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The Human-Animal Interface

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ABSTRACT The human-animal interface is as ancient as the first bipedal steps taken by humans. Born with the human species, it has grown and expanded with the human species' prehistoric and historical development to reach the unprecedented scope of current times. Several facets define the human-animal interface, guiding the scope and range of human interactions with animal species. These facets have not ceased to evolve and expand since their emergence, all the more favoring disease emergence. Placing the human-animal interface in its historical perspective allows us to realize its versatile and dynamic nature. Changes in the scope and range of domestication, agriculture, urbanization, colonization, trade, and industrialization have been accompanied by evolving risks for cross-species transmission of pathogens. Because these risks are unlikely to decrease, improving our technologies to identify and monitor pathogenic threats lurking at the human-animal interface should be a priority.

INTRODUCTION

The human-animal interface is as ancient as the first bipedal steps taken by humans. It has grown and expanded with the human species' prehistoric and historical development to reach the unprecedented scope of current times. Several facets define the human-animal interface, guiding the scope and range of human interactions with animal species. These facets have continued to evolve and expand since their emergence, promoting disease emergence. Placing the human-animal interface in its historical perspective allows us to realize its versatile and dynamic nature. Changes in the scope and range of domestication, agriculture, urbanization, colonization, trade, and industrialization have been accompanied by evolving risks for cross-species transmission of pathogens. Because these risks are unlikely to decrease, improving our technologies to identify and monitor pathogenic threats lurking at the human-animal interface should be a priority.

The human-animal interface is a defining feature of the One Health concept. It is a continuum of contacts and interactions between humans, animals, their products, and their environment, and represents the medium allowing cross-species transmission of zoonotic and emerging human and animal pathogens. The human-animal interface is characterized by a number of attributes that have been acquired throughout the evolutionary history of the human species and the development of mankind (1). The main attributes of the human-animal interface include the evolutionary pathogen heritage of the human species as well as human demographics and behaviors associated with the human inventions of domestication, agriculture and food production, urbanization, worldwide migration, colonization and trade, and industrialization and globalization (Fig. 1). These attributes have not ceased to evolve as mankind has grown and expanded, reaching unprecedented scope in parallel with the unabated growth of human impact on the environment. As such, the human-animal interface represents an ever-growing driver of the emergence of infectious diseases in humans and, perhaps less well recognized, in animal species associated with humans and in wildlife.

In humans, emerging zoonotic infectious diseases can be divided into those caused by pathogens that repeatedly cross the species barrier and result in sporadic cases of infection without further spread in the new host species; those caused by pathogens that cross the species

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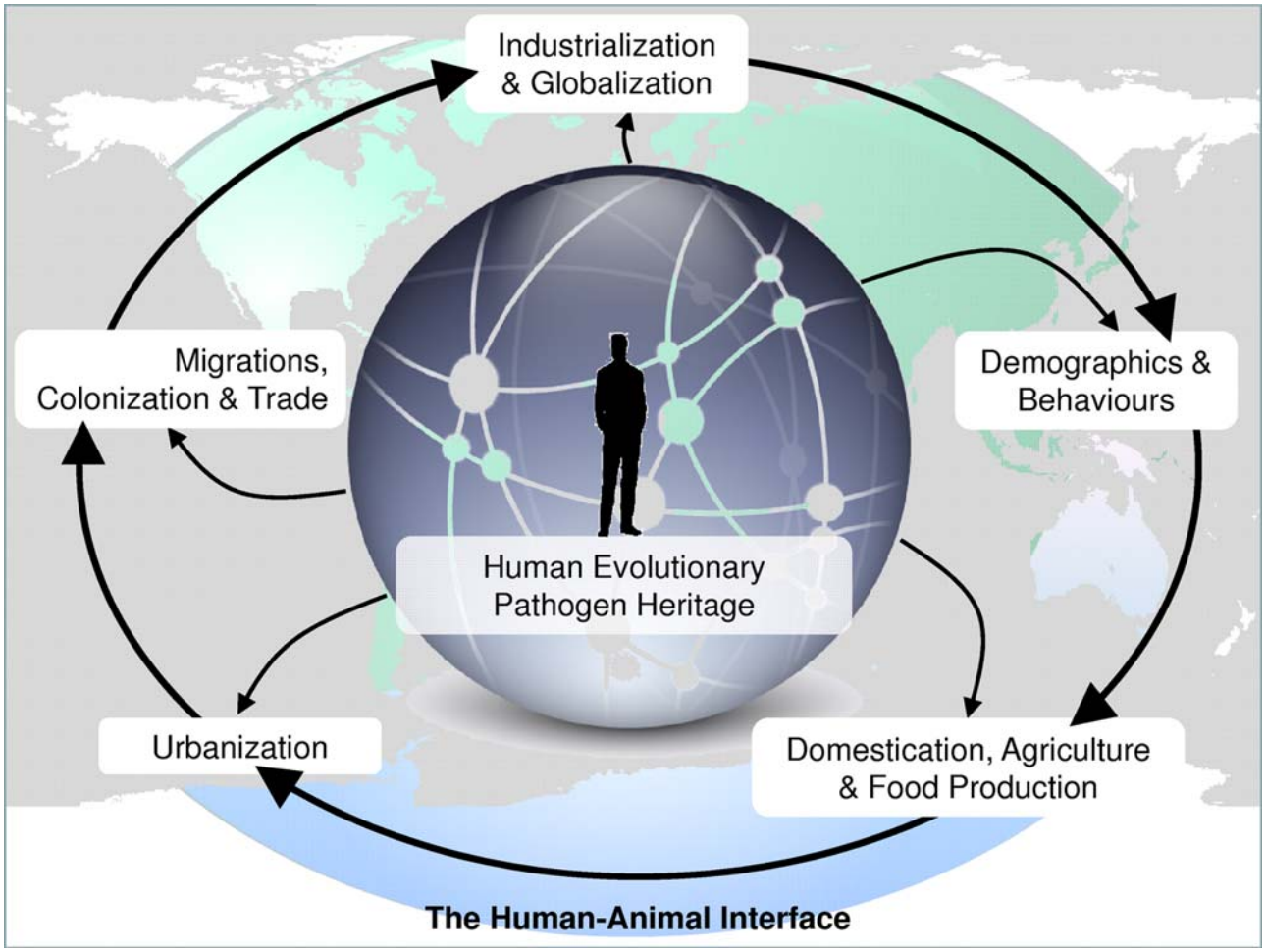


FIGURE 1 Schematic of the human-animal interface. The different facets of the human-animal interface include the evolutionary pathogen heritage of the human species and human demographics and behaviors associated with domestication, agriculture and food production, urbanization, worldwide migration, colonization and trade, and industrialization and globalization. These facets interact and expand as mankind continues to develop. doi:10.1128/microbiolspec.OH-0013-2012.f1

barrier and spread in limited fashion in the new host species; and those caused by pathogens that after crossing the species barrier eventually adapt and spread efficiently in the new host species, resulting in epidemics or even pandemics. Recently developed data have demonstrated that only a few mutations may be sufficient to allow pathogens to acquire efficient transmissibility in a new host species (2–4). The main attributes of the human-animal interface favor both the cross-species transmission of zoonotic pathogens and the emergence, evolution, and eventual establishment of efficiently transmitted novel pathogens in humans. In animals associated with humans, such as domestic, feral, and commensal animals, and in wildlife, emerging infectious diseases also can be divided into these three categories; however, those of the last category are most often identified and reported, due to their potential greater impact. In this article, we will review the characteristics of the main attributes of the human-animal interface and their impact on the cross-species transmission and emergence of pathogens in humans and animals.

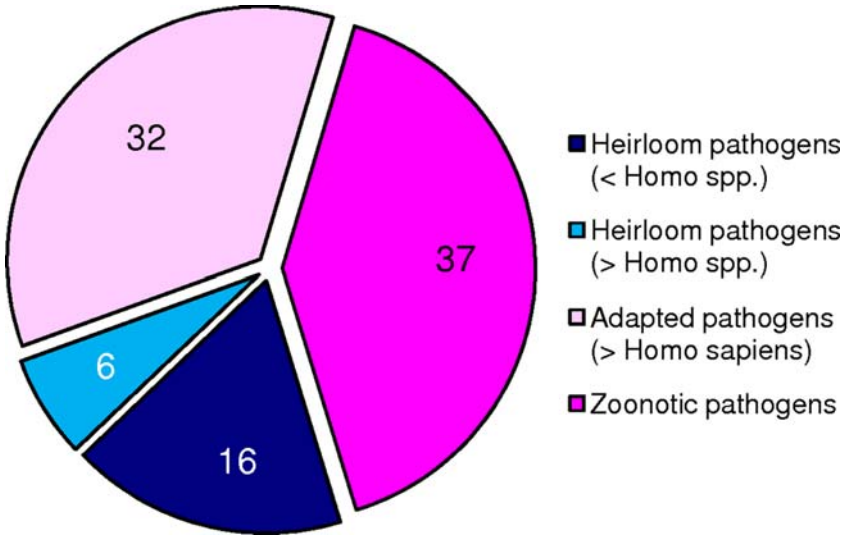
EVOLUTIONARY PATHOGEN HERITAGE OF THE HUMAN SPECIES

The evolutionary pathogen heritage of the human species is often forgotten when considering the human-animal interface, although it represents its most primordial attribute (1). It characterizes the scope and range of the interface that existed between the human species and its ancestral predecessors. It puts forth the

diversity of pathogens that the human species inherited following vertical transmission and cospeciation upon human evolutionary debut (Fig. 2). Thus, a number of strict human pathogens or remnants thereof that exist today, from DNA and RNA viruses (e.g., herpesviruses, endogenous retroviruses) to mycobacteria (e.g., species of the *Mycobacterium tuberculosis* complex), protozoans (e.g., *Plasmodium* spp. and *Trypanosoma* spp.), and ectoparasites (e.g., *Pediculus* lice), are the result of ancestral cross-species transmission of zoonotic pathogens at the birth of the *Homo* genus, some 2.5 million years ago, and of further cospeciation ever since (5–9). Other pathogens and parasites, such as human T-lymphotropic viruses (HTLVs), enteroviruses, various hepatitis viruses, *Helicobacter pylori*, and *Taenia* spp., were acquired by species of the *Homo* genus following horizontal cross-species transmission before the rise of the modern human species (5, 10, 11). These pathogens most likely emerged as a result of predation on prey animal species, including other primates. As these pathogens further adapted and became established in *Homo* spp., they also cospeciated and were transmitted vertically to the modern human species, *Homo sapiens*, about 200,000 years ago. Patterns of cospeciation of these so-called heirloom pathogens and their hosts were highlighted by phylogenetic analyses (5). These analyses revealed pathogen phylogenies that closely mirrored those of their host species, with times of divergence of pathogen species coinciding with those of their respective hosts (12, 13).

Although the evolutionary pathogen heritage of the human species principally defines the prehistoric human-animal interface of >200,000 years ago, understanding its range and scope highlights the diversity of pathogens that the human species was susceptible to at the time of its emergence. Phylogenetic tools and the current genomic era increasingly provide the means to address this diversity and demonstrate that a wide range of pathogens had already crossed the unique human-animal interface of those times. Most of the pathogens that have infected the human species since its evolutionary debut have in common a relatively strict species specificity,

FIGURE 2 Ancestral origins of human pathogens. Most pathogens capable of infecting the human species have originated from animal pathogens that crossed the species barrier, in particular across the domesticated human-animal interface. Human viruses belonging to 32 different genera have their ancestral origins in animal precursors and have adapted to efficiently transmit among humans (light pink), while viruses belonging to 37 different genera are zoonotic pathogens with no or limited ability to transmit among humans (dark pink). The remaining pathogens are heirloom pathogens that cospeciated with the human species. Of these, viruses belonging to 16 different genera were vertically transmitted from hominin ancestral species at the emergence of the *Homo* genus (dark blue), while viruses belonging to 6 different genera were vertically transmitted from related *Homo* spp. to the modern human *Homo sapiens* at the time of its emergence (light blue). doi:10.1128/microbiolspec.OH-0013-2012.f2



tend to cause persistent or chronic infections typically of relatively low pathogenicity in immune-competent individuals, and are transmitted among humans mainly following intimate encounters like mucosal, skin, and blood- or other body fluid-borne contacts (1). These pathogens have cospeciated with the human species, while in parallel, sister pathogen species have cospeciated with other primates and often with most other species of the animal realm. Studying this particular attribute of the human-animal interface may thus improve our understanding of the mechanisms behind some pathogens' limited host range, strict species specificity, and relative inability to currently cross the species barrier.

The particulars of the pathogens inherited upon the emergence and early evolution of the human species and the relative rarity of acute or virulent infections then are in sharp contrast with current times. Epidemiological theory demonstrates that the size of host communities is essential for the evolution and maintenance of more acute and/or more virulent pathogens that induce solid immunity (14, 15). It is therefore likely that the social behavior and demographics of the early human species, in particular of hunter-gatherers, precluded the establishment of such more acute or more virulent pathogens. Therefore, classically acute pathogens, such as measles virus and smallpox virus, were unlikely to emerge at those times. This highlights the importance of the behavioral and demographic changes defining the prehistoric and historical development of the human species in further shaping the modern human-animal interface as we know it today.

DOMESTICATION AND AGRICULTURE

After hunter-gatherers migrated out of the African homeland and dispersed around the globe, significant behavioral innovations took place remarkably simultaneously in several regions of the world (16). About 12,000 years ago, previously highly mobile human groups settled in what would be seen as the world's first villages and domesticated valuable wild plant and animal species for food and feed production. While ancient evidence for these behavioral innovations was first excavated from the soil of the Fertile Crescent, similarly dated evidence has been brought to light in Mesopotamia, China, South America, and the eastern part of North America. The novel farming economies swiftly spread globally from these homelands of agriculture to replace most hunter-gatherer economies around the world.

The behavioral innovations associated with the birth of domestication and agriculture during the so-called Neolithic revolution initiated increasingly close contacts and interactions between animal species and humans, drastically altering the prehistoric human-animal interface (16). Before the Neolithic revolution, interactions between humans and animals were mainly those of predator-prey systems (1). The Neolithic revolution led to animal husbandry and care and associated activities for the production of food. It resulted in a major historical transition characterized by massive emergence of novel human and domestic animal pathogens, as revealed by phylogenetic analyses. Thus, mumps virus, smallpox virus, *Corynebacterium diphtheriae*, and *Bordetella pertussis* emerged in humans soon after the birth of domestication and agriculture, although their animal hosts of origin cannot be identified with certainty (17). Similarly, strains of caliciviruses, rotaviruses, and other pathogens transmitted via environmental reservoirs, such as certain strains of *Salmonella* spp., emerged and spread among cattle, swine, and humans soon after the birth of domestication (1, 5, 18). While it is difficult to trace their exact cross-species transmission history, they have spread recurrently from livestock to humans and vice versa since then. Interestingly, *Taenia* spp. and possibly *Mycobacterium bovis* of cattle also emerged around the time of domestication and have their ancestral origins in the pathogens of humans acquired thousands of years earlier by *Homo* spp. living on the African savannah (10, 19).

The exchange of pathogens between domestic animals and humans, resulting in the emergence of novel pathogens in novel host species, has not ceased since the birth of domestication and agriculture. Domestication and agriculture drive domestic species in close contact not only with humans but also with one another, and favor the evolution and establishment of commensal animal species, such as rats and mice. They result in the mixing of a diverse range of animal species and ideal conditions for the cross-species transmission of pathogens. For example, it has been suggested that feline leukemia viruses emerged following the cross-species transmission of rodent retroviruses and further adaptation of these pathogens to domestic cats (20). Recently canine hepatitis C virus was identified in domestic dogs and estimated to have emerged 500 to 1,000 years ago (21). It is closely related to the human hepatitis C virus, known to infect humans since prehistoric times. It is therefore tempting to speculate that cross-species transmission of hepatitis C-like virus from humans to domestic dogs occurred sometime during the Middle Ages (1). Another recently discovered virus, the human metapneumovirus, closely related to the avian metapneu-

movirus, is thought to have emerged about 150,000 to 200,000 years ago presumably following poultry-to-human transmission (22). It adapted to the human species and spread globally in the human population, so that today, most individuals ≥5 years of age have been infected at least once by this pathogen. Likewise, the recently discovered human bocavirus is proven to be a recombinant parvovirus of cattle and canine host origins, and infects most children before 5 years of age, suggesting that it has been established in the human population for some time (23, 24). Influenza viruses may have emerged as early as the 5th century B.C. or before, as reports of suggestive epidemics can be found in the Hippocratic Corpus. However, it is typically accepted that influenza pandemics occurred recurrently in human populations at least from the 16th century A.D. onward, and their origins can be found in animal viruses that crossed to the human species, most probably after passage in domestic animals, such as swine or poultry (25, 26). Feline panleukopenia virus has been known as a pathogen of domestic cats since the beginning of the last century, and recognized as a naturally occurring pathogen in wild carnivores, such as mink, foxes, and raccoons, since the 1940s. In the late 1970s, canine parvovirus emerged in domestic dogs following cross-species transmission of feline panleukopenia virus and adaptation to its novel host (26). It rapidly spread worldwide and now represents a major pathogen of domestic dogs. These examples certainly highlight the continued cross-species transmission of pathogens between and among animal species and humans at the domestic human-animal interface, followed by adaptation to the newly "colonized" species.

The cross-species transmission of zoonotic and non-zoonotic pathogens between animals and humans and among animal species associated with humans further intensified as the diversity of pet, food, and commensal animal species expanded to the unprecedented levels of current times. Exotic pet species, such as reptiles and rodents, are the source of a plethora of pathogens for humans, from ubiquitous ones such as *Salmonella* spp. to foes that have challenged mankind since medieval times and exotic pathogens such as *Yersinia pestis* and monkeypox virus (27). Remarkably, cross-species transmission of many of these pathogens occurs both from animals to humans as well as between animal species, illustrating the scope of the domestic human-animal interface. Likewise, the unequaled development of bush meat consumption in many developing countries to meet the pressing demand for food by rapidly growing human populations has expanded the range of food animal species in the recent past to unparalleled numbers (28). Animal species used for bush meat have been incriminated in spectacular cross-species transmissions of a number of new zoonotic pathogens, including HIV, Ebola viruses, bat lyssaviruses, and recently discovered coronaviruses, i.e., severe acute respiratory syndrome coronavirus (SARS-CoV) and hCoV-EMC (29, 30). As previously, many of these pathogens cross the species barrier not only from animals to humans but also among animal species. Lastly, the continued encroachment of mankind into natural habitats, in association with the expansion of agriculture, creates novel environmental conditions favoring a wide range of new commensal species that thrive in anthropogenic environments due to behavioral flexibility and adaptability. In the recent past, these species, newly associated with humans, such as fruit bats in Asia and Oceania and New World rodents, have been the sources of whole new groups of zoonotic pathogens, from henipaviruses to New World hantaviruses (31–33). Rodents and bats are mammals belonging to the orders *Rodentia* and *Chiroptera*, respectively, which together represent 60% of all mammalian species. While a few species of rodents have had a long association with humans and their shared pathogens, the wide diversity of rodent as well as bat species makes them an undoubtedly important reservoir pool for zoonotic pathogens in the future. Bats in particular are increasingly recognized as maintenance hosts for a plethora of pathogens typically found to be highly virulent in other mammals, such as rabies and other lyssaviruses, filoviruses, and coronaviruses.

Both commensal and wildlife species used for bush meat create an efficient link between the domestic human-animal interface and wildlife, favoring the cross-species transmission of wildlife pathogens from host species not directly associated with humans. Although evidence for this is largely lacking, some pathogens that emerged soon after the birth of domestication and agriculture may have originated from wildlife reservoirs or commensals. Smallpox virus, for example, is closely related to gerbilpox viruses, and may have crossed to humans from a rodent host (5). *Y. pestis* may have evolved from an ancestral strain of *Yersinia pseudotuberculosis* infecting rodents, possibly in relation to the birth of domestication and associated demographic and behavioral changes in commensals (34). It may have further evolved into different populations, associated with different rodent species and/or geographic areas, and at the origin of the historical plague pandemics in humans. The role of commensal or bush meat species as relays in the cross-species transmission of pathogens of

wildlife is well illustrated in historical and more recent times. Major scourges of ancient and medieval history were associated with commensals, such as typhus and plague. *Y. pestis* at the origin of the Black Death was carried by black rats that accompanied humans along the Silk Road, before causing one of the most devastating historical plague pandemics (35). More recently, bush meat species infected with Ebola viruses in Africa or SARS-CoV in Southeast Asia were but relay species in the cross-species transmission of these bat viruses to humans (28). Likewise, domestic swine and horses were relay species in the cross-species transmission of fruit bat henipaviruses (Nipah virus in Malaysia and Hendra virus in Australia, respectively) to humans (31, 36). The destruction of natural habitats and encroachment of agriculture created altered conditions for fruit bats, which colonized cultured and farmed environments, eventually infecting domestic animals and humans with these novel pathogens. In a way, agriculture and farming practices, in combination with the destruction of natural habitats, led to the colonization of anthropogenic environments by fruit bats and turned them into novel commensal species. Similarly, in South America, the recent encroachment of agriculture into natural habitats led to the colonization of cultures by a variety of rodent species, not unlike the ancient colonization of anthropogenic environments by commensal rodent species of the Old World, resulting in multiple cross-species transmissions of new bunya- and arenaviruses to humans (32, 33).

Although the number of new zoonotic pathogens emerging in the human species following cross-species transmission from domestic, commensal, or wild animals appears to be on the rise, it may be worthwhile to determine whether advances in laboratory technologies and awareness do not significantly account for these exploding numbers. In fact, since its prehistoric kickoff, the domestic human-animal interface has created melting-pot conditions for both host and pathogen species, spurring the cross-species transmission of pathogens (1). It is nevertheless beyond doubt that the trends in cross-species transmissions of animal pathogens to humans and among animal species associated with humans will not subside in the future. Beyond bringing animal species and humans in close contact, domestication and agriculture also initiated food and feed production, allowing population sizes of the human, domestic, and commensal species to boom up to this day. In addition, the unprecedented globalized distribution of food and feed products facilitates the emergence and spread of novel pathogens of humans and animals alike. These demographic changes further fueled cross-species transmissions of pathogens, their emergence, and eventually their long-term maintenance in growing populations.

FOOD PRODUCTION, POPULATION GROWTH, AND HUMAN URBANIZATION

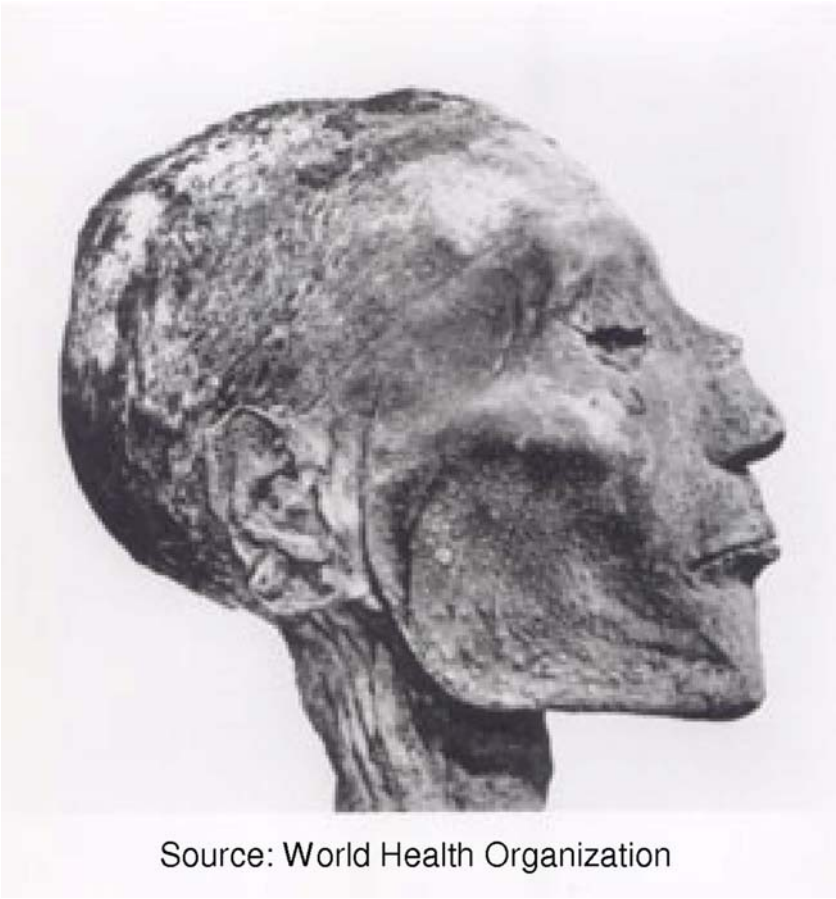
The birth of domestication and agriculture some 12,000 years ago initiated food and feed production that have allowed the massive population growth of the human species and associated animal species to this day (16). As populations grew, humans congregated in villages of expanding size, leading to the start of urbanization. Babylon in Mesopotamia was one of the first cities to reach 200,000 inhabitants during ancient history. As early cities developed, they retained the characteristics of villages, with domestic and food production animal species kept in close proximity to humans. As such, these cities hosted dense populations of humans and of domestic and commensal animals, fueling the cross-species transmission of pathogens, and eventually favoring their long-term maintenance in novel host species. It led to the birth of crowd diseases that have plagued humans and associated animal species ever since. As cities expanded and developed into the major population centers of current times, they grew to host ever larger and denser populations of humans and associated animals, providing fertile soil for the sustained spread of pathogens. In this light, it is interesting to note that more and more mammalian, avian, and other wildlife as well as feral species are being linked with newly emerging habitats associated with human urbanization (37).

Epidemiological theory demonstrates that pathogens causing acute immunizing infections require a critical community size to be maintained in the host population, below which these pathogens are unable to persist (14, 15). Measles virus, for example, confers strong lifelong immunity and is known to require a community of 200,000 to 500,000 individuals to persist in the human population and recur as cyclic epidemics. Similarly, smallpox virus, *B. pertussis*, and other acute pathogens that emerged in humans soon after the birth of domestication and agriculture required critical community sizes to spread and persist, which were met by the growing human population. The invention of food production following the birth of domestication and agriculture gradually set the stage for the evolution of these pathogens to cause acute, virulent, and highly immunizing infections. Growing populations during the last stages of prehistory likely sustained these pathogens in the making, leading to the full-blown crowd diseases

of ancient history and following the rise of urbanization. Thus, the oldest putative physical evidence of smallpox is seen as pustules on the mummified skin of Pharaoh Ramses V (20th Dynasty, 12th century B.C.) (Fig. 3) (38). Later, the report of devastating epidemics in the Hippocratic Corpus convincingly demonstrates the common occurrence of acute infections that swept through human populations by the 5th century B.C.

The demographic changes of the last ages of prehistoric and ancient history, as seen in humans following the invention of food production and accompanied by the rise of urbanization, also affected domestic animal species. These changes likely favored the establishment and maintenance of pathogens, and possibly the evolution of more-acute or -virulent pathogens in these species. It further illustrates the influence of the urban human-animal interface on disease emergence in animal populations associated with humans. Crowd diseases of domestic animals, such as rinderpest in cattle, peste des petits ruminants in sheep and goats, and canine distemper in domestic dogs, which are caused by morbilliviruses closely related to measles virus, likely emerged and evolved as the domestic animal populations grew denser to feed growing populations of humans congregating in villages and cities. An illustrative example is that of *Bordetella bronchiseptica*, a common upper respiratory tract pathogen of a wide range of wild and domestic animals. A *B. bronchiseptica*-like ancestor was likely the precursor of *B. pertussis*, which causes whooping cough in humans (14). While the latter causes acute infections in humans, the former typically causes chronic and mild infections in animal species. As seen previously, sufficiently large human communities were required for the evolution of *B. pertussis* toward an acute form in humans (14). Remarkably, certain strains of *B. bronchoseptica* cause more acute and/or more virulent infections in

FIGURE 3 Evidence of smallpox infection of Pharaoh Ramses V. Poxlike lesions reminiscent of smallpox pustules can be seen on the head of the 3,000-year-old mummy. Source: World Health Organization. doi:10.1128/microbiolspec.OH-0013-2012.f3



swine and dogs, and may have evolved as a result of large population sizes and densities of these domestic animals, not unlike *B. pertussis* in humans.

Urbanization is associated not only with dramatic demographic changes in human and animal populations but also with major behavioral changes, further contributing to the emergence and spread of pathogens in humans and associated animal species. In fact, the settlement of humans in the first villages during prehistory was associated with poorer health compared with that of mobile hunter-gatherers, due to unbalanced diet, more sedentary life habits, and crowded conditions favoring pathogen transmission (39). In its debut, historical urbanization was likewise associated with poor sanitary conditions and crowding. Medieval diseases, such as typhus and bubonic plague, were often associated with commensal host species, in particular rodents, flourishing in cities rich in granaries and deficient in waste treatment (40). The account of the Plague of Athens of 430 B.C. by Thucydides illustrates well the spread of typhoid fever by the fecal pathogen *Salmonella enterica* through a crowded and unsanitary city (41). Remarkably, Thucydides reported the spread of the disease not only in humans but also in animals, suggesting that the pathogen may not have been a strictly human pathogen at that time. As such, urbanization provided ideal conditions for the sustained spread of pathogens and recurring epidemics, from the buildup of sufficiently large host populations to the mixing of humans and animal hosts to the lack of hygiene. Most interestingly, changes in behavior, improvement of hygiene, and the birth of modern medicine are direct responses to the surge of diseases associated with urbanization and the development of the human society (1). Centuries later, it is believed that urbanization and associated human behavioral changes similarly were determinant factors in the efficient spread of a modern scourge of the human species, HIV. Phylogenetic analyses revealed that HIV-1, responsible for the majority of the AIDS pandemic worldwide, had crossed the species barrier from chimpanzees to humans multiple times and decades before the efficient spread of the pathogen in the human population starting in the 1980s (42). Urban migration, poverty, social inequality, sexual promiscuity, and shared use of needles, all of which affected developing cities in Africa at that time, as well as war-related sociocultural changes are thought to be decisive behavioral drivers that allowed for the eventual adaptation of HIV and its efficient transmission in the human population (43).

Behavioral changes affected not only humans migrating to cities but also commensals and other urban-dwelling animal species. In recent times, the prevalence of a number of pathogens, including zoonotic pathogens, has been shown to be greater in wild animal populations residing in urbanized and anthropogenic environments than in those residing in more rural or natural habitats (37). Higher transmission rates of these pathogens are often associated with both higher densities of host populations and behavioral changes, such as the use of human resources for food or shelter. For example, the prevalence of raccoon zoonotic roundworm *Baylisascaris procyonis* is reported to be higher in urbanized environments. Both an increase in parasite species richness and an increase in *B. procyonis* prevalence in raccoons are associated with crowding and the use of aggregated food resources by urban populations. Other examples of disease emergence in wildlife at the urban human-animal interface include *Borrelia burgdorferi* in white-footed mice, chronic wasting disease in mule deer, and West Nile virus in songbirds in North American urbanized areas. Behavioral flexibility and adaptation to anthropogenic environments largely contribute to these species' flourishing populations in urban and residential habitats, and also favor pathogen invasion (37).

In addition to hosting growing populations of urban-dwelling animal species, expanding urbanization also presses the demand for food production and has led to increasing demands for bush meat in many parts of the developing world, in particular Asia and Africa (28). This has two major consequences that inflate the scope of the urban human-animal interface. First, urbanization and associated pressure for food lead to greater encroachment into natural habitats, via the development of road networks and expansion of anthropogenic areas. Habitat encroachment, deforestation, and habitat fragmentation can result in increased contacts between wildlife and humans, spurring the cross-species transmission of pathogens in both directions. Major examples include the cross-species transmissions of a number of pathogens from primates to humans, including retroviruses and filoviruses (28). Second, bush meat species hunted in natural habitats are brought back to cities and urbanized areas for trade and consumption. Live-animal markets have flourished in most Asian and African cities, favoring the introduction of new pathogens in these densely populated areas. Both domestic and wild animals are present in these so-called wet markets, which have facilitated the emergence of a number of zoonotic pathogens, including influenza viruses and SARS-CoV. Shortly after the cross-species transmission of the latter from wild animals kept alive at wet markets to humans, it adapted to efficiently transmit between

humans (29). It hit a dense population that would sustain its transmission, first locally and eventually around the globe. As urbanization continues to expand in developing countries, the toll that bush meat hunting is taking on wildlife populations will increase and represents a major risk lurking at the urban human-animal interface (28).

The rise of urbanization in the last ages of prehistory and into ancient history went hand in glove with the initiation of trade and associated movements of humans and animals between cities and eventually across entire regions and continents. As illustrated by the spread of SARS-CoV (29), trade and movements of humans, animals, and goods are major factors completing the modern human-animal interface. Yet domestication, agriculture, food production and urbanization, worldwide migrations, colonization, and trade and their impact on disease emergence have ancient origins.

HUMAN WORLDWIDE MIGRATION, COLONIZATION, AND TRADE

Human migrations around the globe date to prehistoric times, when groups of hunter-gatherers journeyed out of Africa to colonize the rest of the world, following coastlines or the migration of megafauna (44). Phylogeographic analyses dramatically illustrate the global spread of ancient human pathogens along prehistoric migration routes. For example, phylogeographic analyses of papillomaviruses, polyomaviruses, HTLV, *H. pylori*, and human-associated lice provide remarkable insights into ancient human migrations (5, 45). The chronic infections caused by these pathogens allowed their spread over large distances, despite the relatively slow colonization rate by prehistoric humans. In addition to dispersing pathogens along migration routes, peripatetic prehistoric humans also acquired novel pathogens as they colonized new areas. HTLV-1 strains, for example, were acquired following simian-to-human transmission of primate T-lymphotropic viruses in Asia. Phylogenetic analyses also revealed that HTLV-1 strains were transmitted from humans to other primates, and vice versa, on several occasions (46, 47). While HTLV-2 emerged in Africa about 400,000 years ago, HTLV-1 strains were introduced back to Africa upon prehistoric migrations. The large-scale dispersion of pathogens by humans thus started early in the development of the human species and gradually accelerated as the means to travel and trade progressed.

The historical colonization of new worlds during ancient history, the Middle Ages, and early modern history is associated with spectacular examples of sweeping epidemic waves caused by emerging pathogens in both colonist and resident populations. Invasions of populations by such major diseases are well described in biblical texts. During medieval times, the spread of diseases often was associated with war or conquest. The Justinian plague of the 6th to 8th century A.D. may have been caused by the *Y. pestis* bacillus, originating from the African continent. Its emergence may have been associated with the conquest led by Justinian I of most of the Mediterranean coast, including that of North Africa (35). The spread of this pathogen in humans throughout Europe and North Africa during the following centuries certainly contributed to the fall of the Byzantine Empire. The second plague pandemic, of the 14th century A.D., also was associated with war and conquest. Before the introduction of the Black Death into Sicily and Europe via trade, *Y. pestis* was used by the Mongol army to besiege the Crimean city of Caffa (48). In 1346, the Mongol army catapulted corpses infected with plague beyond the city walls, making use of a devastating biological weapon. The dawn of modern history witnessed colonization and conquest reaching more distant continents. Upon the discovery and early development of the Americas, most pathogens causing crowd diseases in the Old World, such as smallpox and measles viruses, were introduced in immunologically naïve indigenous populations, sometimes even intentionally (49, 50). These introductions resulted in virgin-soil epidemics, which decimated entire populations. In contrast, in Africa, colonists were themselves ravaged by tropical pathogens, such as *Plasmodium* spp., causing malaria, and yellow fever virus (49). These exotic diseases are thought to have hampered the institutional development of the African continent and may have strongly influenced the slave trade (51). Indeed, the influence of infectious diseases is considered primordial and likely shaped the course of early modern human history. In late modern and contemporary history, wars have continued to play a major role in the global spread of infectious diseases, from typhus and typhoid fever to the 1918 influenza pandemic and the spread of HIV-2 (25, 43).

The colonization of new worlds has lately been replaced by worldwide travel practices, for business or tourism, and comes with highly similar risks of spreading infectious diseases to unexposed populations or new geographic areas. Travelers in foreign countries may become exposed to pathogens they have never before encountered, and may within an exceptionally short period of time spread them around the globe. These travel practices have been at the origin of a plethora of

reports of emerging pathogens within the past decades. These range from isolated cases of exotic diseases, such as bat lyssavirus, filovirus, or human HCoV-EMC infections (30, 52, 53), to the global spread of novel pathogens, such as that of HIV and lately of SARS-CoV, which spread to 26 countries within a few months before being brought under control through concerted public health efforts (29). The scope of current travel practices and their impact on the global spread of pathogens that emerged at the human-animal interface is most convincingly illustrated by the recent influenza pandemic of 2009 and the recurrent spread of seasonal influenza viruses around the world. Within weeks after its initial emergence in Mexico, probably following swine-to-human cross-species transmission, the 2009 pandemic influenza virus spread globally via human-to-human transmission on major air-travel routes (54). A strong correlation was found between the geographic distribution of imported cases of infection with this new influenza virus at the start of the pandemic and the international destinations of travelers from Mexico. Likewise, the global spread of seasonal influenza viruses every year follows highly consistent patterns of emergence in Southeast Asia and global migration via travel and trade connections between this region and the rest of the world (55).

Since ancient history, the development of trade and human travel between growing cities has also been an efficient driver favoring the continued circulation of pathogens in human and associated animal populations, and the spread of synchronous waves of disease across the landscape. It acted in synergy with the growing size of host populations, reaching levels sufficient for long-term maintenance of crowd diseases. On a broad geographic scale, *Y. pestis* at the origin of the devastating Black Death epidemic in Europe had been introduced into Sicily via trade routes in the Mediterranean Sea (35). The bacteria had been picked up by black rats in Asia and spread both to conquering armies and to merchants traveling the Silk Road. After entry into Europe, waves of the bubonic plague pandemic ravaged the continent within a few years. On a more restricted geographic scale, measles reports of the 20th century in the United Kingdom have provided invaluable insights into the waves of measles epidemics that sweep through the human population, from large cities hosting large enough communities to maintain the virus toward smaller and more rural communities (56). These waves of disease created remarkable dynamics of synchronous pulses of disease outbreaks radiating from large cities, kept in synchrony via trade and commuting movements of humans, into more rural areas. Likewise, seasonal influenza viruses were shown to be spread via commuting movements such as workflows in the continental United States, further highlighting the driving force of even short-distance movements of humans on the spread of infectious pathogens (57).

Movements of people are accompanied by movements of animal species, and the global spread of zoonotic and nonzoonotic pathogens of animals is an important consequence of this facet of the human-animal interface (27). As for humans, trade and movements of animals have characterized populations associated with humans for millennia. It has been suggested that the distinctively low genetic diversity of some parasites, such as *Trichinella spiralis*, in domestic animal species compared to that in wild counterpart species is a result of early trade and translocation of domestic animals by prehistoric and/or ancient farmers (58). Likewise, the worldwide distribution of a phylogenetic group of closely related Seoul virus variants may point to global dispersion of the pathogen via human-associated migration of Norway rats (*Rattus norvegicus*) (59, 60). The global spread of animal pathogens is well documented during more recent human history and has become of major concern. The introduction of rinderpest virus into Africa during the 19th century resulted in virgin-soil epidemics with high mortality burdens in local cattle breeds and wild ungulates, decimating entire populations (61). Although the virus was not zoonotic, it severely affected human populations dependent on cattle and was responsible for large-scale famines in many African countries. In Europe, the spread of highly infectious pathogens, such as foot-and-mouth disease virus, rinderpest virus, and the anthrax bacillus, resulted in bans of animal movements during epidemics as regulatory measures as early as the 18th century (62). It demonstrates the early recognition of the role this facet of the human-animal interface played in disease emergence and spread.

In current times, animal species subject to travel and trade have become more and more insidious Trojan horses for the introduction of zoonotic pathogens worldwide, in part due to increasing diversity and heavier volume of traded species. Insect vectors are perhaps among the most overlooked animal species that can be dispersed globally via human activities. The global distribution of the Asia tiger mosquito *Aedes albopictus*, an important vector of dengue virus, is associated with the trade of tires, containing water infested with mosquito eggs, via rapid air and sea transport (63). Although the means of introduction of another flavivirus, West Nile virus, into North America remains

unsolved, infected *Culex* mosquitoes trapped in airplanes remain a possibility, alongside the importation of infected birds (64). SARS-CoV was introduced in the human population as a result of the trade of bush meat species in Asia (29). Remarkably, it rapidly adapted and acquired efficient transmissibility in humans, gaining the means for sustained transmission first locally and then around the globe. A major recent introduction of monkeypox virus outside its African native range was a result of the trade of exotic rodent pet species from Africa to North America (65). It resulted in >80 human cases of zoonotic infection. Less exotic zoonotic viruses, such as rabies virus, recurrently threaten to affect animal and human populations alike in disease-free countries, due to the illegal trade of domestic cats, dogs, and other carnivores from countries where the diseases are endemic (27). Likewise, major pathogens of livestock, including foot-and-mouth disease virus, may invade disease-free populations and spread like wildfire following accidental or illegal introductions. In 2001, illegal introduction of meat waste originating from Asia, where foot-and-mouth disease is endemic, resulted in a major epidemic of the disease in the United Kingdom and soon after in other European countries (66). In the United Kingdom alone, the economic consequences of the outbreak amounted to >6 million pounds (67). Last but not least, trade may influence disease emergence not only in humans and associated animal species but also in wildlife, including in relatively pristine environments (68). Trade has been suggested as a plausible cause for the spread of the fungus *Batrachochytrium dendrobatidis*, which causes amphibian chytridiomycosis worldwide (69), as well as for the spread of the fungus *Geomyces destructans*, which causes bat white-nose syndrome in North America (70). Both diseases have been associated with massive wildlife population collapses.

The increasing diversity and heavier volume of traded animal species have been accompanied and fueled by the industrialization and globalization of the food industry in more recent history. This represents one of the most recent facets of the human-animal interface in the present globalized world.

INDUSTRIALIZATION AND GLOBALIZATION

The industrial revolution marks a historical transition in late modern history, spanning the 19th and beginning of the 20th century, and initiating the globalization that characterizes current times. The industrialization of food production was prompted by the unabated growth of the human population and resulted in massive population growth of associated animal species. This unique attribute of the modern human-animal interface is its youngest facet and has brought challenges never faced before.

The industrial revolution not only resulted in massive population growth of animal species associated with humans, including domestic, commensal, and traded species, amplifying the risks at the domestic and urban human-animal interface, but it also resulted in dramatic changes in animal husbandry, in particular farming intensification. This has led to massive encroachment of natural habitats by agriculture and farmed populations, expanding the interface between domestic animals and wildlife. It also has resulted in complex disease dynamics in domestic animals and wildlife, worsening control options in domestic animal populations (71). For example, *M. bovis* and *Brucella* spp. are zoonotic pathogens that may circulate heavily in wildlife populations, typically after initial cross-species transmission from domestic animals. These pathogens, when present in wildlife, are difficult to eradicate from livestock, as is the case in some parts of Europe and in the United States. The emergence of Nipah virus in Asia is directly linked to the encroachment of natural habitats by agriculture and pig farming (31, 36). The combination of fruit tree plantations with pig farming created favorable conditions for the cross-species transmission of this fruit bat pathogen to pigs and humans. Similarly, the combination of agriculture and fish, poultry, and pig farming in China, which is increasingly encroaching on natural water bird habitats, likely favors the circulation of influenza viruses between domestic animals and wild water birds (72, 73).

The industrialization of food production also has led to the emergence and evolution of increasing diversity in known as well as novel animal pathogens, which may rapidly disseminate worldwide via globalized trade. The origin of the high diversity of foot-and-mouth disease virus strains circulating in Eurasia has been traced to a radiation and rapid expansion event that occurred during the 19th century, coinciding with the industrial revolution (74). The emergence of human metapneumovirus from an avian metapneumovirus ancestor some 150 to 200 years ago likewise coincides with the industrialization of the poultry industry (22). The massive expansion of strain diversity of influenza viruses in swine and poultry in the recent past also correlates with the increase in the industrial populations of swine and poultry worldwide (Fig. 4) (75). In combination with intercontinental trade, complex strain dynamics and reassortments have ensued, creating an increasing pool

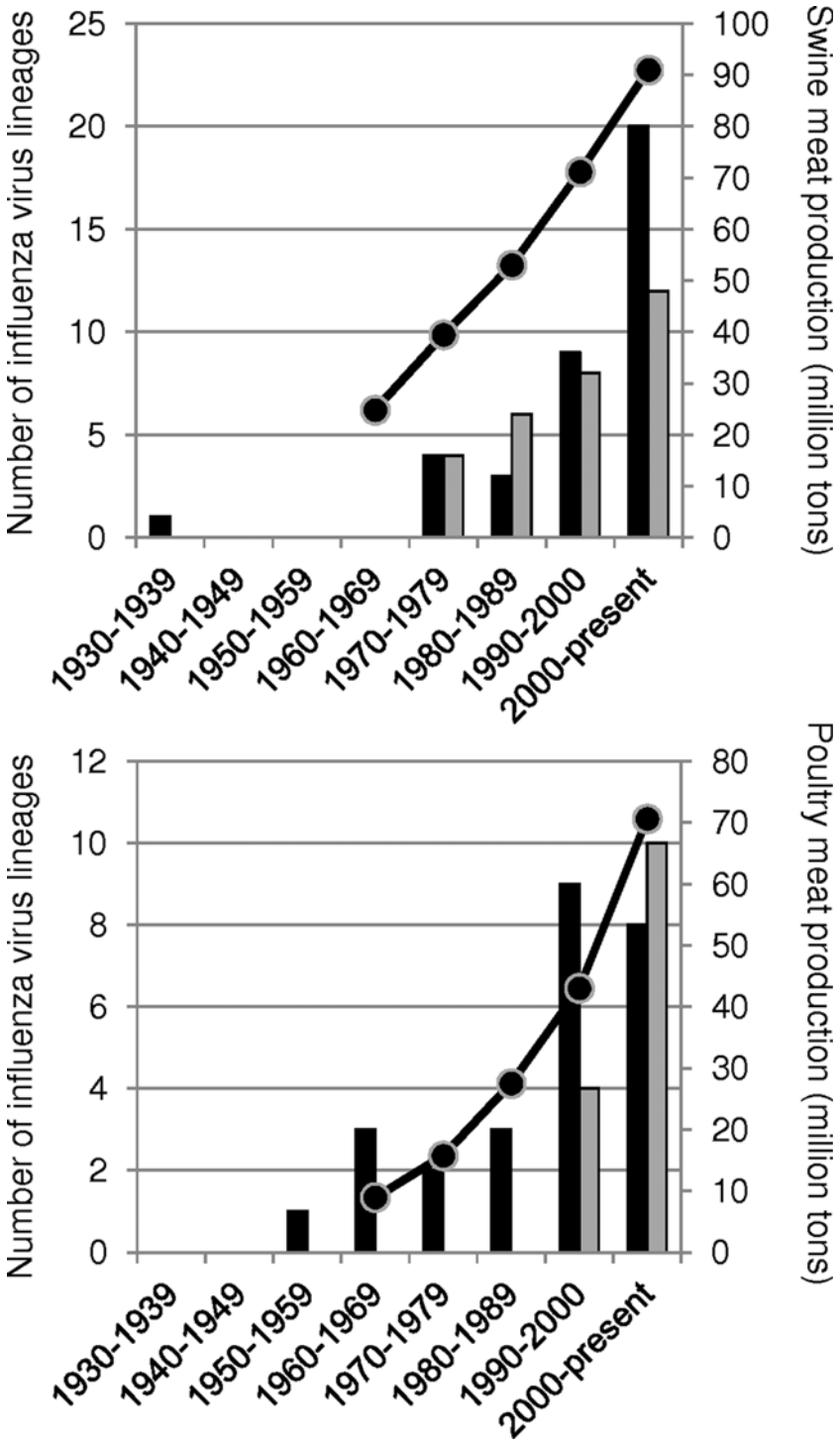


FIGURE 4 Diversity of avian and swine influenza viruses. The annual productions of swine and poultry meat have dramatically increased since the 1960s (upper and lower panel, connected dots). Concurrently, the number of new influenza virus lineages in swine (upper panel, black bars) and the number of outbreaks of highly pathogenic avian influenza in poultry (lower panel, black bars) have increased similarly since the discovery of the virus in pigs in the 1930s and in poultry in the 1950s. These increases in viral diversity have been accompanied by an increase in the number of swine and avian influenza virus subtypes or lineages that have caused infection in humans (upper and lower panels, gray bars). Modified from reference 75. doi:10.1128/microbiolspec.OH-0013-2012.f4

of potentially zoonotic influenza viruses in these animal populations. The circulation of influenza viruses in dense populations of poultry further allowed the emergence of highly virulent strains, called highly pathogenic avian influenza viruses, severely altering the epidemiology of the viruses. In particular, some strains of highly pathogenic avian influenza viruses may infect humans directly from bird hosts and cause often fatal respiratory and extrarespiratory disease. Similarly, changes in husbandry practices leading to dense and large populations of animals in industrial farms kept at maximal production efficiency have resulted in the emergence of new

forms of prions in cattle, causing bovine spongiform encephalopathy in cattle, a new variant of Creutzfeldt-Jakob disease in humans, and a similar disease in domestic animals like cats (76). Changes in the treatment of cattle offals in the United Kingdom in the 1980s were implemented to increase production efficiency of meat and bone meal, used as a protein-rich ruminant feed supplement. These changes resulted in insufficient treatment for the destruction of nondegradable host proteins such as prions. The trade of contaminated meat and bone meal spread these new pathogens across and beyond Europe, causing an epidemic in cattle and humans. Because of the long incubation period, and in spite of all the successful but draconic intervention measures taken, cases of disease have been appearing for decades following the emergence of the pathogens and continue to appear today. Industrialization as such has created favorable conditions for the evolution and emergence of previously unmet pathogens. It is likely that these pathogens may not persist without industrial populations of domestic animals, highlighting the unique challenges brought by the industrial facet of the human-animal interface today.

Another consequence of the industrial revolution is certainly the routine use of antimicrobials in the human as well as in domestic animal populations, and the associated rise of antimicrobial resistance at the human-animal interface (77). Antimicrobial resistance initially appeared in hospitals, where most antibiotics were used, soon after their introduction. Bacterial strains resistant to multiple drugs arose in the late 1950s. Antimicrobial resistance in pathogens of animals were reported at about this time, and followed the use of antimicrobials in food production animals initiated in the 1950s for therapeutic as well as subtherapeutic and growth efficiency purposes. Although the impact of antimicrobial resistance in animal populations on human health is under debate, it is considered a significant problem that may cause heavier health burdens in the future (see reference 80).

Lastly, and among the greatest challenges of current times, industrialization likely has had a major impact on and may continue to affect global climate in the future (78). Changes in climatic conditions may further favor disease emergence at the human-animal interface, by favoring certain host-pathogen systems strongly associated with environmental conditions. Global warming thus may expand or modify migratory patterns of aquatic mammals and birds, as well as the geographic range of insect vectors of zoonotic pathogens currently considered as exotic, such as *Plasmodium* spp., Chikungunya virus, Rift Valley fever virus, Crimean-Congo hemorrhagic fever virus, dengue viruses, and yellow fever virus. Although correlating changes in the geographic distribution of vector-borne pathogens with climate change remains a challenge, the expansion of the range of tick-borne encephalitis virus in Europe and of *B. burgdorferi*, the agent of Lyme disease, in Europe and North America calls for future research (79).

CONCLUDING REMARKS

The human-animal interface is a continuously evolving entity that has affected the human species since its first bipedal steps on the earth's surface. Its attributes have not ceased to evolve and expand as mankind has developed throughout history. Understanding its evolving nature and expanding scope is a determinant for humans' race against infectious pathogens lurking across this interface. As it will continue to allow the emergence of new pathogens in humans and associated animals, developing improved tools and technologies to screen and combat pathogens before they cross the human-animal interface and adapt to spread efficiently in new hosts must be considered a priority. In recent history, two pathogens have been brought to extinction, namely, smallpox and rinderpest viruses. However, combating pathogens at the human-animal interface likely represents an advantageous head start in our battle against infectious diseases. New pathogens of humans that have their origins in animals can become major human scourges within decades, as most recently demonstrated by the human metapneumovirus and HIV. In contrast, concerted public health efforts and medical research allowed the arising SARS-CoV pandemic to be nipped in the bud as soon as the pathogen started to spread around the globe. This is a unique chapter in human history, highlighting that successes can be achieved at the forefront of combating pathogen emergence.

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