Akio Yamada · Laura H. Kahn
Bruce Kaplan · Thomas P. Monath
Jack Woodall · Lisa Conti *Editors*

Confronting Emerging Zoonoses

The One Health Paradigm

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Preface

According to the United Nations, the global population is estimated to reach 8.1 billion in 2025 and increase to 9.6 billion in 2050. In developing countries, the population is projected to increase to 8.2 billion in 2050. Sustainably supporting these unprecedented populations will require integrating a "One Health" approach in medicine, public health, and agriculture.

In a recent presentation by Jimmy Smith, the Director General of the International Livestock Research Institute, it was projected that total livestock production would increase 92 % by 2050. To feed these enormous numbers of humans and livestock, 61 million hectares of additional cropland would be needed worldwide. Direct and indirect interactions between different species of animals, including humans, are anticipated to increase, leading to the emergence of more zoonotic pathogens. These novel pathogens might have the capacity for interhuman spread and even pandemic potential among humans. To mitigate the burden of emerging infectious zoonotic diseases, efficacious monitoring of diseases of wild and domesticated animals would be required. This interspecies disease surveillance would enable early disease detection at the interface of humans, livestock, and wildlife and would promote rapid response capabilities.

Although emerging infectious diseases pose health threats to people regardless of their economic status, the poor in many developing countries suffer the brunt of the burden from "neglected zoonotic diseases." In these countries, the poor depend upon small livestock like goats and poultry for their livelihoods, but many of these animals harbor zoonotic diseases. Industrialized countries, in contrast, have much better biocontainment capabilities in their livestock production. Prevention is critical but is often hampered by the diversion of necessary resources for diseases with higher priorities in the human medical communities such as heart disease, cancer, and diabetes.

Furthermore, the provincial silo approach to zoonotic and neglected diseases makes matters more difficult because prevention and response measures are not implemented using a collaborative, interdisciplinary One Health approach. These diseases, which affect all species, require that disciplines with expertise in different

areas work together. One Health is a concept that underpins the multidisciplinary or transdisciplinary approaches to zoonotic diseases. This is equally applicable to other health and health care categories that fall under the One Health Umbrella (http://www.onehealthinitiative.com/OneHealth2) such as comparative medicine/translational medicine.

Contributors to this book provide an overview of the current understandings of zoonotic and emerging infectious diseases using examples where the One Health approach was successfully applied. The book also highlights some of the challenges societies face in confronting several specific zoonotic diseases. A chapter is included on comparative medicine to demonstrate the broad scope of the One Health concept.

This book is dedicated to those studying zoonotic diseases and comparative medicine in both human and veterinary medicine, to those involved in the prevention and control of zoonotic infections, and to those in the general public interested in the visionary field of One Health.

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Chapter 1
The Origin of Human Pathogens

Gabriel Trueba

Abstract Modern human infectious diseases are thought to have originated in domestic animals during the Neolithic period or afterwards. However, recent genetic, phylogeographic and molecular clock analyses of microbial genomes point to a much older Paleolithic origin (2.5 million to 10,000 years ago) and suggest that many of these pathogens coevolved with ancestral hominids in Africa. Another group of human pathogens seems to have derived recently from non-human hominids.

Keywords Evolution • Molecular clock • Phylogeny • Zoonosis

1.1 Introduction

Some scientists contend that many modern human infectious diseases arose during the Neolithic period or afterwards due to close contact with domestic animals and their pathogens (Diamond 1999; Pearce-Duvet 2006; Wolfe et al. 2007). There is indeed evidence of a recent origin of measles virus from bovine rinderpest virus (Furuse et al. 2010), and bubonic plague (*Yersinia pestis*) from *Y. pseudotuberculosis*, a zoonotic bacterium carried by rodents (Cui et al. 2013). As a consequence of this view, the origins of many human infectious diseases, such as tuberculosis, malaria, smallpox, and pertussis have focused on domestic animals and environments outside of Africa. However, the combination of genetics, molecular clock analysis and phylogeography provide evidence that some of these diseases arose much earlier in the Paleolithic period and probably when our hominid ancestors were still isolated in Africa (Forster 2004). Some of these findings are in agreement with paleontological and archeological discoveries.

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1.2 Older Origins

Tuberculosis was the typical example of a disease thought to have originated in the Neolithic period and transmitted from cattle to humans (Diamond 1999). This scenario implied that the human *Mycobacterium tuberculosis* bacterium derived from a bovine *M. bovis* ancestor.

Recent analyses of genomic deletions and nucleotide polymorphisms suggests that the ancestor of *M. tuberculosis* Complex (MTCP) may actually have originated from a group of smooth mycobacteria found in humans in East Africa (Gutierrez et al. 2005; Wirth et al. 2008). Molecular clock analysis of strains belonging to MTCP indicates that the common ancestor may have existed 2.6–2.8 million years ago (Gutierrez et al. 2005). This ancient date places the origin of the disease at a time when our hominid ancestors were living in Africa. Furthermore, there is evidence of a genetic bottleneck of *M. tuberculosis* occurring about 40,000 years ago, possibly the result of the human migration out of African to Eurasia (Gutierrez et al. 2005; Wirth et al. 2008). In congruence with the molecular data, tuberculosis lesions and mycobacterial DNA have been found in pre-Columbian Americans (Stone et al. 2009) who most likely did not have contact with domesticated cattle. Furthermore, rather than evolving from bovines as originally hypothesized, recent analyses of genome deletions and phylogeny suggest that *M. bovis* (and other animal adapted MTCP mycobacteria) derived from a mycobacteria more similar to the human adapted *M. tuberculosis* than to *M. bovis*. These studies clearly contradict the notion that the human *M. tuberculosis* derived from *M. bovis* (Smith et al. 2009; Garnier et al. 2003; Wirth et al. 2008). Nevertheless the evolutionary relationship between *M. tuberculosis* and *M bovis* seems to be complex; current evidence suggest that the most recent common ancestor of MTCP may have evolved into two groups: *M. tuberculosis* and a group of mycobacteria infecting different animal species; *M. bovis* may have emerged from the group of animal adapted mycobacteria (Smith et al. 2009).

The presence of *M. bovis* in badgers and its possible connections with livestock have been investigated using whole genome sequencing analysis and showed that the transmission of *M. bovis* between cattle and badgers is recent, however the direction of the transmission remains unresolved (Biek et al. 2012).

Another mycobacterial disease, leprosy was first recorded in humans around 600 B.C. in India (Stone et al. 2009). Based on historic documents, it was thought that this disease was later brought to Europe during Greek military campaigns (Stone et al. 2009). In support of this recent origin is an absence of leprosy in pre-Columbian Americans (Stone et al. 2009), and little genetic variation among isolates of *Mycobacteria leprae* (Gómez-Valero et al. 2007; Monot et al. 2005), the causative agent of this infectious disease. By contrast, phylogeography using single nucleotide polymorphism (SNP) analyses point to *M. leprae* originating in Africa during the Paleolithic (Monot et al. 2005; Monot et al. 2009). This ancient date suggests that the current presence of little genomic variation may be due to a recent bottleneck (Monot et al. 2009; Monot et al. 2009), possibly due to *M. leprae*'s low

rate of infection (Smith 1904). This low infection rate could also explain the absence of leprosy in pre-Columbian Americans, even though their ancestors may have themselves been infected. Interestingly, a mycobacterial species (*M. lepromatosis*) has been discovered recently in Mexico and the Caribbean. However, this bacterium seems to have diverged around 10 million years ago from *M. leprae* and may have been brought to the American continent by the first human immigrants (Han et al. 2009). Molecular clock analysis suggests that the ancestor of *M. leprae* diverged from *M. tuberculosis* around 66 million years ago, prior to the origins of the genus *Homo*, 2.5 million years ago (Forster 2004). Analysis of non-synonymous nucleotide substitutions suggests that *M. leprae* underwent genomic decay between 10 to 20 million years ago (Gómez-Valero et al. 2007; Monot et al. 2009). See Sect. 1.4 below.

Other diseases whose origins have been subjected to major debates are human treponematoses, which include syphilis (caused by *Treponema pallidum* subsp. *pallidum*), bejel (caused by *T. pallidum* subsp. *endemicum*), yaws (caused by *T. pallidum* subsp. *pertenue*) and pinta (caused by *T. pallidum* subsp. *carateum*) (Scolnik et al. 2003). The genomes of the four subspecies display very few differences, suggesting a recent common *Treponema* ancestor. However *T. pallidum* seems to be a pathogen that has co-evolved with human ancestors; typical yaws-like lesions have been found in prehistoric human bones and ancestral hominids, indicating a Paleolithic origin of treponematosis (Rothschild and Rothschild 1996).

Most of the debate has focused on the origins and spread of syphilis. Recent phylogenetic and SNP analyses of treponemal genes suggest that a New World lineage of *T. pallidum* subsp. *pertenue* may be the origin of the subspecies *pallidum* (Harper et al. 2008). Also there are interesting parallelisms between human treponematosis and similar infections in primates (please see Sect. 1.4) The change from casual to venereal route of transmission in *Treponema pallidum* remains a puzzle. However, non-venereal *T. pallidum* subsp. *pertenue* has been found to cause chancre-like (syphilis-like) lesions in Guyanese indigenous people (Scolnik et al. 2003). *Neisseria gonorroheae*, another venereal pathogen, may have evolved from a linage of *Neisseria meningitides* (upper respiratory tract inhabitant) during the Neolithic (Saunders et al. 1999) and it may be related to the emergence of large villages. In this case there is no evidence of recent zoonotic origin of pathogenic of human *Neisseria* which may suggest co-evolution within hominids.

Bordetella pertussis, the etiologic agent of whooping cough, was thought to have originated recently from *Bordetella bronchiseptica* infecting domestic animals such as pigs and dogs (Diamond 1999; Pearce-Duvet 2006; Wolfe et al. 2007). Although analysis of DNA sequences of multiple loci (MLST) indicated that *B. pertussis* evolved from *B. bronchiseptica* (Diavatopoulos et al. 2005), recent molecular clock estimations suggest that the divergence time between *B. pertussis* and *B. bronchiseptica* associated with domestic animals was 1.1 to 5.6 million years ago (Diavatopoulos et al. 2005), before the origin of *Homo sapiens*, 0.2 million years ago (Forster 2004) and therefore also before the domestication of pigs and dogs. Genomic decay in *B. pertussis* may have been the result of evolution among ancestral hominids and adaptation to these hosts (Diavatopoulos et al. 2005; Bentley and Parkhill 2004). Additionally, human strains of *B. parapertussis*

(a bacterium causing less severe whooping cough in humans) have diverged from animal *B. bronchiseptica* 0.7 to 3.5 million years ago and from a different clade than *B. parapertussis* isolated from domestic animals, however a recent report suggests that strains of *B. parapertussis* of human and ovine origins may be more closely related than previously described (Park et al. 2012)

Some *B. bronchisepica* infecting humans seem to belong to different lineages from those infecting domestic animals whereas other clades appear to be zoonotic (Diavatopoulos et al. 2005). Human pathogenic *Bordetella* may have originated from related bacteria infecting other animals during the Paleolithic period (Diavatopoulos et al. 2005).

Variola (Smallpox) virus was also thought to have originated in domestic animals (Diamond 1999; Pearce-Duvet 2006; Wolfe et al. 2007). However correlation of phylogenetic analysis and historical records indicate that variola virus belongs to a different lineage than cowpox virus (Li et al. 2007). Recent analysis suggests that this virus originated in an African rodent during the Paleolithic period (Li et al. 2007), however other authors have presented evidence of a more recent divergence (approximately 3,500 years ago) between the virus from the African rodent and the variola virus (Babkin and Babkina 2012).

1.3 Evidence of Co-evolution with African Primates

Mycobacterium leprae has been found in wild primates showing signs of leprosy (Hubbard et al. 1991; Clark-Curtiss and Walsh 1989). The significance of non-human primate leprosy is unknown because of lack of genetic information of the etiologic agents. At this point it is not possible to decipher if these primates, like armadillos (Truman et al. 2011), contracted *M. leprae* from humans or vice versa, or whether this bacterium belongs to a distinct but phylogenetically related linage (co-evolution within primates). While it is unknown whether this leprosy from non-human primates could be passed to humans, there is some evidence that leprosy from armadillos could be zoonotic in some regions (Truman et al. 2011).

Similarly, *T. pallidum* subsp. *pertenue* infection rates are high in both humans and primates in yaws-endemic areas of West Africa (Centurion-Lara et al. 2006). A simian yaws-like skin disease caused by a variant closely related to the human *T. pallidum* subsp. *pertenue*, which does not appear to be the result of recent cross infection from humans, has been described (Harper et al. 2008; Centurion-Lara et al. 2006), although inoculation with the simian strain can cause a yaws-like infection in humans suggesting that cross species transference is also possible (Harper et al. 2008). Additionally, *T. pallidum* subsp.*pertenue* has been reported to cause genital ulcerations in African primates (Knauf et al. 2011) and the tropism to genital epithelia of these non-human primate strains could be an example of

parallel evolution. These data suggest that skin treponematosis may have evolved within African primates and ancestral hominids.

Other microorganisms which may have co-evolved with African hominids are herpesviruses (McGeoch et al. 2005), papillomaviruses (Gottschling et al. 2007), *Helicobacter pylori* (Linz et al. 2007), *Streptococcus pneumoniae* (Kilian et al. 2008), *Taenia solium*, *T. saginata* (Hoberg et al. 2001), and even human intestinal microbiota (Ochman et al. 2010).

1.4 Evolving to Human-Specific Pathogens

Pathogen crossing of host-species barriers is a common occurrence in natural environments (zoonosis and anthroponosis). However, acquiring traits enabling efficient transmission within a given host species is a more unusual event. Evolutionary adaptation of many bacterial pathogens to a specific host transmission may be accompanied by a trade off which reduces the competence to cross host species barriers and often involves genome decay (Bentley and Parkhill 2004).

Adaptation to transmission within a new host (i.e. human to human transmision) seems to occur more frequently in pathogens infecting phylogenetically related hosts (Davies and Pedersen 2008; Holmes 2008). Molecular similarities between cells from closely related animal species may facilitate this adaptation process (Holmes 2008). The recent evolution of the human pathogens such as hepatitis B virus (Simmonds and Midgley 2005; Vartanian et al. 2002; Tatematsu et al. 2009), HIV (Keele et al. 2006), HTLV (Wolfe et al. 2005), falciparum malaria (Liu et al. 2010) from African primates follows this pattern (Fig. 1.1). Close contact of modern humans with their genetically closer hominid species such as *Homo neanderthalensis* (Green et al. 2010) (or other archaic humans) may have also played a role in the introduction of some of these infectious diseases to modern humans (Fig. 1.1). For instance, the possible emergence of the typhoid fever agent *S. enterica* serovar Typhi (Kidgell et al. 2002) and *E. coli* (Pupo et al. 2000) roughly coincides with the time estimates of the interaction between *Homo sapiens* and *H. neanderthalensis* (Green et al. 2010).

Close contact with phylogenetically distant animals can also result in the evolution of new host-specific pathogens; animal pathogens becoming human pathogens (measles, bubonic plague, smallpox, and swine and avian influenza) and human pathogens becoming pathogens of other animal species (taeniasis, tuberculosis and infectious gastritis).

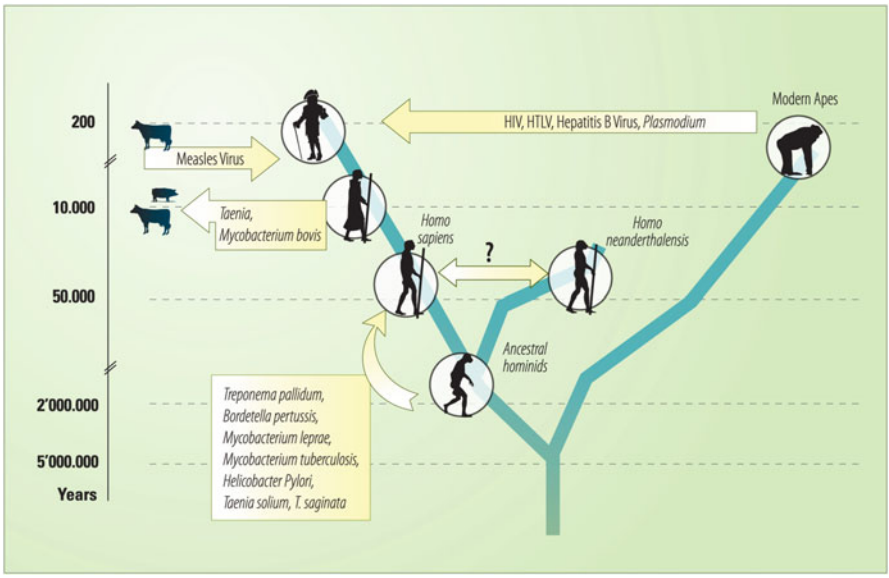

Fig. 1.1 Probable origins of human-specific infectious diseases. *Arrows* indicate suggested direction of the original transmission

1.5 Conclusions

Many problems exist in inferring phylogenetic relationships (Felsenstein 2003) and molecular clock estimations (Feng et al. 2008; Graur and Martin 2004; Sharp and Simmonds 2011; Bromham and Penny 2003), however it is possible to conclude that recent evidences (molecular clocks analyses, single nucleotide polymorphisms and phylogeography) suggest that many modern human infectious disease did not arise from domestic animals during the Neolithic period as previously thought. Rather, these diseases have a much older origin (Paleolithic period); some of them may have co-evolved with hominids whereas others may have originated in wild animals. In other cases, such as measles and possibly parapertussis, the evidence suggests a Neolithic origin from zoonotic agents present in domestic animals (Sharp and Simmonds 2011; Park et al. 2012). Despite the recent evidence that many human-infectious diseases have originated in primates, the study of infectious diseases of primates (especially non-human hominids) is still a neglected field of research. African primates, including human's closest relatives (chimpanzees and bonobos) also share the same habitats in many regions of central Africa. Most importantly, many people in this region consume ape meat and are exposed to blood and other fluids from these animals (Wolfe et al. 2005). African primates remain an untapped source of information required to complete the puzzle of the mechanisms of origin and evolution of many human pathogens.

As the genomic data from a wider population of microbial pathogens and commensals from humans and other animals are available, we will have a better understanding of the mechanisms that govern transmission and microbial adaptation to different animal species. The discovery of the factors involved in host species crossing and the evolution of human specific pathogens may help the identification of human activities, which can potentially promote the emergence of new infectious diseases.

There is a complex relationship between human activity, animal microbial diseases, human microbial diseases and the environment. A better understanding of the evolutionary processes implicated in the emergence of new diseases may require the collaboration of many disciplines, an idea promoted by the One Health concept.

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Chapter 2
Drivers of Emerging Zoonotic Infectious Diseases

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Abstract This chapter discusses drivers of emerging infectious diseases (EID) of humans that have an origin in other vertebrate animals (zoonoses). This is a broad topic, worthy of a book in its own right. This chapter will therefore provide only an overview of key concepts of drivers of the emergence of zoonotic diseases, and particularly infectious diseases with a major disease burden in humans. As the authors mainly work in Asia, the focus of this chapter is Asia, but many of the lessons learned in this region are likely to apply elsewhere.

More than 60 % of the world population live in Asia, a region with some of the fastest developing economies in the world. Yet, despite tremendous advances, infectious diseases still remain a major burden for the human population in Asia. Of the estimated 2.1 million deaths in children aged less than 5 years in Southeast Asia in 2010, 47 % are attributable to infectious causes (Liu et al., Lancet 379:2151–2161, 2012). As such, Asia is both vulnerable to imported EIDs and a global focus of major social and environmental change that may facilitate the emergence and dissemination of new pathogens. However, it would be too simplistic to present the extensive changes in Asia as inevitably increasing the risk of

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EIDs. Some aspects of socio-economic change might serve to reduce the overall risk of infectious disease emergence, but all ecosystem changes have the potential to provide new opportunities for microorganisms to spill-over into human populations.

Keywords Driver • Emerging infectious disease • One health • Zoonosis

2.1 The Concept of Emergence

Emerging infectious diseases are often perceived to be 'novel' pathogens of humans, but EIDs are more broadly defined as diseases that are increasing in their incidence, geographic or host species range, or their impact (due for instance to the acquisition of resistance to antimicrobial drugs or new virulence factors) (Fauci and Morens 2012). This encompasses both newly recognised pathogens and known pathogens that are 're-emerging' (Box 1). The development and introduction over time of new, more sensitive technologies for identifying microbial diversity, such as molecular methods to identify elements of the microbial genome, coupled with geographical heterogeneities in the availability of these technologies, make it difficult to accurately assess the rate at which new infectious diseases emerge. The difficulty is further compounded by changes over time in the ease of publishing articles in the bio-medical literature. Attempts have nevertheless been made, and 335 emerging infectious disease events were identified between 1940 and 2004, an average of five per year, with a peak in the 1980s associated with the emergence of HIV/AIDs and its associated opportunistic infections (Jones et al. 2008).

New human pathogens must come from somewhere, and unsurprisingly they most often arise from animals; with which we share genes, physiology, microorganisms, and environments. Around 60 % of current human infectious diseases are zoonotic, and those that exclusively infect humans were probably shared with other animal species at some time in the past (e.g. measles, mumps, dengue, pertussis, hepatitis B). In addition, around 60 % of recent emerging infectious diseases of humans have arisen from animals, with an estimated 72 % of these having their origin in wildlife species (Jones et al. 2008). The recognition of the shared susceptibility of humans and animals to many diseases has led to the concept of One Health. The infection of humans by the microorganisms of animals is a natural consequence of ecology and evolution (Karesh et al. 2012). Microbes are an abundant life form and ecological factors (specifically the environmental living conditions) critically define the niches that they inhabit. Microbes that normally colonise or infect animals are able to 'spill over' to humans when they possess the ability and are given the opportunity to exploit a similar niche (e.g. the gut or bloodstream) of humans. The same is true for microbes of wild animals that spill over to domesticated animals. Once provided this opportunity to infect a new host, a process of Darwinian competition will select those natural variants of the microorganism that are best able to survive and replicate in the new environment. In this way microorganisms adapt to humans, and may become so well adapted as to become exclusive pathogens of humans (Fig. 2.1) (Wolfe et al. 2007).

Box 1. Categories of Infectious Diseases (Fauci, NEJM, 2012)

1. *Established infectious diseases*: endemic diseases that have been around for a sufficient amount of time to allow for a relatively stable and predictable level of morbidity and mortality. Examples are common diarrheal pathogens, drug-susceptible malaria, tuberculosis, helminthic and other parasitic diseases;
2. *Newly emerging infectious diseases*: diseases that recently have been detected in the human host for the first time. Nipah virus, severe acute respiratory syndrome virus (SARS), human metapneumovirus (hMPV), and new influenza subtypes (swine H1N1, avian H5N1, or avian H7N9) are examples in this category. Often RNA viruses causing respiratory diseases are in this category.
3. *Re-emerging infectious diseases*: Diseases in this category can be subclassified as follows:
   - Diseases that appear either in new regions, as we have seen for West Nile virus (WNV) in the Americas.
   - Already known diseases that have become drug-resistant. Recent examples are drug resistant bacterial infections (penicillin resistant pneumococcal pneumonia, carbapenem resistant hospital acquired infections), drug resistant malaria, and oseltamivir resistant influenza.
   - Already known diseases that reappear after apparent control or elimination, or under unusual circumstances. Examples in category are the deliberate release of anthrax in the USA in 2001, or the reappearance of dengue on Florida, USA.

2.2 Shared Ecologies

The conditions or events (the 'drivers') that result in the successful cross–over of an animal microbe into humans are not well characterised, but emergence is often precipitated by changes to ecological or biological systems (Wilcox and Colwell 2005). Such changes include altered patterns of contact between wild and domestic animals (e.g. Nipah virus), of direct human and wild animal contact (e.g. HIV, Ebola), and changes in species abundance or diversity (e.g. Hantavirus; Lyme disease). Species diversity, including the diversity of insect vectors and pathogenic microorganisms, increases towards the equator (Guernier et al. 2004), and Jones et al. found a correlation between the emergence of zoonotic pathogens and the diversity of mammalian wildlife species (Jones et al. 2008). Whilst high animal host and pathogen species diversity may be associated with a high burden of infectious diseases and an increased risk of disease emergence, biodiversity loss may, perhaps counter-intuitively, be associated with increased disease transmission. Biodiversity

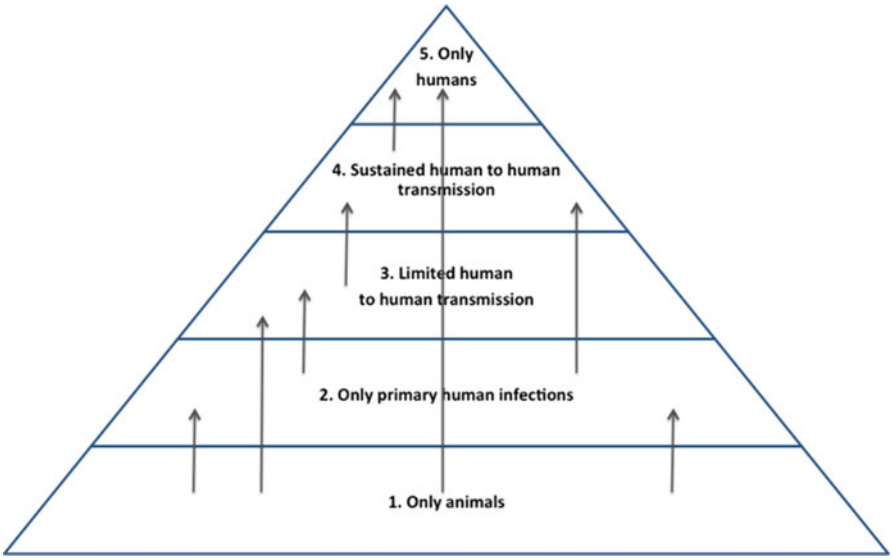

Fig. 2.1 Five stages of how exclusive animal pathogens can adapt to and infect humans (Wolfe et al. 2007). Stage 1: The pathogen is still exclusively infecting animals. Stage 2: The pathogen has been transmitted from animals to humans under natural conditions but not yet from human to human. Stage 3: There is limited transmission from animals to humans and between humans. These are often severe and lethal diseases due to for instance filoviruses (e.g. Ebola). Stage 4: Animal disease that have sustained transmission between humans (e.g. influenza). Stage 5: A microbe that exclusively infects humans (e.g. measles, syphilis)

loss directly disrupts the functioning and stability of ecosystems, producing effects that can extend well beyond the particular lost species (Hooper et al. 2012). Changes in species abundance and diversity may favour pathogen amplification and 'spill-over' through a variety of mechanisms, including reduced predation and competition resulting in increased abundance of competent hosts, and the loss of 'buffering species' leading to increased contact between amplifying host species and compatible pathogens (Keesing et al. 2010). Tropical regions with a rich pool of existing and potential pathogens that are increasingly connected, but also experiencing high rates of ecosystem disruption and biodiversity loss, may therefore be at a particularly high risk of disease emergence.

Human pathogens occasionally re-emerge as a result of dynamics that are beyond the control of humans. For example the Hantavirus outbreaks in the Southwestern U.S. in 1991–1992 and 1997–1998 have been attributed to changes in the abundance of infected rodents following periods of heavy snow and rainfall and vegetation growth leading to abundant production of rodent food. However, many ecological disturbances resulting in an EID seem to originate in the direct actions of humans. A wide range of anthropogenic factors have been linked to infectious disease emergence, including changes in land-use, travel, trade, and demographics. Notably, most of these associations are speculative and supported

by little hard data because ecological and biological systems are highly complex and multi-layered (Woolhouse 2011). Demonstrating or predicting the impact of particular conditions or events on the functioning of a system is difficult, with further inference of the impact of any changes on the risk of pathogen emergence posing a formidable challenge.

2.3 Socioeconomic Development and Altered Ecosystems

Socioeconomic development is associated with large increases in demand for natural resources. The demand for water, wood, pulp, agricultural land, living space, roads, minerals and power has had an enormous impact on the landscapes of Asia. Deforestation occurred throughout the 1990s and the area of primary forest in Asia has continued to decline (FAO 2012). Deforestation, forest fragmentation, and afforestation are all alterations in habitat, which change species composition and the interaction between wild animals, domestic animals, insect vectors and humans, providing new opportunities for microbial transmission and potential emergence. There are well-documented examples of deforestation and forest encroachment resulting in increases in infectious diseases, such as yellow fever, Mayaro, and Chagas disease in the Americas (Saker et al. 2004). The clearing of forest and planting of large cacao plantations was linked to the emergence of Oropouche virus in Brazil. In Asia there are already very high pressures on productive land, and the peak in land-use change in Asia has probably passed. Many areas are now in an era of increasing intensification of land productivity. This intensification is driven largely by demographic pressures, which are predicted to result in a 70 % increase in food production by 2050, with decreased consumption of grains and increased demand for meats, fruits and vegetables (FAO 2011a, b).

The increased demand for food, and meat in particular, when combined with demands for natural resources from industry and domestic consumers, and river damming for hydroelectric power, is resulting in a large increase in stress on water resources (FAO 2011b). The consequences of intensified agricultural production include the depletion and degradation of river and groundwater, reduced soil quality, and biodiversity loss. A direct and predictable effect of reduced access to clean water for low-income families is an increase in the risk of water-washed diseases (diseases that increase when the availability of water for personal hygiene is limited e.g. diarrhoeal and respiratory infections, trachoma), and water-borne diseases such as typhoid and hepatitis E. However, unquantified risks arising from the intensification of agriculture are pollution of freshwater with pesticides and fertilizers, loss of biodiversity, and land abandonment by small-scale farmers. The potential consequences of these changes on the risk of emergence of zoonotic infections have not been assessed.

2.4 Wildlife Trade

Wild animals are an important source of food (bush meat) in some developing countries and bush meat has been implicated in the emergence of HIV, and the spill over of monkeypox, Nipah and Ebola virus (Brashares et al. 2011). Whilst the reservoir of the SARS coronavirus is thought to be bats, wild civet cats traded for food are thought to have acted as an intermediate host, transmitting the SARS virus to humans through live animal markets (Li et al. 2005). Wild animal products are popular in Asia as traditional medicines, tonics, delicacies, or as symbols of wealth. Although all ten countries in the Association of Southeast Asian Nations (ASEAN) are signatories to the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), Asia continues to host the largest illegal wildlife trade in the world (Rosen and Smith 2010). The smuggling of H5N1-infected birds of prey into Europe, the frequent smuggling of bush meat from Africa into the U.S., and the importation into the U.S. of pet rodents infected with monkeypox show that both the legal and illegal trade in wild animals and wild animal products is a potential conduit for the international spread of zoonotic pathogens (Bair-Brake et al. 2013; Van Borm et al. 2005)

2.5 Urbanization, Consumer Behavior, and Market Chains

Between 2011 and 2050 the world population is expected to increase by 2.3 billion (a 32 % increase), and the increase will be concentrated in urban areas of developing countries (UN-DESA 2012). Whilst mega-cities (cities with a population of at least ten million) receive a lot of attention, most urban dwellers live in small cities, with half of the global urban population in 2011 living in cities of less than 500,000 people (UN-DESA 2012). This can be perceived positively as cities generally offer better economic opportunities, better educational opportunities, better living conditions, better nutrition, better sanitation, and therefore better health than underdeveloped rural areas. At the same time it is likely to mean that in many low to middle income countries, health and veterinary infrastructure in rural areas will not improve, or may even deteriorate, adversely affecting the likelihood of the early detection of EID. The demand for food in urban centres will increase and result in livestock and their products being transported over large distances from a wider catchment area, and thereby increase risk of spread and amplification of EID. Urbanisation is one facet of changing human sociocultural systems, which also includes changing consumer demands and dietary habits (Janes et al. 2012). The consequence is a spatial concentration of people and animals; not necessarily co-located, but connected through increasingly complex networks of rural and peri-urban farms and markets, distributors, agricultural workers, and consumers.

2.6 Livestock Production Systems

2.6.1 Intensification of Production

Due to the increase in global human population and economic development, demand for livestock products has risen dramatically over the last 50 years, with the per capita consumption of meat in developing countries more than tripling since the early 1960s and egg consumption increasing fivefold (FAO 2011a, b). The increased demand for meat has been met by more intensive and geographically concentrated production of livestock, especially pigs and poultry (Steinfeld et al. 2006). Much of this has been through expansion of both the number of small-scale production units and large commercial farms. High-density monoculture of domestic animals is a form of low biodiversity that poses a particular threat for the spread of infectious diseases from farmed animals to humans. Where domesticated animals are a conduit of spread from wild animals to humans, high density livestock production may promote spread of zoonotic diseases. Genetic diversity within an individual host species is important since genetic diversity limits the potential for devastating epidemics (King and Lively 2012).

The Nipah virus outbreak in Malaysia and Singapore in 1998–1999 is a good example. Once Nipah virus crossed from wild bats to domestic swine, an explosive outbreak in high-density swine farms resulted in widespread exposure of humans and over 250 human cases of encephalitis (Pulliam et al. 2012). Other examples where intensified livestock production practices may have led to emergence of a zoonosis include:

- *Streptococcus suis* causes severe sepsis and meningitis in humans and is associated with areas of intensive pig production (see Fig. 2.2). Risk factors for human infection include swine slaughtering and the eating of undercooked pig products (Wertheim et al. 2009). Outbreaks in swine herds of porcine reproductive and respiratory syndrome virus also potentially increases the rate of invasive *S. suis* infection in swine, which in turn leads to an increased risk of *S. suis* infection in humans (Hoa et al. 2013).
- Highly pathogenic avian influenza A subtype H5N1 crossed-over from wild aquatic birds (the natural reservoir of influenza A viruses) to humans via massive amplification in domestic poultry.
- The human Q-fever epidemic in the Netherlands during 2007–2010 caused by the bacterium *Coxiella burnetii* is thought to have arisen when economic drivers led to an increased density of dairy goat farming, which resulted in amplification of *Coxiella burnetii* prevalence and consequent increased spill- over to humans (Roest et al. 2011; Georgiev et al. 2013).

The classical foodborne diseases such as *E. coli*, campylobacteriosis and salmonellosis associated with livestock products have been a significant problem in high-income countries for some time (CDC 2011; Painter et al. 2013). One of the key factors, in particular in the case of *Campylobacter*, has been the integration of