The Importance of Understanding the Human–Animal Interface

From Early Hominins to Global Citizens

Leslie A. Reperant, Giuseppe Cornaglia and Albert D. M. E. Osterhaus

Abstract The complex relationships between the human and animal species have never ceased to evolve since the emergence of the human species and have resulted in a human–animal interface that has promoted the cross-species transmission, emergence and eventual evolution of a plethora of infectious pathogens. Remarkably, most of the characteristics of the human–animal interface—as we know it today—have been established long before the end of our species prehistorical development took place, to be relentlessly shaped throughout the history of our species. More recently, changes affecting the modern human population worldwide as well as their dramatic impact on the global environment have taken domestication, agriculture, urbanization, industrialization, and colonization to unprecedented levels. This has created a unique global multi-faceted human–animal interface, associated with a major epidemiological transition that is accompanied by an unexpected rise of new and emerging infectious diseases. Importantly, these developments are largely paralleled by medical, technological, and scientific progress, continuously spurred by our never-ending combat against pathogens. The human–animal interface has most likely contributed significantly to the evolutionary shaping and historical development of our species. Investment in a better understanding of this human–animal interface will offer humankind a future head-start in the never-ending battle against infectious diseases.

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1 Introduction

The human–animal interface constitutes a well-recognized barrier for cross-species transmission of infectious agents that is increasingly appreciated in the one-health concept. It depends on the continuum of contacts between humans and animals, either directly or indirectly through their products and their environments. The human–animal interface has sustained horizontal transmissions of so-called zoonotic pathogens from animals to humans, causing individual cases of disease or sparking outbreaks of variable magnitude, some of them eventually leading to devastating plagues. Arguably, the human–animal interface has also mediated the vertical transmission and co-evolution of infectious agents from primates via early hominins to *Homo sapiens*—so-called heirloom pathogens (Cockburn 1971). These eventually resulted in the evolution and establishment of either well adapted non-pathogenic agents or remnants thereof, such as endogenous retroviruses, or alternatively of well adapted human infectious agents that developed into human pathogens with relatively high species specificity. Although generally less commonly appreciated, the human–animal interface has also allowed the horizontal introduction of human pathogens into animal populations and of animal pathogens into new geographical areas and new host species. The latter introductions have been driven to a large extent by human activities, from ancient colonization of new worlds to more recent global trade and travel practices.

The human–animal interface has existed since the first bipedal steps of mankind and has undergone perpetual changes as human societies developed (Fig. 1). It continues to face substantial changes today, all the more dramatic as environmental and anthropogenic changes affecting human–animal interactions are accelerating dramatically. Understanding this versatile human–animal interface is crucial for characterizing the permanent yet continuously evolving risks of cross-species transmission of pathogens between animals and humans. The attributes of

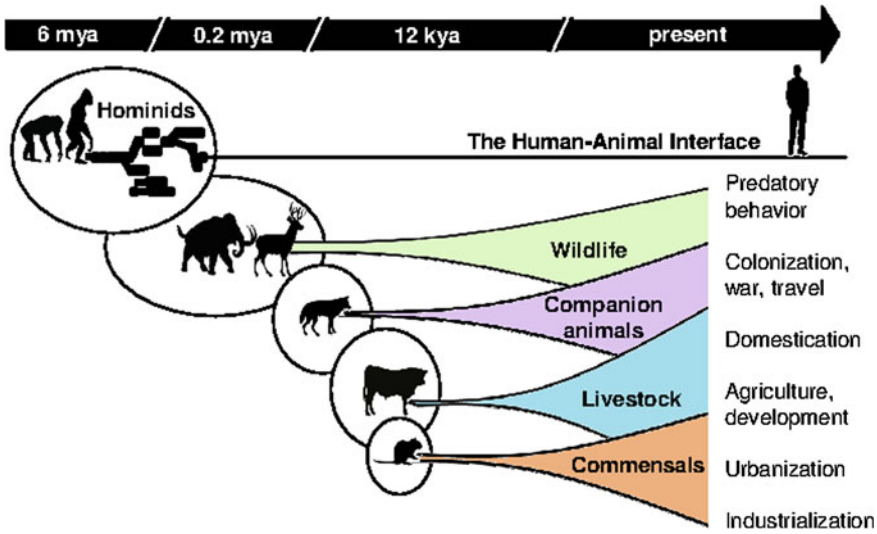

Fig. 1 Main attributes of the human–animal interface since prehistorical times to present. The nature of the animal species implicated in the human–animal interface is indicated (colored surface areas represent population size/density). The principal human behaviors implicated in the human–animal interface are indicated on the right part of the diagram. *mya* Million years ago; *kya* thousand years ago

the interface across centuries, associated risks and illustrative examples of landmark as well as less known cross-species transmission events are the subject of this review.

2 Before Prehistory: From Early Hominins to "Stone-Agers"

The oldest putative hominins, *Ardipithecus kadabba*, *Sahelanthropus tchadensis,* and *Orrorin tugenensis*, date back from the late Miocene, some 6–7 million years ago (mya) (Haile-Selassie et al. 2004; Brunet et al. 2002; Senut et al. 2001). Femurs of the latter species provide the earliest evidence for bipedality. The discovery of more than 110 specimens of a descendant hominin species, *Ardipithecus ramidus*, dated from the Pliocene, 4.4 mya, together with more than 150,000 specimens of contemporaneous plant and animal fossils, unveiled some of the paleobiology and ecology of the first hominins that lived in Africa (Gibbons 2009). Although earlier species may have been more primitive in a number of characters, these three genera appear to be very similar. They were probably largely bipedal, although in a primitive way, retaining arboreal abilities. They inhabited woodlands with patches of forests and were more omnivorous than extant apes. They likely fed both in trees and on the ground of browse and fruits, and probably occasionally of eggs and small animals. The shape and size of their

canines indicate that they were less socially aggressive than extant apes. Later hominins, *Australopithecus* spp. and *Paranthropus* spp., spanning from approximately <4 to <1 mya, were fully bipedal and typically occupied a wider niche, from woodland to grassland and more open environments. Their omnivorous diet was more flexible, and included harder, more brittle, and more abrasive food, including meat. Based on recent findings, the usage of stone tools for flesh removal from bones and access to bone marrow dates back from at least 3.4 mya, before the emergence of the genus *Homo*, about 1.1 million years later (McPherron et al. 2010).

Although the pathogen legacy of early hominins to our—and sister extinct—species may be regarded as largely speculative, phylogenetic analyzes reveal long associations and co-speciation of a number of pathogens with the developing human species. Most compelling evidence has been obtained from distinctive patterns of genetic evolution of viruses from diverse families, as well as of a few species of mycobacteria, protozoans, and ectoparasites, the phylogeny of which mirrors that of their hosts. A classic example is that of lice species, which are strict ectoparasites of birds and mammals. Co-speciation of *Pediculus* lice in primates is indicated by the divergence of the species parasitizing humans on the one hand and chimpanzees on the other, some 5–6 mya, around the time of divergence of the lineages of their respective host species (Weiss 2009).

High host species specificity is a characteristic of most of so-called heirloom pathogens, and the persistence or chronicity of the infection they typically cause appears to be a common determinant for co-speciation, especially for host species living in social groups. Isolation of host populations, upon geographical or behavioral separation, likely resulted in isolation of pathogen populations and pathogen population bottlenecks, leading the way to further diversification (Van Blerkom 2003). Together with strong selective pressures exerted by the host, this is believed as the dominant force that led to correlations between host and pathogen phylogenies, revealing ancient host-pathogen associations.

Both representatives of DNA and RNA viruses have been proposed as ancient pathogens of hominins, that eventually co-speciated with the human species. The relative genetic stability of most DNA viruses—of which replication accuracy is safe-guarded by the host error-correcting machinery—and their tendency to cause persistent infection likely have facilitated their host-linked evolution. Strong evidence for co-speciation with hominids exists at least for members of the Herpes-, Papilloma-, and Polyomaviridae families (Van Blerkom 2003). These three families of viruses have in common a wide host range but relatively strict species specificity, persistence, or chronicity of infection, and intimate transmission modes mainly associated with mucosal, skin, or blood-borne contacts.

Because of the similarity of their replicative strategy with that of DNA phages, herpesviruses are regarded as ancient viruses, of which direct ancestors may have arisen at the dawn of parasitism. Phylogenetic analyzes of the genes of numerous species of herpesviruses revealed that their evolution and diversification closely followed that from their invertebrate all the way to their mammalian host species, pointing to co-speciation (McGeoch et al. 2000, 2006). Humans are infected with

eight species of herpesviruses belonging to the three subfamilies of α-, β-, and γ-herpesviruses. These subfamilies comprise both avian and mammalian viruses. They arose around the time of the divergence of mammals from their reptilian ancestors, some 180–220 mya. Because birds and mammals diverged about 310 mya, the emergence of avian α-herpesviruses in a more recent era (80–120 mya) most likely indicates cross-species horizontal transmission between mammals and birds. On the other hand, the timescale of diversification of mammalian herpesviruses in these three subfamilies approximates that of mammalian diversification. In particular, the α- and β-herpesviruses, and to a lesser extent the γ-herpesviruses, show tight correlations with the phylogenies of primates, rodents, ungulates, and carnivores (Fig. 2). Early hominins thus were likely already infected by viruses of each subfamily. The most recent common ancestor (MRCA) of herpes simplex viruses 1 and 2 (α1-herpesviruses) is estimated to have occurred about 8 mya, further indicating that early hominins—like humans today—were already infected with a number of herpesviruses. Interestingly, herpesviruses contain a repertoire of genes of host origin of which the products interfere with host immune responses and cellular regulation pathways. These "gene orthologs" were captured by herpesviruses since the time of their emergence (Wang et al. 2007). Some are common to members of the three subfamilies, indicating ancient capture. Others have been captured more recently, sometimes independently in different lineages, which can further be used to support a history of co-speciation. Similar to the herpesviruses, poxviruses have a long history of gene capture, resulting in "gene orthologs" that can provide insights into their past evolution (McLysaght et al. 2003). Although the phylogeny of poxviruses tends to mirror that of their vertebrate hosts, these viruses are also known to readily cross-species barriers. One member of the Poxviridae family, *Molluscum contagiosum*, is nevertheless recognized as an ancient pathogen of hominins (Van Blerkom 2003).

The evolutionary histories of members of the Papilloma- and Polyomaviridae families are other examples of likely host-linked evolution, with phylogenetic trees largely congruent with the phylogeny of their mammalian host species (Van Blerkom 2003). However, their phylogenies are more complex than those of herpesviruses, suggesting additional evolutionary mechanisms behind their diversity, including cross-species transmission and recombination. Similarly, it has been proposed that viruses belonging to the Parvo- and Adenoviridae families have co-speciated with their vertebrate hosts and infected early hominins, yet definite evidence for this is lacking.

In contrast to DNA viruses, RNA viruses have an error-prone genome, leading to faster rates of evolution—although varying greatly—and tend to more often cause acute infections, at least in host species living in social groups. They have an unmatched ability to evolve and adapt to new host species, and thus are generally less species-specific than DNA viruses. As a result, cross-species transmission of RNA viruses generally does occur more readily. Together with highly variable rates of evolution, this makes it difficult to trace with certainty their ancient evolution (Van Blerkom 2003). For example, it is yet not possible to draw definitive conclusions on the possible associations of some of the hepatitis viruses

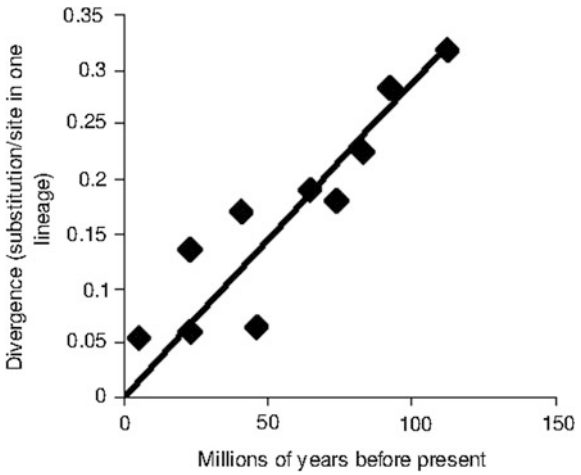

Fig. 2 Comparison between divergences for branch points in the herpesvirus tree and dates of corresponding events in mammalian evolution. Modified from McGeoch et al. (2000). Divergence events and times: humans/chimpanzees, 5.5 mya (million years ago); human/cercopithecidae, 23.3 mya; mice/rats, 40.7 mya; feliformia/caniformia, 46.2 mya; Suidae/ruminants, 64.7 mya; carnivores/perissodactyls, 74.0 mya; artiodactyls/perissodactyls, 83.4 mya; primates/ungulates, 92.0 mya;primates/rodents (sciurognathi), 112 mya

with early hominins, in particular hepatitis B virus (belonging to the Hepadnaviridae family; DNA viruses that use a RNA intermediate during replication), hepatitis A virus (belonging to the Picornaviridae family), and hepatitis C and related GBV-C viruses (belonging to the Flaviviridae family), although these viruses or their ancestors were present early during the emergence and evolution of *Homo* spp. in Africa. In contrast to other RNA viruses, members of the Retroviridae family use a reverse transcriptase to generate a DNA copy of their RNA genome. This DNA copy may integrate into the cellular genome as provirus, and as such, exhibits slower rates of evolution. Endogenous retroviruses have derived from proviruses integrated into the genome of germ cells, thus being carried along by subsequent generations of hosts as genetic traits. They have under natural circumstances lost the ability to produce infectious particles. They are transmitted vertically as "signatures" of ancient infections offering a spectacular means to explore ancient host-pathogen associations (Gifford and Tristem 2003). The oldest endogenous retroviruses of vertebrate hosts are thought to have arisen 60–80 mya. Today, up to 8 % of the human genome consists of endogenous retroviruses, belonging to at least 31 distinct lineages, most of which are present in extant Old World monkeys and apes. This suggests that they integrated into the primate genome more that 30 mya, and were part of the early hominin legacy to humans. Furthermore, the comparison of sequence data of antiviral genes demonstrated that the human TRIM5 gene, coding for a potent antiretroviral protein, has been under positive selection at least for the past 4–5 million years, indicating ancient

interactions and co-evolution of hominins and (exogenous) retroviruses (Emerman and Malik 2010).

Members of the *Mycobacterium tuberculosis* complex (MTBC) are other strict human pathogens, the origin of which may date back from the era of early hominins (Gagneux 2012). These bacteria cause life-long chronic or latent infection, and are spread via close contacts. Limited genetic variation characterizes most MTBC isolates, and suggests that these pathogens went through a bottleneck 20–35 thousand years ago (kya), followed by rapid clonal expansion. It was thought that the bottleneck marked the emergence of these pathogens in humans. However, analyzes of additional MTBC isolates sampled from human patients in East Africa revealed ancestral lineages predating the bottleneck (Gutierrez et al. 2005). The MRCA of the MTBC may have occurred more than 2.5 mya, and thus may have infected early hominins, before further diversification.

Not only pathogens spread by close contacts may have been major pathogens of early hominins, eventually co-evolving with the human species. Vector-borne protozoans *Plasmodium* spp. and *Trypanosoma* spp. are believed to have had ancient interactions with hominins. In particular, the divergence of *Plasmodium falciparum*, causative agent of severe malaria in humans, from *Plasmodium reichenowi*, which infects chimpanzees, is thought to have occurred about 5–7 mya, around the time of divergence of the chimpanzee and human lineages (Ollomo et al. 2009). Likewise, early hominins were probably infected by *Trypanosoma brucei,* the causative agent of sleeping sickness in Africa (Stevens et al. 1999). The presence of trypanolytic factors in the serum of humans and extant apes may represent another indirect clue for ancient associations and co-evolution of hominins and trypanosomes (Stevens and Gibson 1999).

The complete picture of the diversity of the microbiome of early hominins may never be drawn. The current genomic era, along with the discovery of an ever-growing number of viruses and microorganisms in humans and animal species alike, will provide increasing evidence for long-lasting host-pathogen associations maintained through the evolutionary development of the human species. These associations will undoubtedly highlight the scope of the most primordial and ancestral human–animal interface.

3 The Old and Middle Stone Ages: From the Emergence of *Homo* spp. to Hunter–Gatherers

The Stone Age is nearly contemporaneous to the emergence and evolution of the genus *Homo*, and encompasses the late Pliocene, the Pleistocene, and the early Holocene. The Old and Middle Stone Ages correspond to the Paleolithic and Mesolithic periods, respectively, spanning from approximately 2.5 mya to 12 kya. The first *Homo* species known to emerge was *Homo habilis*, which inherited the ability to use and manipulate stone tools from its australopithecine ancestors;

ability which would be maintained, developed, and refined through the evolutionary history of modern humans. Migration of *Homo* spp. out of the African homeland started as early as 1.8 mya with evidence of the presence of *Homo erectus* in the Middle East and as far as South-East Asia (Bar-Yosef and Belfer-Cohen 2001). Limited but recurrent gene flow between populations may have occurred since then across Eurasia and Africa (Templeton 2002).

Homo sapiens is thought to have originated in East Africa around 200 kya. It migrated out of Africa about 80–100 kya and colonized South-East Asia and Australia some 50–60 kya, Central Europe about 50 kya, Central Asia 40 kya, and the Americas 15–20 kya (Oppenheimer 2012). *H. sapiens* lived in small nomadic groups of hunter–gatherers, probably counting not more than 30–50 individuals. Highly mobile, their foraging strategy was directly associated with the distribution and availability of food resources. It involved the development and use of a variety of specialized tools, technologies, and hunting strategies, such as the development of fishing tools or the cooperative hunting of large game (Chatters 1987). The migration patterns of *H. sapiens* across continents were likely associated in part with their exploitation of marine resources along coastal environments, or with the migration of megafauna. Although most domesticated animals became associated with humans within the last 12 thousand years (see below), hunter–gatherers domesticated the wolf (*Canis lupus*) in Eurasia as early as 40–100 kya, giving rise to morphologically distinct domestic dogs 15 kya (Vila et al. 1997).

Scavenging and eventually fishing and hunting together with the unprecedented mobility of *Homo* spp. represent behavioral innovations that drastically shaped the prehistoric human–animal interface. The transition of *Homo* spp. omnivorous diet from predominantly herbivorous toward strongly carnivorous shaped it toward a predator–prey interface. Such an interface resulted in the acquisition of pathogens of prey, including pathogens specialized in using predator–prey relationships for transmission, such as helminths, and eventually led to the establishment and evolution of novel human pathogens. Human tapeworms (*Taenia* spp.) likely originated from ancestral species using large African ungulates as intermediate hosts and carnivores as definitive hosts (Hoberg et al. 2001). They were acquired by *Homo* spp. upon consumption of large game, most probably bovids, and adapted to the developing human species upon two independent host shifts, at least 0.8–1.7 mya. Other possible zoonotic transmission events followed by host shifts and adaptation to the human species include that of *Helicobacter pylori*, which may have colonized *Homo* spp. in the African homeland about 60 kya (Linz et al. 2007). Their original host species remains nevertheless unknown; *H. pylori* have been isolated in a wide range of animal species, including carnivores and herbivores.

A number of primate pathogens may also have emerged in Africa during early human evolutionary history, as a result of cross-species transmission. This indicates that close interactions between *Homo* spp. and other primates likely occurred, potentially including predation and consumption of primate meat. Phylogenetic analyzes strongly support that the emergence and evolution of human T lymphotropic virus of type II (HTLV II; belonging to the *Retroviridae* family)

resulted from a simian-to-human transmission event that occurred at least 400 kya in Africa (Vandamme et al. 2000). A similar scenario may have led to the emergence of the various hepatitis viruses (A, B, C, and GB viruses) and enteroviruses, such as poliovirus (belonging to the *Picornaviridae* family) in humans (Van Blerkom 2003). Yet, further study on the extent of natural infection of primates by these or related pathogens are needed to reach definitive conclusions.

The unprecedented mobility of *Homo* spp. together with their flexibility in habitat usage likely also contributed to the emergence of new pathogens following novel exposure opportunities. For example, the increasing use of open environments by *Homo* spp. is thought to have promoted their infection by *Schistosoma* spp., trematodes using mainly fresh-water snails as their intermediate hosts. The divergence of *Schistosoma* spp. infecting humans from those infecting rodents and ruminants is estimated to have occurred more than 1 mya (Despres et al. 1992). The migration of *Homo* spp. out of their African homeland similarly led to contact with species of new worlds and new opportunities for cross-species transmission of zoonotic pathogens. For example, it resulted in the cross-species transmission of HTLV I and *Plasmodium vivax* in Asia, and of hepatitis B virus of subtype F as well as GB viruses of types A and B in South America (Van Blerkom 2003). As previously, primates were the most likely sources of these pathogens, further supporting close interactions between primates and *Homo* spp.—or sharing of habitat—as the latter migrated out of Africa.

In addition to the acquisition of novel pathogens, human ancient migration across continents also resulted in the diversification of pathogens that had originated in the African homeland. Phylogenetic analyzes of pathogen diversity revealed that some may be used as valuable tools for reconstructing ancient human migrations (Van Blerkom 2003; de The 2007). These include phylogenetic analyzes of papillomaviruses and polyomaviruses, HTLV, *H. pylori*, and lice, resulting in patterns which phylogeographically coincide with those of early humans. These examples illustrate the role of prehistoric humans in disseminating pathogens to new geographical areas. The role of prehistoric humans in introducing pathogens into novel host species is less clear. However, the phylogeography of HTLV indicates that multiple cross-species transmission events have occurred between humans and other primates, in both directions, resulting in today's diversity in primate T lymphotropic viruses (Slattery et al. 1999; Verdonck et al. 2007). It is likely that pathogens carried by domestic dogs similarly may have been introduced into new geographical areas or new host species at the time of human ancient migrations. Rabies virus (of the *Rhabdoviridae* family) may be such a pathogen that disseminated as dogs were carried along to new continents. In fact, it has been suggested that infectious diseases may have significantly contributed to the extinction of New World megafauna (Prescott et al. 2012; Alroy 2001).

Although some scenarios depicted above remain largely speculative, many characteristics of the human–animal interface are present remarkably early upon the emergence and evolution of our species in and out of Africa. It mediated both the cross-species transmission of zoonotic pathogens and the introduction of

pathogens into new geographical areas and novel host species. Although not different from today, the timescale is of a completely different order of magnitude. In this light, it is tempting to speculate that infectious pathogens associated with *Homo* spp. in its debuts may have had a major role in the evolution of our species (Van Blerkom 2003).

4 The New Stone Age: Villages, Agriculture and Domestication

The New Stone Age, or Neolithic period, spanning from approximately 12 to 5 kya, marks the settlement of human bands, the development of agriculture and farming, and the domestication of various plant and animal species as food and feed resources. At that time, only one hominin species had persisted: *Homo sapiens sapiens* . Gradual behavioral and cultural changes—from mobile hunter–gatherers to settled village-farmers—most probably originated in the Fertile Crescent (Diamond 2002), and led to the development of the world's first villages and towns, such as Jericho in the Levant. This town, which limits were surrounded by a stone wall, contained an estimated population of 2000–3000 individuals (Kuijt and Goring-Morris 2002). These behavioral and cultural changes yielded to the domestication of most valuable plant and animal species, particularly abundant in this region, including wild flora like wheats, barley, and peas, as well as wild fauna like sheep, goats, cows, and pigs (Diamond 2002). Villages, agriculture, and domestication arose independently in at least four regions (China, Mesopotamia, South America, and the eastern part of North America), and further spread globally, gradually replacing hunter–gatherer economies in most parts of the world.

The introduction of food production led to the explosive human population growth, still unrelenting to this day, and allowed the development of technology and societal organization. While hunter–gatherers had lived in a relatively peaceful relationship with microorganisms, by keeping their own numbers at a level the local environment could sustain, the Neolithic farmers created conditions that would eventually let humans experience and maintain crowd diseases. Pathogens were able to maintain themselves in large populations of humans, animals, or in the soil, eventually preventing acute diseases from dying out, as would have been the case in small bands of hunter–gatherers. Crowd diseases could arise only with the buildup of large, dense communities. Agriculture could sustain 10–100 times higher human population densities than did the hunting–gathering lifestyle, and sedentary farmers living amid their own sewage or even spreading their feces and urine as fertilizer on the fields provided ideal conditions for the emergence of both crowd and zoonotic diseases (Diamond 1977).

While settlement and food production initiated these major demographic changes that would shape the scope of the human–animal interface in the ages to come, domestication represents another major revolution affecting the prehistoric

human–animal interface and completing its final shape as we know it today. Domestication is part of the first of major historical transitions that characterize the development of the modern human species and its relationships with the environment (Diamond 2002). Domestication of plants and animals, associated with the processing and storage of food, prompted close and sustained interactions between humans, live animal species and their products, as well as demographic booms in both domesticated animals and commensal species. Husbandry practices generated crowded conditions for domestic livestock, facilitating the emergence, spread, and evolution of infectious pathogens within these species. Agricultural practices opened rich ecological niches for today's commensals, such as several rodent species, spurring likewise unprecedented demographic growth of pest species, their association with humans and unmatched fertile soils for their pathogens. Cross-species transmission of zoonoses to humans leading the way to eventual establishment and evolution of new human pathogens represents a small but crucial step across the domesticated human–animal interface.

Many human pathogens likely have their origins in the Neolithic revolution, including mumps virus (of the *Paramyxoviridae* family), smallpox virus, *Corynebacterium diphtheriae,* and *Bordetella pertussis* (Wolfe et al. 2007). These pathogens typically cause acute infections; therefore large human communities (counting up to hundreds of thousands individuals) are generally needed to sustain them, independently of animal reservoirs. The invention of food production would eventually allow for such demographic growth. Their strict establishment in human populations thus may have occurred somewhat later after domestication had set the stage for their original (and recurrent) cross-species transmission. The respective hosts of origin of these pathogens, whether domesticated, commensal, or wild, remain to a large extent elusive. While the phylogenetically closest species of measles virus and smallpox virus are rinderpest virus (infecting cattle), and camelpox or gerbilpox viruses, respectively, it is unknown whether these animal host species were sources or recipients of these human pathogens.

Other pathogens with a large host range and low species specificity that are transmitted via environmental reservoirs also likely expanded their host range at the time of domestication, to include the modern human species. Among them are the caliciviruses and rotaviruses, which typically cause acute respiratory or gastrointestinal infections. Although they may have been originally pathogens of domesticated, commensal or even wild animal species, cross-species transmission between humans and animals must have occurred in both directions. For example, frequent interspecies transmission of calici- and rotaviruses between humans, cattle, and pigs complicates the picture and makes it difficult to assess with certainty their origins in either host species (Van Blerkom 2003). Likewise, the recent discovery of the human bocavirus—a parvovirus with bovine and canine parvovirus ancestry suggests cross-species transmission and recombination of these viruses (Allander et al. 2005). For other pathogens, such as *Taenia* spp., it is recognized that humans were the source of the distinct species that have emerged in cattle and pigs at the time of domestication (Hoberg et al. 2001). Likewise, a comparative genomic approach comparing *M. tuberculosis* in humans to

Mycobacterium spp. in animals suggested that they share a common ancestor, around the time of the Neolithic transition (Comas and Gagneux 2009). Cross-species transmission also occurred between animal species associated with the Neolithic human–animal interface. For example, some strains of feline leukemia virus may have been acquired by domestic cats after cross-species transmission of retroviruses from commensal rodents during this period (Roca et al. 2004).

It is most probable that recurrent cross-species transmission of zoonotic pathogens, without further establishment in the human population, occurred also increasingly frequently as agriculture progressed. These recurrent events may have been favored by the adaptation and evolution of commensal species, such as rodents and anthropophilic insect vectors, which, in addition to domesticated animals, may have created successful bridges between wild animal reservoirs and humans. The destruction of wild lands, with the ceaseless plowing of land and chopping of forests made by African farmers, attracted rats, mice, ticks, and fleas to live closer to humans, and provided ideal breeding habitats for mosquitoes. These early slash-and-burn techniques created the water-filled, sunlit ruts that *Anopheles* mosquitoes need for rapid breeding, further setting the ground for malaria's long relationship with humans (Nikiforuk 1991). In fact, skeletal and dental indicators of health status demonstrate that early farmers generally had poorer health than foragers, suffering from nutritional deficiencies as well as infections, in particular those caused by intestinal parasites and vector-borne pathogens (Larsen 2006). Domestication might also have favored the establishment of *Brucella abortus*, *Bacillus anthracis,* and the food-poisoning *Salmonella* bacteria in cattle, pigs, or poultry, thus increasing the risk of the corresponding diseases in the human population (Hare 1967).

The impact of ancient human activities associated with settlements, agriculture, and domestication on microorganisms can be detected as dramatic genomic changes in species that eventually adapted to, and associated with the human species. These genomic changes include the increasing number of mobile elements such as insertion sequences in prokaryotes upon host shift (Mira et al. 2006). This has been shown to occur for a number of pathogens of both humans and domesticated animals and plants, during the Neolithic. Major examples include *B. pertussis*, strict human pathogen causing whooping cough, *Yersinia pestis*, causing plague in humans, and transmitted by rodents via fleas, *Burkholderia mallei*, primarily a pathogen of equids, and *Pseudomonas syringae*, which specializes on tomato plants. The expansion of insertion sequences in these species was estimated to have occurred several thousand years ago, with a most recent estimate for *B. mallei*, coinciding with the more recent domestication of the horse, 4–5 kya.

The nearly complete replacement of hunter–gatherer economies by farming economies followed the spread of these behavioral and cultural changes from the original homelands of agriculture to the rest of the world. Most domesticated plant and animal species, as well as commensal species, were brought across continents to new geographical areas. This was likely accompanied by the spread of their infectious diseases and initiating new waves of introductions of both human and animal pathogens into new regions. It has been suggested that distinctively low

genetic diversity in a number of livestock parasites, such as *Trichinella spiralis*, a zoonotic nematode parasite of swine, compared to that of related pathogens of wild host counterparts, may reflect ancient dissemination following the translocation of domesticated animals by early farmers (Rosenthal 2009). The Neolithic revolution thus created new niches for pathogens, with dense, growing and mobile populations of domestic animals and commensals that characterize the domesticated human–animal interface up to this day.

5 The Bronze and Iron Ages and Ancient History: The Rise of Urbanization and Trade

The Neolithic period gave rise to the development of pottery and technology associated with the processing and storage of cultured and domesticated food, allowing for human unabated demographic growth and societal development, eventually leading to the discovery, manufacture, and use of metals. From 3 to 5–6 kya, copper and bronze were used for tools and weapons, before the use of iron and steel was discovered. These last ages of prehistory initiated the transition into ancient history (spanning from approximately 2.5 kya to the fifth century after Christ), characterized by the full development of writing, centralized governments, law codes, social stratification, empires and cities, as well as the beginnings of organized warfare. Many pathogens that emerged in humans during the Neolithic revolution were likely maintained and evolving in the human species because of increasing densities and population sizes of human communities, eventually transitioning into historical ages (Dobson and Carper 1996). While the early prehistoric human–animal interface was mainly centered on novel interactions between humans and animal species and their products, the late prehistoric and ancient historical human–animal interface revolved increasingly around the dramatic demographic and societal changes affecting human populations.

Most acute infections caused by strict human pathogens today require large population sizes to be maintained as childhood diseases or to recur as cyclic waves or epidemics. Links between communities, generated by frequent migratory movements, allow for the spread of traveling waves of disease, and relative synchronies of local and regional epidemics (Grenfell et al. 2001). Because measles virus induces strong and long-lasting protective immunity, it requires a large human population to persist, and large metropoles are typically the sources of infection for other smaller communities, resulting in pulses of synchronous waves starting in cities and radiating to smaller towns and villages. The minimum population size needed for the maintenance of measles virus has been estimated to be in the range of 200–500 thousand individuals. Similar critical community sizes likely existed for smallpox, of which the most ancient physical evidence rests as pustules on the mummified skin of Pharaoh Ramses V (Hopkins 1980). Nevertheless, it is likely that these critical community sizes were smaller during these

ancient times than today, and that sequential outbreaks in smaller communities, linked by emigration and immigration movements, may have allowed their persistence (Dobson and Carper 1996). Indeed, most ancient historical cities may have contained a community in which size ranged between 10 and 20 thousand individuals; although Babylon is considered the oldest and first city to reach a population of 200 thousand individuals during this period. As illustrated in Mesopotamia, numerous cities were erected relatively close to each other, allowing for trade and exchange between these urban communities, in addition to long-distance trade with more distant cities. It is therefore likely that the demographic conditions that developed at that time were slowly shaping the evolution of human pathogens causing acute infections. Crowded populations and poor sanitation also probably favored the maintenance and evolution of pathogens transmitted via environmental reservoirs, and may have facilitated the evolution of changing virulence.

It is indeed remarkable that most pathogens of prehistoric humans were typically causing chronic or persistent infections, potentially in combination with low levels of virulence, while more modern humans at the beginning of classical history increasingly acquired pathogens causing acute infections and/or more severe diseases. For example, *Bordetella bronchiseptica* is a common pathogen infecting a wide range of wild and domestic mammals. It generally causes very mild or asymptomatic chronic infection of the upper respiratory tract in these species. *B. pertussis* is a strict human pathogen, which most probably emerged and evolved from a *B. bronchiseptica*-like ancestor during the Neolithic revolution. But in contrast to the latter, it may cause acute respiratory infection leading to whooping cough that can be severe and life threatening. It has been proposed that the evolution of such an acute form of infection tightly depends on a critical population size above which acute pathogens are buffered from extinction (King et al. 2009). Interestingly, certain strains of *B. bronchiseptica* cause more acute and/or more virulent infections in swine and dogs, and potentially evolved as a result of higher population sizes and densities of these domestic animals. In fact, ancient historical cities not only sheltered human communities, but also retained characteristics of earlier villages, in which domestic and food production animals were kept in close proximity to humans within the walls of towns. Together with poor sanitary conditions, these crowded conditions facilitated the continued emergence and evolution of directly and indirectly transmitted pathogens in both domestic animals and humans. While directly transmitted pathogens may have evolved toward more acute pathogens due to dense and large host populations (King et al. 2009), indirectly transmitted pathogens may have evolved toward more virulent pathogens, as their transmission depended mainly on environmental reservoirs (Galvani 2003).

The particular urban conditions of these ancient times created a unique human–animal interface, characterized by close relationships between booming populations of humans and of domestic as well as commensal animals, further subjected to intense trade and mixing. A most successful melting pot for pathogens was realized, initiating an unprecedented evolutionary boom in the diversity of human-associated scourges and plagues. In particular, these conditions seem to underlie

the most famous epidemics of Classical Antiquity, generally known as the "Plague of Athens", which broke out early in the summer of 430 BC and was masterly described by Thucidides. *Salmonella enterica* sequences have been amplified in several victims unearthed from a mass burial site, thus suggesting a retrospective diagnosis of typhoid fever. The crowded and unsanitary conditions in the city, besieged by the Spartan army, must have favored the spread of the epidemic, and it is worth noting how one of the most outstanding features of Thucidides' account is the reported contraction of the disease by animals, which might suggest the intriguing possibility that the strain of *S. enterica* accounting for the Plague of Athens was an ancient strain not yet exclusively adapted to human hosts (Papagrigorakis et al. 2008). Importantly, the emergence of these new scourges and plagues was eventually accompanied by the birth of medicine in Europe with Hippocrates' *Corpus*, written and completed during the fifth century BC, followed and further developed by Galen, at the end of the second century AD.

The rise of urbanization and trade that characterized the world from the Bronze Age to the end of Classic Antiquity contributed to the creation of a common microorganisms breeding ground through the development of world trade routes, which by Roman times effectively joined the populations (and the disease pools) of Europe, Asia, and North Africa. The pandemic waves of plague in the Middle Ages would soon have tested the efficacy of this communication system.

6 The Middle Ages and Early Modern History: Colonization and Wars

The Middle Ages and early modern history span from the fifth to the end of the eighteenth century AD. This period is marked by invasions and wars between rival cultures, and the modern colonization of new worlds, via world trade and conquest routes. Organized warfare develops and the slow conquest of new territories is paced by horse gaits on land and sailing winds on seas. The medieval human–animal interface is principally one of poverty and poor sanitation, in part associated with colonization, wars, unrest, and social stratification. The major infectious diseases that predominated during this period and up to our early modern history were either crowd diseases caused by human-adapted pathogens, such as smallpox, measles, cholera, tuberculosis, and leprosy; or vector-borne and zoonotic diseases mainly associated with insect or rodent vectors, such as plague, typhus, malaria, and yellow fever. Precarious and poor sanitary conditions associated with the massive movements of humans along trade and conquest roads would drive the surge of these zoonotic pathogens. On the one hand, novel exposures of both colonists and indigenous residents to novel pathogens would follow the colonization and invasion of new territories; on the other hand, the vector or reservoir hosts of these new infections would be carried along and introduced into new regions and across continents. The extent of the resulting epidemics, the

devastating human toll claimed by these pathogens, and the disease they caused, have been reported in writing with enough details so that their causative agents can be identified today with near certainty. It is interesting to note that a newly discovered pathogen of domestic dogs, canine hepatitis C virus, is thought to have emerged during the Middle Ages, 0.5–1 kya (Kapoor et al. 2011). Although its origin remains unknown, it is tempting to speculate that it may have evolved from the human hepatitis C virus, upon cross-species transmission favored by war and poverty (e.g., following consumption of dead human liver) or the poor sanitary conditions of these times.

The plague, caused by the bacterium *Y. pestis*, is a landmark disease that arose in the Middle Ages, illustrating well the attributes of the medieval human–animal interface (Perry and Fetherston 1997). It is transmitted to humans by rodents via fleas, yet can also be transmitted directly between humans in its pulmonary form. According to recent studies, however, the poor competence of fleas would not be fully compatible with flea-borne transmission alone, which would prompt the potential role of body lice as an inter-human vector for bubonic plague (Ayyadurai et al. 2010).

It has been claimed that 200 million individuals may have fallen victim to plague throughout our recorded history. Since the 'Athens plague' was indeed typhoid fever, the first indisputable plague epidemics occurred from 541 to 750 AD, and it is widely known as the first plague pandemic (or Justinian plague). The second pandemic, often referred to as the Black Death (1347 to 1351 AD), occurred in the fourteenth century. Its first epidemics in Europe had an estimated death toll of 17–28 million individuals, representing 30–40 % of the population of Europe, and were followed by relentless epidemic cycles until late into the seventeenth century. While the first plague pandemic may have contributed to the weakening of the Byzantine Empire, the second pandemic is believed to have accelerated or directed dramatic changes in societal systems and medical education and practice. Anecdotally, the plague epidemic of the mid 1660s forced the closure of Cambridge University for 18 months, during which Newton laid the foundations of his famous discoveries in mathematics and physical science.

The medieval emergence of the plague in Occidental regions was likely associated with the dissemination and expansion of one of its main reservoir hosts, the black rat. Originally from South-East Asia, the black rat is thought to have colonized western regions along trade routes, via land and seas (McCormick 2003). It may have become infected with *Y. pestis* along the Silk Road from contacts with fleas of naturally infected burrowing rodents of the steppes of Central Asia. With its commensal proclivity, the black rat flourished in the great late Roman cities, rich in granaries and poor in waste treatment. Harboring large populations of fleas, these expanding populations of rats fuelled plague epidemics among humans. The re-emergence of the plague at the onset of the second pandemic has often been related to more violent introductions of the bacillus into plague-free populations, as in 1346, the Mongol army catapulted plague-infected corpses over the walls of the Crimean city of Caffa (Wheelis 2002). However, subsequent spread occurred independently of this event and likely resulted from introductions of infected rats

and fleas via trade routes across the Mediterranean Sea, with Sicily as Black Death's first port of entry into Europe. Although the reasons behind the intermezzo between the two plague pandemics remain a mystery, the receding epidemics from the eighteenth century onwards may be due at least in part to the colonization of Europe by the brown rat, which does not harbor anthropophilic fleas and displaced the black rat from cities.

Typhus is another disease caused by rodent pathogens, *Rickettsia prowazekii* and *Rickettsia typhi*, transmitted via lice and fleas, respectively. Typhus has remained a scourge late into our modern history, going hand in hand with war, unsavory imprisonment, and periods of unrest. Large epidemics sweeping across Europe and Asia occurred in the fifteenth century. In contrast to plague, it is believed that typhus spread eastward along the Silk Road. Typhus was also introduced into the New World upon its discovery. There, together with measles and smallpox, it severely affected the natives, who encountered these pathogens for the first time (Acemoglu et al. 2003). These scourges likely shaped the fate of the colonization of the Americas. There is no evidence that Native Americans had suffered from the epidemic diseases that ravaged Europe, before the discovery of the continent in the fifteenth century. To many European colonists, native Americans appeared more robust and healthier than themselves. Thus epidemic diseases traveling westwards found Native Americans unprotected by natural immunity. The horrendous mortality registered since 1494 in Santo Domingo was possibly the result of a swine influenza epidemic, as eight hogs taken on board Columbus's ship appear to have brought the infection. American pre-Columbian Indians had few if any domestic animals, and were first exposed to domestic animal pathogens when Columbus landed with horses, cows, sheep, goats, and pigs. It was not long before North American Indians were being decimated by human-borne diseases (Kraut 1994).

On the other hand, the colonization of new worlds by Europeans also resulted in novel exposures to exotic pathogens, such as *Plasmodium* spp. causing malaria and yellow fever virus (of the *Flaviridae* family) in Africa. These mosquito-borne diseases were the main causes of high mortality in European colonists and settlers in Africa, and have largely hampered institutional and economic development on this continent (Acemoglu et al. 2003). Malaria and yellow fever were also introduced into the Americas, and spread as virgin soil epidemics into native and colonist populations alike, due to the absence of prevailing immunity. Because of the acquired and, in some cases, genetic resistance of native Africans to these diseases, malaria and yellow fever likely were decisive factors in the development of the slave trade (Curtin 1968). These diseases, and in particular yellow fever, undoubtedly played a major role, centuries later, in the bargain sale of Louisiana by Napoleon Bonaparte during the USA presidency of Thomas Jefferson. The passing of slavery law for these new US territories eventually led to the crisis of the Union.

An obvious and recurrent question associated with the human–animal interface of these times is why the exchange of dreadful pathogens between the Americas and Europe was so unequal, and why not a single major killer from across the

Atlantic spread back to Europe. Factors possibly contributing to the apparent absence of lethal crowd epidemics in the pre-Colombian Americas may include the late rise of dense human populations on this continent, and the lack of intensive long-distance trade. An intriguing interpretation points to the essential role of domestication and highlights how only five animals of any sort became domesticated in the New World, namely: the turkey (Mexico and U.S. Southwest), the llama/alpaca, the guinea pig (Andes region), the Muscovy duck (tropical South America), and the dog (throughout the Americas). Domesticated species were a rarity and typically remained isolated from each other, possibly hampering the emergence of crowd diseases (Diamond 1977, 2002).

7 Late Modern History: The Industrial Production and Post-colonial Era

While major periods of unrest, social stratification, colonization and war define our early modern history, industrial, political, and cultural revolutions are hallmarks of our late modern history spanning the nineteenth and beginning of the twentieth century. Industrial revolutions resulted in major innovations in the chemical, electrical, petroleum, and steel industries, eventually leading to the mass production of food resources associated with the development of mechanization and new preservation technologies. Political and cultural revolutions, typically associated with major wars, revolved mainly around the spread of social movements, heralding the steady progress of globalization. The industrial revolution marks a major historical (and epidemiological) transition, characterized overall by decreased human mortality. It is commonly accepted that the observed decreased mortality arose from improvement of the nutritional status in developed countries and to the advances of hygiene and medicine (McKeown 1986). Paradoxically, major diseases also emerged at the industrial and modern human–animal interface, due to dramatic changes in human and domestic animal populations during this period. Such cross-species transmission events would eventually recur more and more frequently, as the industrial and developing societies progressed. This initiated a third major epidemiological transition characterized by the current rise of emerging infectious pathogens, and the ever-going race between infectious diseases and medicine (Barrett et al. 1998).

The dramatic changes associated with new technology often modified the environment to such an extent that they seriously affected interactions between humans, animals, and pathogens. A typical example is that of Sardinia, in the second half of the nineteenth century, where the oak forests covering the whole island were cut to be converted into coal (used for industrial purposes and burned for the production of electricity and/or heat) or to be used in the rail network of the recently unified kingdom of Italy. Deforestation, followed by a dramatic reduction in rainfall, severely affected the original Sardinian climate and turned it into a hot

and dry climate more typical of nearby Africa, with 8 months of drought followed by 4 months of unrelenting precipitations. This favored the development of large areas of wetlands and marshes, a perfect habitat for *Anopheles* mosquitoes and the expansion of malaria (Tognotti 1966). It is intriguing to note that thousands of years after Neolithic farmers had been chopping their forests at the birth of agriculture, nineteenth century's humans had altered their environment exactly in the same way.

The industrial revolution also resulted in a human–animal interface characterized by massive increase of domestic and food animal populations, as well as intensification of farming and husbandry practices—still continuing to this day. These unprecedented crowd conditions are undoubtedly major drivers of the emergence and spread of pathogens in domestic animal populations, allowing their increasingly more frequent cross-species transmission to humans. As such, this period of human history seems to repeat and expand the changes that occurred upon the Neolithic revolution and first (pre-)historical transition. However, the development of new schools of thought led to improvements in hygiene and medicine that gradually limited the impact of directly and indirectly transmitted pathogens. Among the major discoveries are those of Ignaz Semmelweis, pioneering antisepsis for obstetrical and surgical procedures, and John Snow, elucidating the water-borne source of cholera by use of epidemiological investigations; discoveries eventually leading to the development of the germ theory of disease, embraced among others by Louis Pasteur, Joseph Lister, and Robert Koch. The decline in the incidence of tuberculosis in the last decades of the nineteenth century paralleled the improvement in living conditions but probably owed more to a recognition that infected milk was a primary source of the pathogen, and to public campaigns designed to improve hygiene in dairies and to encourage citizens to boil milk before drinking it (Halliday 2007).

Whereas improvements in hygiene and medicine certainly limited the impact of "traditional" pathogens to a large extent, the industrial revolution and its impact on environment, housing and working conditions, favored transmission and emergence of novel pathogens. Among the more recent zoonotic pathogens that allegedly emerged in those years is the influenza virus (of the Orthomyxoviridae family). Although influenza virus epidemics may have occurred since the time of Hippocrates, the first well-described influenza pandemic is that of 1918, caused by the dreadful "Spanish flu" virus (Taubenberger and Morens 2006). Influenza viruses are originally avian pathogens, and in particular of wild waterbirds. Domestic species, such as poultry and swine, are susceptible to infection with these viruses, and are typically the sources of zoonotic and eventually pandemic viruses that can sweep through the human population, eventually giving rise to human-adapted seasonal influenza A viruses that claim tens of millions of human lives in interpandemic periods. At the onset of the pandemic of 1918, both swine and humans were victims of the influenza virus that eventually resulted in the death of probably more than 50 million individuals. This occurred at a time that war activities of World War I caused the deaths of about 8 million people. The massive increase in both poultry and swine populations since the industrial

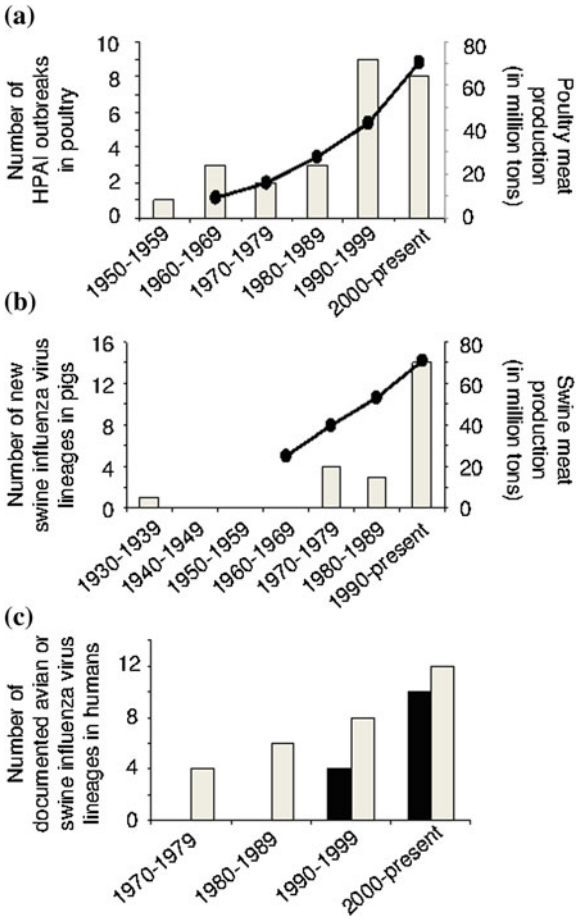

Fig. 3 **a** Number of highly pathogenic avian influenza outbreaks in poultry since the 1950s (*gray bars*) and trends in global poultry meat production (*black points*). **b** Number of new swine influenza virus lineages detected in pig populations since 1930 (*gray bars*) and trends in global swine meat production (*black points*). **c** Number of documented avian (*black bars*) and swine influenza virus lineages (*gray bars*) in humans since 1970. Subtypes are indicated for each decade; *sw* swine influenza virus; *av* avian influenza virus. Modified from Reperant and Osterhaus (2012)

revolution—and *a fortiori* in the last century—is tightly associated with an increase in the diversity of avian and swine influenza viruses in these species, as well as in the frequency of their cross-species transmission to humans (Fig. 3). Another zoonotic virus, unknown until the beginning of the twenty-first century, similarly is thought to have crossed the human–animal interface following the industrial revolution. Human metapneumovirus (of the *Paramyxoviridae* family) is closely related to the avian metapneumovirus of poultry, and causes respiratory infections in humans. Although it was described only in 2001, this pathogen has circulated widely in the human population worldwide, probably since its emergence following avian-to-human transmission, more than a century ago (de Graaf et al. 2008).

The industrial and modern human–animal interface not only prompted cross-species transmission of novel zoonotic pathogens that could eventually adapt to humans, it also affected the epidemiology of domestic animal pathogens, leading

to a high diversity of lineages (as seen for avian and swine influenza viruses) and to expanding geographical ranges. For example, the diversity of foot-and-mouth disease (FMD) virus (of the *Picornaviridae* family) strains infecting domestic ungulates in Eurasia is believed to stem from a radiation and rapid expansion event that occurred during the nineteenth century (Tully and Fares 2008). Cattle breeds imported to Africa at the end of the nineteenth century introduced rinderpest virus in local breeds and wild ungulates, sparking virgin soil epidemics that decimated entire domestic and wild populations. Although this virus did not pose a direct zoonotic risk, its impact on ungulate populations translated into devastating famines in many African countries (Normile 2008). Because of their dramatic impact, the emergence and spread of pathogens in booming and expanding domestic animal populations were rapidly accompanied by the development of counter-measures and intervention strategies, such as the restriction on movements of animals and the development and use of vaccination. The ban on animal movements during an epidemic was first introduced by the King of France in 1739 and extended during the nineteenth century as a regulatory measure against rinderpest, anthrax, and FMD in Europe (Blancou 2002). Additional measures to be implemented included slaughter of infected animals and disinfection of premises and utensils. The principles of vaccination, pioneered by Edward Jenner in 1796 for the prevention of smallpox, were applied and vaccines developed against a number of human and animal diseases, a number which would not cease to increase ever since.

Demographic changes and urbanization affected developing countries during this period, but the improvement in nutritional and health status did not compare to those in developed countries, at least in part due to the post-colonial disruption of infrastructures. Bush meat consumption is an ancient and primordial practice and resource in tropical and developing countries, such as Africa and Asia. It is increasingly used to sustain expanding human communities as well as in war zones, to eventually have reached dramatic levels today (Wolfe et al. 2005). This facet of the modern human–animal interface, directly bringing in contact growing human populations with wild animal species and their products, is also a major factor in the continued and increasingly more frequent emergence of zoonotic pathogens faced by human society up to this day: up to 75 % of current emerging zoonotic pathogens originate from wild animal species (Taylor et al. 2001; Woolhouse and Gowtage-Sequeria 2005). Almost a century ago, it resulted in multiple cross-species transmissions of the causative agent of probably the most devastating modern human plague caused by human immunodeficiency virus (HIV; of the *Retroviridae* family). HIV infection eventually leads to acquired immunodeficiency syndrome (AIDS), a disease that has spread pandemically since the 1980s of the last century. As seen previously, there is a long history of cross-species transmission of retroviruses between humans and primates, most probably as a result of blood-borne contact during butchering and consumption of primate meat. HIV currently circulating in the human population emerged on at least seven independent occasions. HIV-1 is divided into three lineages, two of which were likely a result of chimpanzee-to-human transmission of simian immunodeficiency

viruses (SIV), while the third one may have resulted from a gorilla-to-human transmission event (Van Heuverswyn et al. 2006). HIV-2 is divided into six subtypes arising from at least four independent cross-species transmission events between sooty mangabeys and humans. It has been estimated that the MRCA of HIV-1 of group M—widely distributed in the human population and responsible for the bulk of the AIDS pandemic—dates back from the beginning of the twentieth century. While bush-meat hunting and consumption may have fuelled the cross-species transmission of the virus from chimpanzees to humans, changes in human demographics and behavior in Africa and the rest of the world at that time, such as urbanization, traveling, sexual promiscuity, as well as shared use of needles, likely facilitated and eventually allowed its emergence, worldwide spread, and adaptation to the human species.

8 Contemporary History: The Globalization Era

Our contemporary history, largely founded in the industrial revolution and built on the associated booming populations of humans, domestic and food production animals, has revealed the shrinking nature of our developed and developing world. Globalization appears to define our current human society. Mass movements of people, from commuting to cross-continental scales, are accompanied and associated with mass movements of animals and goods. From unabated development to global tourism, humans are exploiting and infringing on new habitats and new environments, taking domestication, agriculture, urbanization, industrialization, and colonization to new and unprecedented levels, creating a multi-faceted global human–animal interface.

The growth of domestic and food production animal populations is far from slowing down, and rather paralleled by the unabated growth of the size and consumption levels of the global human population. Increasingly complex farming and trading systems are being developed as industrialization progresses to optimize the production efficiency of food animals and their products. Intensive farming and the trading—both legal and illegal—of live animals and their products have resulted in the global spread of zoonotic and non-zoonotic pathogens. For example, FMD virus, because of its high infectivity, is among the most devastating non-zoonotic pathogens trade and global movements contribute to spread around the world. In 2001, the virus was introduced in the UK by feeding swine with illegally imported meat from Asia, where the virus is endemic, sparking an epidemic in several European countries with heavy economical consequences (Gibbens et al. 2001). In the UK alone, the estimated agricultural and industrial costs associated with the epidemic reached up to 6.3 billion pounds (Thompson et al. 2002). Failure from following adequate heating treatment of swine feed was likely at the origin of this epidemic. Changes in the heating treatment of cattle offals in the UK in the 1980s—used as meat and bone meal in ruminant feed, being a protein-rich nutritional supplement—resulted in the emergence of a zoonotic

pathogen of a rare sort: a non-degradable host protein, or prion, responsible for bovine spongiform encephalopathy. The trade of contaminated meat and bone meal from the UK spread the pathogen among countries, resulting not only in a devastating epidemic among cattle in and beyond Europe, but also in hundreds of human cases of the new variant of Creutzfeldt Jacob disease, one or more decades later (Brown et al. 2001). In Asia, the complex farming and trading dynamics of a wide diversity of poultry species are driving complex epidemiological and evolutionary dynamics of avian influenza viruses, including the highly pathogenic avian influenza virus (HPAIV) H5N1. The trade of poultry, typically sold live at wet markets, allowed the emergence in 1997 of HPAIV H5N1, which infected 18 people leading to six deaths in Hong-Kong (de Jong et al. 1997). It now circulates in a wide range of poultry and other bird species, and has infected more than a dozen of mammalian species (Reperant et al. 2009). To date, it has caused about 600 documented hospitalized human infections with a case-fatality rate of close to 60 % (WHO 2012). If this virus were to acquire efficient transmissibility among humans, as recently shown possible in the ferret model (Herfst S et al., under review/in press), it could be at the basis of a pandemic of unprecedented severity in modern history. Several other avian influenza viruses of concern are low pathogenic viruses of the currently identified 17 H subtypes, several of which have become established in poultry populations in China (Choi et al. 2004; Cheung et al. 2007). Swine influenza viruses are also candidate precursors of pandemic influenza viruses, as demonstrated in 2009. The farming and trading practices applied to domestic swine populations in North America recently have been shown to generate conditions favorable for the emergence, evolution, and spread of diverse lineages, with occasional cross-species transmission to humans (Nelson et al. 2011). The latest pandemic virus of 2009 was a reassortant virus with gene segments from swine viruses of Eurasian and American origins, respectively, further demonstrating the global circulation and exchange of influenza viruses and their gene pools (Smith et al. 2009).

The global movement of animals associated with legal and illegal trade is not restricted to food production animals and concerns as well pets, including exotic species, and wildlife (Chomel et al. 2007). Rabies, a viral disease that kills about 50,000 people annually, likely has been introduced by humans via domestic dogs to new geographical areas since times immemorial; it continues to constitute a recurring threat to countries where the virus is controlled successfully, associated with the illegal importation of dogs and other carnivores from rabies-endemic countries today. Unless pre-exposure vaccination is practiced or post-exposure treatment is carried out rapidly, this largely neglected disease is invariably fatal in humans and most warm-blooded animal species, and thus is among the most serious diseases long associated with the domesticated human–animal interface. Yet, domestication in our global society has taken unprecedented proportions, with the trade of an increasing range of exotic pet species. For example, pet reptiles are an increasing source of *Salmonella* infection. In the early 1970s, the US Food and Drug Administration banned the distribution and sale of baby turtles after a quarter million infants and small children were diagnosed with turtle-associated salmonellosis.

Nowadays, it is estimated that approximately 3 % of American households own 7.3 million reptiles, the majority being iguanas (Burnham et al. 1998). CDC is currently investigating an outbreak of human *Salmonella* infections associated with feeder rodents (i.e., rodents sold as food for pet reptiles and amphibians) in the USA. The same strain was implicated in a 2009 outbreak in the United Kingdom and a 2010 outbreak in the USA, both linked to frozen feeder rodents (CDC 2012).

Due to their nature, exotic pet species carry an unmatched range of "exotic" pathogens. The outbreak of monkeypox virus in humans in the USA in 2003 was the result of the importation of infected African rodents, including rope squirrels (*Funisciurus* spp.), Gambian giant rats (*Cricetomys* spp.), and African dormice (*Graphiurus* spp.), which subsequently infected prairie dogs in quarantine. In total, 81 human cases of monkeypox were diagnosed (Di Giulio and Eckburg 2004). On a broader scale, the legal and illegal trade of wildlife and wildlife products represents a major source of emerging infectious diseases, from local scales, involving bush-meat hunting and wet markets, to cross-continental scales. It expands the diversity of animal species coming into contact with humans and their domestic animals. These diseases may affect humans, their domestic animals, or other wild animal species, thus also expanding the dire consequences of their cross-species transmission across the contemporary human–animal interface. Although the animal reservoirs of Filoviruses like Ebola virus are unknown, bush-meat hunting in Africa, in particular of primate species, is typically incriminated as the source of recent violent outbreaks in humans (Wolfe et al. 2005). As growing human populations in urban areas feed the demand for bush-meat, intensive hunting and trade are likely to pose an increasing risk for the cross-species transmission of these and other pathogens in African countries. Wet markets in Asia, hosting a diversity of wild animal species, were the sources of the novel coronavirus that triggered the severe acute respiratory syndrome (SARS) epidemic in 2003 (Peiris et al. 2003). As for Ebola viruses, the animal reservoirs of the virus were unknown at the time of its emergence in humans. Civet cats found infected with the virus at the wet markets were the stepping stones in the chain of transmission of this new pathogen to humans (Song et al. 2005). For both filoviruses and the SARS coronavirus, bat species are now considered the most likely reservoir hosts (Li et al. 2005; Monath 1999). These two examples illustrate the complex cross-species transmission dynamics at the human–wild–animal interface that arise from the intensifying trade of wildlife and their products. Among the most spectacular examples of global spread of a wildlife disease is that of the emerging chytrid fungus *Batrachochytrium dendrobatidis*, affecting and threatening amphibian populations worldwide. Its emergence is thought to have followed the international trade of an African clawed frog, *Xenopus laevis*, starting in the 1930s (Weldon et al. 2004). The pathogen is now found on every continent that has amphibians, and is likely the cause of the dramatic amphibian population declines and extinctions recently witnessed in many parts of the world. The trading component of the contemporary human–animal interface has undoubtedly taken domestication and the exploitation of animal species to levels beyond the imaginable, realizing unparalleled melting-pot conditions for the emergence of new human and animal pathogens.

Agriculture, born during the Neolithic revolution, continues to expand, meeting the demands of our growing global society. Agricultural development in South America and Asia has altered the population dynamics of new commensal species, including a large diversity of rodent and bat species. The discovery in the past decades of an ever increasing diversity of arena- and hantaviruses in South American rodent species, of which some have caused severe disease in humans upon zoonotic transmission, correlates with the agricultural development characterizing this part of the world (Charrel and de Lamballerie 2003; Zeier et al. 2005). Destruction of natural habitat for agricultural purposes has been associated with rodent colonization and population expansion that favored the cross-species transmission of these novel pathogens to the human species. Arena- and hantaviruses have co-evolved with their rodent hosts: they cause asymptomatic chronic infections in these hosts, and their phylogeny closely mimics that of their hosts, in a similar way to that of the heirloom pathogens of humans. Cross-species transmission of these viruses typically may turn them from harmless to life-threatening pathogens for both humans and domestic animals. While New World arenaviruses (such as Junin, Machupo, and Guanarito viruses) cause hemorrhagic fever syndromes in humans, New World hantaviruses (such as Sin Nombre, Oropouche, and Andes viruses) cause acute pulmonary syndromes. Most occurrences of these virus infections in humans are the result of zoonotic transmissions; however, most arena- and hantaviruses have only limited ability to transmit from human-to-human, raising questions about the limiting factors that determine their adaptation to the human species, eventually posing an epidemic or even pandemic threat.

In Asia, the destruction of natural habitat for agricultural purposes has been associated with fruit bat colonization and population expansion. These were and continue to be at the origin of recurring outbreaks of henipavirus infections in domestic animals and humans (Field et al. 2001). The development of fruit tree plantations integrated with pig farming in Malaysia provided ideal conditions for the cross-species transmission of Nipah virus (see chapter in this volume). Fruit bats that colonized the plantations contaminated fruits with their virus-loaded saliva; contaminated fruits eventually were eaten by pigs. These developed respiratory and neurological disease, and further transmitted the emerging pathogen to humans. Nipah virus is now known to circulate over most of the range of *Pteropus* fruit bats in Asia. In Bangladesh, the virus is directly transmitted from bats to humans possibly via the consumption of contaminated sap juice, and may also have limited ability to transmit between individuals. The related Hendra virus has likewise been transmitted from fruit bats to horses in Australia, and can further infect humans in contact with diseased horses, upon zoonotic transmission (Field et al. 2001).

Like agriculture, growing urbanization worldwide infringes on natural habitats and creates favorable conditions for commensal species, providing shelters and ample food resources to sustain their ever-growing populations. Urban and peri-urban environments are colonized by opportunistic mammalian and bird species, favoring the emergence or re-emergence of zoonotic pathogens. In Europe, the geographical range of the zoonotic tapeworm *Echinococcus multilocularis*, causing

severe liver disease in humans, is currently expanding (Deplazes 2006). This is in part associated with colonizing and flourishing populations of red fox definitive hosts in cities and periurban areas (Deplazes et al. 2004). West Nile and Usutu viruses are flaviviruses transmitted by mosquito vectors, with birds as reservoir vertebrate hosts. In Europe and North America, where these viruses have recently emerged, bird reservoirs, notably passerines, act as amplifying hosts up to city centers and densely populated areas. Humans bitten by infected mosquitoes act as dead-end hosts, and may develop severe neurological disease (Hubalek and Halouzka 1999).

Industrialization, associated with the development of intensive food animal production and trading systems, agriculture and urbanization, has had strong impacts on the environment. In particular, by affecting the global climate, these environmental changes may be affecting the human–animal interface in an unprecedented way. This environmental interface is reviewed by Colwell and Dazsak in this volume.

The worldwide challenge of antimicrobial resistance, although largely elicited by the abuse in medical practice, has added a new dimension to the human–animal interface. After the introduction of antimicrobial agents in veterinary medicine, bacteria resistant to antibiotics rapidly emerged, and the importance of spread of antimicrobial-resistant bacteria from animals to humans became more and more recognized. Resistant bacteria from animals can be transmitted to humans not only by direct contact, but also via food products of animal origin. Not only clonal spread of resistant strains occurs, but also transfer of resistance genes. Approximately 50 % of all antibacterial agents used annually in the EU are given to animals, not only for therapy and prevention of bacterial infections, but also as feed savers, antimicrobial growth promoters, or performance enhancers (APE). Since 1969, molecules that are used for therapy in humans and/or animals may not be used as APE in most EU-member states. However, many of APE that are used today in the EU are analogs of and show cross resistance with therapeutic antibiotics (van den Bogaard and Stobberingh 2000). The establishment of methicillin-resistant *Staphylococcus aureus* (MRSA) in farm animals in the early 2000 has provided a reservoir of infection for humans and dairy cattle, particularly in continental Europe, described as livestock-associated MRSA (LA-MRSA). LA-MRSA were significantly associated with veterinarians in contact with livestock, and a strong direct association was found between LA-MRSA acquisition and exposure to live pigs (Graveland et al. 2011).

While the modern relationships between humans and animal species and the environment have set the stage for increasingly more frequent cross-species transmission of zoonotic pathogens, the mass movements of people from local to cross-continental scales allow their emergence and spread within local communities and around the world, with unprecedented speed. In particular, global tourism and global business travel have accelerated the dynamics of emergence and spread of zoonotic pathogens, complicating source tracing and control strategies. Exotic diseases are brought back upon return from exotic journeys and considerably expand the scope of differential diagnosis approaches upon presentation of often

non-specific clinical signs, such as fever, neurological, intestinal, or respiratory symptoms. Current examples include spectacular cases of filovirus and bat rabies infections in the Netherlands (Timen et al. 2009; van Thiel et al. 2007). These infections did not result in onward transmission of the pathogens in the human population. Yet, when emerging pathogens acquire the ability to transmit between individuals, the globalization of the human society allows for their rapid spread around the globe, making their efficient control difficult. The unstoppable spread of the latest influenza pandemic within a matter of weeks in 2009 is a clear example of a lost race against a highly transmissible pathogen. In 2003, the emergence of the SARS coronavirus from wet markets in Asia was followed by its global spread in a matter of weeks. Within 4 months, more than 8000 cases of SARS were reported in 26 countries, with a case-fatality rate of 10 % (Peiris et al. 2003). The economic impact of the outbreak was estimated in the range of 30–140 billion US dollars (Skowronski et al. 2005). However, for the first time in human history the control of the emerging pandemic was accomplished through an unprecedented pathogen discovery effort, followed by an exhaustive public health effort, both coordinated by WHO, effectively nipping the first pandemic of the century in the bud.

9 Future: The Eradication Era

Although the global human–animal interface is the culmination to unparalleled levels of all its facets originally drawn at different periods of human pre-historical and historical development, the race between the ever increasing range of infectious diseases fuelled by the complex mix of predisposing factors in our modern society is largely paralleled by the development of equally complex mix of intervention strategies invented and implemented by humans. The latter includes the coordinated and timely use of the achievements of medical, molecular, mathematical, social, and other sciences. Recently, this resulted in the timely identification of the SARS coronavirus, allowing concerted public health efforts to successfully control the emerging epidemic before the newly introduced pathogen could cause a full blown pandemic. Although this will prove much more difficult for more transmissible pathogens, as was the case for the latest pandemic influenza virus of 2009, the SARS episode is unique in our recorded history. Among other most successful and hard-won achievements of modern medicine are the eradications of two long-time plagues of humans and domestic animals: smallpox and rinderpest, respectively. In both cases, a combination of mass vaccination, intensive surveillance, and case containment successfully brought these pathogens, that have devastated human and animal populations for at least thousands of years, to extinction, with last identified cases in 1977 and 2001, respectively (Normile 2008; Fenner 1977). Stimulated by these successes, concerted public health efforts are currently applied for the eradication of measles and polio.

Although these successful eradications may represent victories over infectious diseases and put the ball in our camp, the dynamic nature of infectious pathogens, in particular due to their epidemiological and evolutionary flexibility and adaptability, call for words of caution against losing the ball from sight. With the eradication of pathogens and the waning of immunity that had characterized the human population for millenia, we start to face new challenges and issues, by opening niches for colonization by related pathogens lurking in the animal world. Monkeypox virus may be considered a looming threat at the global human–animal interface, which one day upon the regular interspecies transmissions could fully adapt to more efficient human-to-human transmission and fill the niche left empty by the eradicated smallpox virus (Stittelaar and Osterhaus 2001). Similar future threats may come from animal morbilliviruses after the eradication of rinderpest or the future eradication of measles (de Swart et al. 2012). In the new era of cutting-edge technology, the plethora of classical and novel molecular techniques currently leads to the discovery of an array of hitherto unknown human and animal microorganisms and viruses, some of which may be candidates to fill newly emerging niches at the modern human–animal interface. Therefore, perhaps rather than investing in trying to influence the complex mix of predisposing factors of emergence at the human–animal interface, investment in these and other newly emerging technologies and intervention strategies may eventually lead to preventing disasters caused by emerging infections, allowing us not only to win major battles, but also to win the apparently never ending war between mankind and its relentlessly emerging microbial foes.

10 Conclusions

The human–animal interface has developed since the first bipedal steps of humankind into a complex pattern of interactions between humans and animals in recent eras strongly affected by the unprecedented impact that humans proved to have on their global environment. By looking back into the evolution and history of our species, it is tempting to conclude that the human–animal interface has significantly contributed to the shaping of this evolution and history, via cross-species transmission of a large number of more or less versatile pathogens. Since the human impact on the global environment shows no signs of decline, investment in a better understanding of the human–animal interface, using our state-of-the-art technology, may well secure a leading edge in the never-ending battle against infectious diseases coming from the animal world.

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