Zoonoses 1

Ecology of zoonoses: natural and unnatural histories

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More than 60% of human infectious diseases are caused by pathogens shared with wild or domestic animals. Zoonotic disease organisms include those that are endemic in human populations or enzootic in animal populations with frequent cross-species transmission to people. Some of these diseases have only emerged recently. Together, these organisms are responsible for a substantial burden of disease, with endemic and enzootic zoonoses causing about a billion cases of illness in people and millions of deaths every year. Emerging zoonoses are a growing threat to global health and have caused hundreds of billions of US dollars of economic damage in the past 20 years. We aimed to review how zoonotic diseases result from natural pathogen ecology, and how other circumstances, such as animal production, extraction of natural resources, and antimicrobial application change the dynamics of disease exposure to human beings. In view of present anthropogenic trends, a more effective approach to zoonotic disease prevention and control will require a broad view of medicine that emphasises evidence-based decision making and integrates ecological and evolutionary principles of animal, human, and environmental factors. This broad view is essential for the successful development of policies and practices that reduce probability of future zoonotic emergence, targeted surveillance and strategic prevention, and engagement of partners outside the medical community to help improve health outcomes and reduce disease threats.

Introduction

Pathogens shared with wild or domestic animals cause more than 60% of infectious diseases in man.1 Such pathogens and diseases include leptospirosis, coccidiosis and echinococcosis, toxoplasmosis, anthrax, brucellosis, rabies, Q fever, Chagas disease, type A influenza, Rift Valley fever, severe acute respiratory syndrome (SARS), Ebola haemorrhagic fever, and the original emergence of HIV.2-6 Zoonotic diseases are often categorised according to their route of transmission (eg, vector-borne or foodborne), pathogen type (eg, microparasites, macroparasites, viruses, bacteria, protozoa, worms, ticks, or fleas), or degree of person-to-person transmissibility. The greatest burden on human health and livelihoods, amounting to about 1 billion cases of illness and millions of deaths every year, is caused by endemic zoonoses that are persistent regional health problems around the world.2 Many of these infections are enzootic (ie, stably established) in animal populations, and transmit from animals to people with little or no subsequent person-to-person transmission—for example, rabies or trypanosomiasis.

Key messages

- Nearly two-thirds of human infectious diseases arise from pathogens shared with wild or domestic animals
- Endemic and enzootic zoonoses cause about a billion cases of illness in people and millions of deaths every year, and emerging zoonoses are a rising threat to global health, having caused hundreds of billions of US dollars of economic damage in the past 20 years
- Ecological and evolutionary perspectives can provide valuable insights into pathogen ecology and can inform zoonotic disease-control programmes
- Anthropogenic practices, such as changes in land use and extractive industry actions, animal production systems, and widespread antimicrobial applications affect zoonotic disease transmission
- Risks are not limited to low-income countries; as global trade and travel expands, zoonoses are increasingly posing health concerns for the global medical community
- Ecological, evolutionary, social, economic, and epidemiological mechanisms affecting zoonoses’ persistence and emergence are not well understood; such information could inform evidence-based policies, practices, and targeted zoonotic disease surveillance, and prevention and control efforts
- Multisectoral collaboration, including clinicians, public health scientists, ecologists and disease ecologists, veterinarians, economists, and others is necessary for effective management of the causes and prevention of zoonotic diseases

Search strategy and selection criteria

We selected high-quality references that showed rigorous scientific methodologies in their research and analyses. We searched Web of Science for reviews and research articles published between Jan 1, 1990, and June 1, 2012, with the search terms “zoonotic disease” and “antimicrobial resistance”, and filtered results for “animals”, “wildlife”, or “wild animals”. We chiefly selected publications from the past decade but did not exclude commonly referenced or highly regarded older publications. We also searched reference lists of articles identified by this search and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references. Non-peer-reviewed sources such as reports from the World Organization for Animal Health, the Food and Agriculture Organization, and WHO were also reviewed to provide direct information or additional supporting references. Additional references and materials were suggested by anonymous reviewers and additional reviewers invited by the authors.
Other zoonotic pathogens can spread efficiently between people once introduced from an animal reservoir, leading to localised outbreaks (eg, Ebola virus) or global spread (eg, pandemic influenza). Zoonoses made up most of the emerging infectious diseases identified in people in the past 70 years which, although relatively rare compared with endemic zoonoses, are a substantial threat to global health and have caused economic damage exceeding hundreds of billions of US dollars in the past 20 years. Apart from the appearance of a pathogen for the first time in human beings, the distinction between endemic and emerging zoonoses can be viewed as temporal or geographical. An endemic disease in one location would be regarded as an emerging disease if it crossed from its natural reservoir and entered the human or animal populations in a new geographical area, or if an endemic pathogen evolved new traits that created an epidemic (eg, drug resistance).

Transmission of pathogens into human populations from other species is a natural product of our relation with animals and the environment. The emergence of zoonoses, both recent and historical, can be considered as a logical consequence of pathogen ecology and evolution, as microbes exploit new niches and adapt to new hosts. The underlying causes that create or provide access to these new niches seem to be mediated by human action in most cases, and include changes in land use, extraction of natural resources, animal production systems, modern transportation, antimicrobial drug use, and global trade. Although underlying ecological principles that shape how these pathogens survive and change have remained similar, people have changed the environment in which these principles operate. Domestication of animals, clearing of land for farming and grazing, and hunting of wildlife in new habitats, have resulted in zoonotic human infection with microorganisms that cause diseases such as rabies, echinococcosis, and the progenitors of measles and smallpox that had historically affected only animal populations through changes in contact and increased transmission opportunities from animals to people. As human societies have developed, each era of livestock revolution presented new health challenges and new opportunities for emergence of zoonotic pathogens.

In the past few decades, accelerating global changes linked to an expanding global population have led to the emergence of a striking number of newly described zoonoses, including hantavirus pulmonary syndrome, monkeypox, SARS, and simian immunodeficiency virus (the animal precursor to HIV). Some of these zoonoses, such as HIV, have become established as substantial new human pathogens that circulate persistently without repeat animal-to-person transmission. SARS could have established, but was contained by rapid global response to its emergence; other zoonoses, such as Ebola virus and Nipah virus, have not become established because of local control efforts or their intrinsic inability to transmit efficiently between people. However, others such as hantavirus pulmonary syndrome, which is enzootic in rodents in many locations, cause sporadic and infrequent clusters of infections in human beings. In all cases, these emerging zoonoses are defined by their relatively recent appearance (or detection) in a population or, in some cases, an amplification of transmission that increases the incidence, prevalence, or geographical distribution of previously rare pathogens.

Emergence of a zoonosis depends on several factors that often act simultaneously to change pathogen dynamics. The capacity of a pathogen to transmit or spread in a population is commonly quantified by the basic reproduction number (R₀), which can be described mathematically. Formally, R₀ is the average number of secondary cases an infected individual can cause in a specific population in which all individuals are susceptible. If R₀ is greater than 1, the number of cases caused by a pathogen will increase and cause an epidemic. By contrast, when R₀ is less than 1, the number of cases will diminish and the pathogen will eventually become extinct. For many pathogens, R₀ is correlated with density of susceptible hosts (and contacts between them), thus one way that a new zoonosis can fail to become endemic in people is if the human population is sparse. This straightforward relation between population density and the ability of new zoonoses to colonise people might underpin the emergence of a series of endemic diseases thousands of years ago (eg, the Egyptian plagues, smallpox, and rubella), when populations aggregated into towns or cities and thus reached the density at which R₀ for person-to-person transmission of pathogens introduced from animals exceeded 1, or could exceed 1 by evolving person-specific adaptations.

### Panel 1: Basic reproduction number (R₀)

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Ecology of zoonoses: why pathogens do what they do

Understanding infectious diseases beyond the scale of individual clinical cases requires assessment of ecological and evolutionary perspectives. An epidemic is fundamentally an interaction between populations of two species, pathogen and host, and hence has formal similarities to predator–prey and other consumer–resource systems that ecologists have studied for decades. Multityear cycles of immunising diseases such as measles have been understood by direct analogy to predator–prey cycles, and are driven by alternating periods of predator population growth (when prey are abundant) and decline (when prey are depleted). Similarly, interactions between pathogen strains can be understood through assessment of principles of ecological competition: one recent study explained the striking diversity of pneumococcal serotypes, and the epidemiological effect of the polyvalent conjugate vaccine, by interpretation of components of the acquired immune response in terms of stabilising and fitness-equalising ecological mechanisms. Such parallels are intrinsic and pervade all aspects of infectious disease—even the central epidemiological concept of $R_0$ is borrowed from population ecology. Similarities apply to both macroparasites (helminths and arthropod ectoparasites) and microparasites (viruses, bacteria, and protozoa). One difference is that microparasites have short generation times and can be subject to strong selection pressures from host immunity, other organisms present in the microbiome, and antimicrobial drugs, all of which are key potential components of the ecosystem in which the microbes live. As a result, pathogen evolution can occur in very short timescales: significant evolutionary changes can occur in the course of one epidemic or even during individual infections. A conspicuous example is the development of resistance in bacteria in response to antimicrobial therapy and, in a slightly longer timescale, the antigenic change in influenza viruses that results in the need for frequent updating of the influenza vaccine formulation.

The dynamics of zoonotic disease transmission are deeply embedded in the ecology and evolutionary biology of their hosts. A zoonosis comprises interaction between at least three species: one pathogen and two host species, with people and another animal species acting as the reservoir of the infection. For vector-borne zoonoses, the ecology is complicated because the ecology of numerous other vector and reservoir host species can change transmission dynamics. Directly transmitted zoonoses can also have several reservoir hosts, potentially serving different roles in pathogen dynamics, such as amplification or transmission to human beings. For example, the zoonotic paramyxovirus Nipah virus has fruit bat reservoir hosts in Malaysia. The virus became established in domestic pig populations, amplifying viral transmission and leading to a large outbreak in human beings in 1998–99. More than 100 people died during this outbreak and more than 1 million pigs were killed to control the disease.

Changes in abundance of animal hosts can strikingly affect disease incidence in people. A decrease in the abundance of a preferred animal host can cause an arthropod vector to shift feeding patterns to human beings, leading to a disease outbreak. For example, when rinderpest was first introduced to east Africa, cattle and wildebeest populations depleted rapidly and tsetse flies switched to feeding on people, causing a large epidemic of sleeping sickness. Environmental changes (including anthropogenic effects) might change the abundance of a wildlife reservoir host, increasing transmission within the reservoir and the risk of zoonotic transmission. El Niño events in 1991–92 and 1997–98 led to human hantavirus cases in the southwestern USA via an ecological cascade: increased precipitation caused vegetation growth, allowing rodent densities to rise, allowing an increase in hantavirus infections in rodents. This increase did not cause population declines in rodents because, like many wildlife reservoirs of zoonotic pathogens, hantavirus causes mild or subclinical infections in this group. However, the increased prevalence in rodents increased the risk of infection in people.

Ecological principles also apply at the scale of individuals. Infected hosts contain a population of pathogens that grows and evolves according to the same principles as a free-living plant or animal population. Processes of viral replication, immune clearance, and tissue tropism can be understood by analogy to ecological processes of reproduction, mortality, and dispersal between habitats. The microbial ecology of zoonotic pathogens within their reservoir hosts can be a key determinant of risk to human health. For example, feeding different diets to beef cattle before slaughter leads to different environmental conditions within the gut, and a shift in the balance of competition among microbial species, which can change the abundance of human pathogens such as *Escherichia coli* O157:H7. The ecological principle of competitive exclusion is the basis for common approaches to control of zoonotic pathogens in livestock and poultry.

Meta-genomic studies show that the community of commensal bacteria within healthy hosts plays an important part in defence against pathogens. Furthermore, disruption of this community through changes in diet or use of antimicrobials can allow the growth of other organisms, some of which might be pathogenic. This mechanism underlies differential susceptibility to *Clostridium difficile* infection and might also increase the risk of zoonotic infections (as reported for salmonella). This factor underscores the importance of study of the full microbial community within hosts (microbiome), and not just pathogens.
Zoonotic disease risk and global demand for food

Increasing demand for food due to an expanding global population has led to a substantial susceptibility of our populations to food-borne zoonoses. Pathogens in the livestock production chain are a particular risk, with repeated outbreaks from meat, eggs, milk, and cheese, or meat byproducts incorporated into foods as flavouring, oils, or stock. Globally, most types of domesticated and wild vertebrates and many invertebrates are foods for people; such foods are capable of harbouring zoonotic bacteria, viruses, or parasites.

Knowledge of the ecology of many foodborne pathogens and their range of hosts is poor. When disease outbreaks occur in people, the animal source is often difficult to identify, restricting epidemiological investigation and ecological understanding. As for many zoonoses, foodborne pathogens often cause mild or subclinical disease in reservoir hosts, and because surveillance systems for wildlife and domestic animals are not universally adequate for detection of clinical disease or pathogen presence, humans beings often act as sentinel populations for zoonoses.

The volume of consumption of wildlife products for food is at least an order of magnitude lower than it is for domestic livestock. However, human being–animal contact associated with hunting, preparation, and consumption of wild animals has led to transmission of notable diseases. Such diseases include HIV/AIDS, which was linked to the butchering of hunted chimpanzees, and Ebola haemorrhagic fever linked to the hunting or handling of infected great apes or other wild animals. All these disease transmissions are examples of organisms or pathogens exploiting new host opportunities resulting from human behaviour. For central African countries alone, estimates of annual wild meat consumption total 1 billion kg. Solutions to increased demand for bushmeat are not straightforward, and although substitution of protein from domestic animal production might seem logical, increased livestock production in developing countries without adequate disease-management practices might lead to the emergence of other pathogens due to the introduction of new hosts.

Many foodborne zoonoses are enzootic in livestock (eg, bovine tuberculosis, brucellosis, salmonellosis, and some helminth infections), especially in low-income and middle-income countries, and result in endemic infections and outbreaks of disease in people. Cultural and farming practices such as stocking rates, mixing of species, methods of confinement, and feeding, and lack of proper implementation of disease-control methods—because of weak veterinary infrastructures and insufficient public–private partnerships to support and strengthen them—can serve to maintain or spread zoonotic diseases in livestock and provide a source of new infections in susceptible human populations (panel 2). The techniques with which animals are slaughtered and processed, and how products are stored, packed, transported, and prepared at the place they are consumed, also enable foodborne disease outbreaks. Outbreaks of trichinosis in people are often linked to the consumption of incompletely cooked meat from pigs and wild boars and, occasionally, wild game. Cysticercosis (caused by the larval stages of the dog tapeworm Taenia solium) affects 50 million people every year. Echinococcosis (caused by the larval stages of the dog tapeworm Echinococcus granulosus for which ungulates serve as the intermediate host) affects 200 000 people every year, resulting in relative economic impacts equivalent to US$4–1 billion annually for treatment and control in humans and animals. Other notable foodborne parasites include trematodes (liver, lung, and intestinal flukes), which are a neglected disease group despite contributing to a substantial disease burden in southeast Asia and posing a serious impediment to public health and economic prosperity in the region.

Panel 2: Emergence of highly pathogenic avian influenza A H5N1

Although smallholder herds and flocks remain important for the livelihoods and food security of millions of people, intensification of livestock production is rapidly occurring worldwide. This process has inherent advantages in terms of increased productivity, economies of scale, ease and efficiency of surveillance, and application of herd health. However, ecological risks of intensified production (eg, increased host density and contact rates, reduction of genetic diversity within populations, and selection of genetic stock for improved feed conversion rather than disease resistance) without effective disease-control practices, were shown by the emergence of highly pathogenic avian influenza A H5N1. This form of avian influenza evolved from a less virulent strain in domestic poultry to become very virulent, probably as a result of increased mixing between flocks and species in an environment where biosecurity improvements have not kept pace with the rate of livestock intensification. The organism expanded its geographical range through various movement and marketing practices, contamination of inanimate objects and environments, and in some cases transmission back to migratory birds. More than 579 cases of H5N1 influenza in people have been reported globally, resulting in 341 deaths, and more than 230 million birds have been killed by the disease or culled in counter-epizootic measures. However, the virus continues to circulate in avian populations. More effective control of this disease in poultry, such as improved surveillance, prevention, and response programmes, could have prevented cases of disease in people and protected livelihoods.
Land-use change, extractive industries, and zoonoses

Many zoonoses can be linked to large-scale changes in land use that affect biodiversity and relations between animal hosts, people, and pathogens. Land modification, irrespective of reason, changes vegetation patterns, vector and host species dynamics (eg, abundance, distribution, and demographics), microclimates, and human contact with domestic and wild animals. All these factors are crucial in disease ecology. The effects have been well studied and described for vector-borne diseases such as malaria and Lyme disease.4 In northeastern USA, a historical cycle of deforestation, reforestation, and habitat fragmentation changed predator–prey populations and led to the emergence of Lyme disease.6 Prevalence of human alveolar echinococcosis (caused by Echinococcus multilocularis, a tapeworm of wild and domestic canids, with small mammals serving as intermediate hosts) in Tibet is correlated with overgrazing and degradation of pastures and the resulting increase in small mammal densities.19

In tropical regions, changes in land use have been linked to the occurrence of Chagas disease,25 yellow fever,26 and leishmaniasis.27 Such changes are particularly intense in tropical regions where primary forest is opened up to mining, logging, plantation development, and oil and gas extraction. This deforestation poses a threat to global health because many of these regions are emerging disease hotspots—rich in wildlife biodiversity and probably rich in the diversity of microbes, many of which have not yet been encountered by people.4 Increased access to tropical forests for these extractive industries might increase the risk of zoonotic disease by changing habitat and vector community composition, modifying the distribution of wildlife populations and domestic animals, and increasing exposure to pathogens through increased human contact with animals.28 29

Human contact with wildlife is increased on a large scale through road building, establishment of settlements, and increased mobility of people, and the extractive process itself.30 Where these changes take place, hunting, consumption, and trade in wildlife for food often increases.31 32 If sites are poorly managed, increased populations can strain existing infrastructure, leading to overcrowding, poor sanitary conditions, improper disposal of waste, and a lack of potable water.33 All of these changes increase the risk of cross-species transmission of pathogens, resulting in zoonotic disease. Additionally, new human inhabitants (recent immigrants) might not have immunity to zoonotic diseases endemic to the area, making them particularly susceptible to infection.

Extractive industry companies often have to do assessments of the environmental and social effect of their processes. However, assessments of the health effect that include principles of disease ecology are rarely done because standard operating procedures in developing countries and specific laws or regulations often do not require an assessment for health risks at a community level.41 Furthermore, although some guidelines include zoonotic disease from domestic animals in their intended scope, few adequately address the range of potential zoonotic pathogens.

Antimicrobial drug resistance and zoonoses

Antimicrobial resistance is an important clinical problem in veterinary and human medicine. Better regulation of antimicrobial use in animals and more judicious use by human beings is needed than exists at present.53 Use of antibiotics is the most direct mechanism for the evolution of antimicrobial-resistant infectious diseases in people. However, because many organisms carried by livestock are zoonotic and the transmission of drug-resistant genetic material between bacterial populations by phages can occur by other means, the widespread use of antimicrobial drugs for prophylaxis and as growth promoters in livestock production has led to worries about a possible route for the emergence of antibiotic resistance in people.54

From an ecological perspective, antimicrobial resistance is a natural occurrence; genes conferring resistance probably originated as an evolutionary response to antimicrobial drugs produced by free-living bacteria, fungi, and plants to protect themselves from infection or competition (panel 3).11 12 The early antibiotics used in human medicine were all derived from natural bacterial and fungal sources. In turn, the use of these compounds would have resulted in selection for resistance in bacteria, and horizontal transfer via transposons and plasmids allowed these genes to spread rapidly through microbial populations and communities. Resistance is emerging today on the same evolutionary principles. Microbial populations are adapting subject to the same forces of competition and selection, but the current widespread use of antimicrobial agents in people far exceeds that of any time since their development as drugs.

Increased intensification of livestock production during the 20th century led to problems with infectious diseases that transmitted easily in dense host populations. In response, agricultural industries introduced a range of antimicrobial drugs because of their prophylactic qualities.55 Some of these antibiotics are also used extensively in animal feed, to enhance growth rates, improve feeding efficiency, and decrease waste production of animals.56 Whether or not the use of antibiotics in agriculture has exacerbated drug resistance in people has been debated widely.49 Farmworkers exposed occupationally to antibiotics have an increased prevalence of resistant gut bacteria, and resistant pathogens of relevance to human medicine—including meticillin-resistant Staphylococcus aureus—have been identified in farm animals, although the transfer of
these bacteria from people to farm animals is also a plausible explanation.\textsuperscript{56,57} Several pathways exist through which antimicrobial-resistant zoonotic pathogens could be transmitted from livestock to people, including through food consumption, direct contact with treated animals, waste management, use of manure as fertiliser, faecal contamination of run-off, movement of fomites through water and wind, and translocation or migration of animals.\textsuperscript{63,69,70} Moreover, 30–90% of veterinary antibiotics are excreted after administration to livestock, mostly in unmetabolised form, presenting a direct route for environmental contamination.\textsuperscript{66,69}

Although known to occur, the extent of transfer of antimicrobial-resistant organisms from animals to people is unclear.\textsuperscript{66} Reduction of the use of antimicrobial drugs in animals might not be a complete solution, because diversity in antimicrobial resistance in people is unlikely to be always related to geographical overlap with livestock.\textsuperscript{71} Furthermore, the potential for reversal of resistance is unknown, as is whether it would occur in clinical settings after a change in antimicrobial use. Substantial reductions in levels of resistant strains have been shown after termination of drug use,\textsuperscript{72} although persistence has been noted.\textsuperscript{72} Thus, reversion to drug susceptibility probably depends on occurrence of natural dilution of microbial populations with susceptible strains and fitness costs of resistance.\textsuperscript{72}

**Perspectives**

The continuing effect of the HIV/AIDS pandemic is a reminder of the risk of zoonotic pathogens spreading from their natural reservoirs to man. What is far less broadly appreciated is that none of the approaches commonly used to search for potential new human pathogens—such as tracing back the source host of a human disease—probably would have identified simian immunodeficiency virus as a potential risk to man. Thus, bold new approaches are needed.\textsuperscript{73}

According to estimates from the UN, the global population will increase from 6.9 billion to 9.7 billion by 2050, and more than half the global population already lives in urban areas. Changes to food production systems provide more food security for growing populations, but also change zoonotic disease risks in ways that challenge disease control. The effect of endemic zoonotic diseases results in an annually recurring burden to the health and livelihoods of people worldwide, but disproportionately burdens low-income and middle-income countries.\textsuperscript{74} Costs of zoonotic diseases are not restricted to expenses of human or animal treatment and control efforts. The disruptions to commerce and society caused by disease outbreaks can account for a large share (and in some cases almost all) of the economic costs from disease. For example, SARS cost an estimated $30–50 billion despite causing illness in fewer than 9000 people.\textsuperscript{75}

Understanding the ecology of zoonotic diseases at the human being–animal interface is a complex challenge. It requires knowledge of animal and human medicine, ecology, sociology, microbial ecology, and evolution, and the underlying issues that drive increased transmission of pathogens in humans, wildlife, and livestock: an idea described as a One Health perspective.\textsuperscript{76,77} Meeting the challenge will also require an understanding of how the environment is changing, and how these changes affect microbial dynamics across the system. Therefore, prevention and
response to zoonotic diseases and elimination or mitigation of transmission routes to prevent their emergence will need multisectoral collaboration.

Because zoonoses affect developed and developing countries alike, and spread readily across national boundaries, mitigation and control needs collaboration between ministries of health, environment and agriculture, and intergovernmental agencies involved in health, trade, food production, and the environment. International disease-prevention efforts will be enhanced by the implementation of WHO’s International Health Regulations, which allow for reporting of a broad range of human disease events, and through support of implementation of international standards for animal health and zoonoses produced by the World Organization for Animal Health, which includes reporting obligations for animal diseases including zoonoses. The need for improved veterinary services in many low-income and middle-income countries is implied by the gap in broad awareness of zoonotic diseases and their ability for detection and prevention in animals, and the ability to quantify and report their occurrences. Because disruptive effects to commerce and society can account for a large share of the economic costs of disease, integration of control strategies in animals into zoonotic disease control efforts might prove more cost effective than would control in people alone.

Recent advances in understanding of patterns of zoonotic disease emergence and spread have begun to be integrated into human infectious-disease-control programmes, although substantial progress needs to be made. Enhancing the role ecologists play in control programmes could include production of more accurate mathematical model outputs by collaboration with clinicians with real-time data, participation in both prospective and retrospective study design, and field studies to identify key risk factors to target surveillance and interventions. Collaboration between public health scientists, who normally use epidemiological techniques with human case data, and disease ecologists who often work with wildlife or livestock data to model risk in human beings, should be encouraged. These disease ecology approaches might be particularly useful in driving advances in prediction of the emergence and spread of novel zoonoses. Understanding of the relation between environmental changes, wildlife population dynamics, and the dynamics of their microbes can be used to forecast risk of human infection with enzootic or endemic zoonoses (figure). All zoonoses have non-human reservoir hosts, and the dynamics of the pathogen in these hosts often determines the risk of outbreaks in people. This risk can vary with geography, seasons, or through multiyear cycles, and can depend on factors such as changes in land use, weather, climate, or environment. Investigations into the dynamics of zoonotic pathogens in their wildlife reservoir could act as an early warning system to better inform the risk of outbreaks in people. This risk can vary with geography, seasons, or through multiyear cycles, and can depend on factors such as changes in land use, weather, climate, or environment. Investigations into the dynamics of zoonotic pathogens in their wildlife reservoir could act as an early warning system to better inform the risk of outbreaks in people.
intrinsic value. Although studies of common endemic zoonoses are often underfunded and regarded as neglected tropical diseases, studies of zoonotic disease emergence are challenged because they are often intensive, retrospective, and sometimes expensive (eg, studies to understand the cause of Nipah virus emergence or wildlife reservoirs of Ebola virus). Furthermore, emerging zoonotic disease studies are often considered as animal-focused or academic research (eg, studies to understand how dynamics of a pathogen in a wildlife host can change seasonally), when they are actually translational research efforts essential to guide clinical or public health interventions (eg, seasonal variation in dynamics drives variation in risk to people).

The complex ecology of antimicrobial resistance and foodborne zoonoses suggests new avenues for research, including an understanding of the microbiome from people and that of the animals they contact, and what causes zoonotic microbes to proliferate in some conditions. Effects of the use of antibiotics in animal production are not well understood, and the translation of this science could be enhanced by involvement of physicians, veterinarians, and ecologists in the design and interpretation of studies. Standardised data collection and long-term monitoring are needed, as are risk assessments for development of multidrug resistance or multibacterial infections in human beings resulting from antimicrobial use in food animals and from wildlife.63–65 Exploration of alternatives such as probiotics, diets to promote healthy or protective gastrointestinal flora, new methods of immune-system modulation, bacteriophages, bacterial cell wall hydrolyses, and antimicrobial peptides is warranted to help reduce the need for antimicrobial use in people and animals.66–67

Industries based on the extraction of natural resources provide materials and economic incentives, but might lead to the release of pathogens that are new to human hosts. Guidelines for safe or best practices that include ecological knowledge to reduce the risk of disease emergence or occurrence are urgently needed. Such guidelines ought to be mandated through the funding mechanisms that support large-scale development projects or be required by financial insurers.

Wide gaps in public health, veterinary and medical infrastructure, and training exist between developed and developing countries. These gaps affect disease prevention, surveillance, and control. Furthermore, little integration of ecological approaches in zoonotic disease prevention and control efforts has occurred in most countries. These challenges need to be addressed urgently, and the One Health approach perhaps provides a wider, holistic view with which to achieve this aim. Although the causes and risks of zoonoses vary widely from one region or culture to the next, our global connectivity demands the attention and alertness of health professionals everywhere. That human activities are a driving force for where and how zoonoses occur not only means that improved health-care systems are needed, but also that multisectoral, policy-level approaches should be instigated to decrease the burden of endemic zoonoses and prevent emergence of new ones.

Contributors
All authors contributed equally to the writing and revision of the report. WBK developed the outline of the report, compiled sections, and integrated reviewer and additional comments with CCM. AD and JOL-S wrote panel 1, JL wrote panel 2, MB wrote panel 3, CCM wrote the key messages, and PF provided illustrations from which the figure was adapted.

Conflicts of interest
We declare that we have no conflicts of interest.

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