibacterial infections, from the use of antimicrobials in livestock as well as from wildlife. To reduce the need for antimicrobial use in people and animals, alternatives such as probiotics, diets to promote healthy or protective gastro-intestinal flora, and new methods of immune system modulation need to be explored.[31]

Extractive industries, such as mining and oil production, can be part of disease prevention as well, by helping to minimize the opportunities that enable transmission of pathogens that are new to human hosts. Guidelines are needed urgently for safe or best practices that include ecological knowledge to reduce the risk of disease emergence or occurrence. Disease risk analysis tools can be used to determine the potential health impacts of ecological change from potential human activities, allowing for proactive interventions that will mitigate risks. For example, industries establishing work sites (such as mining operations) in remote areas could be required to provide food sources for their employees to reduce subsistence hunting of wildlife. Such guidelines could be required by development banks or other public agencies that finance large-scale projects, or by insurers.

The wide gaps that exist between industrialized and developing countries in public health, veterinary, and medical infrastructure and training affect efforts to prevent, monitor, and control disease. In addition, ecological approaches for preventing and controlling zoonotic disease are not used in most countries. These challenges need urgent attention, and the One Health approach provides a promising holistic framework for achieving this aim.

Although the causes and risks of zoonoses vary widely across regions and cultures, increasing global connectedness demands the attention and alertness of health professionals everywhere. Because human activities are a driving force for where and how zoonoses occur, not only are improved healthcare systems needed, but multisectoral approaches to mediate the impact of human activities on disease dynamics are indispensable to contain zoonoses and prevent the emergence of new ones.