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
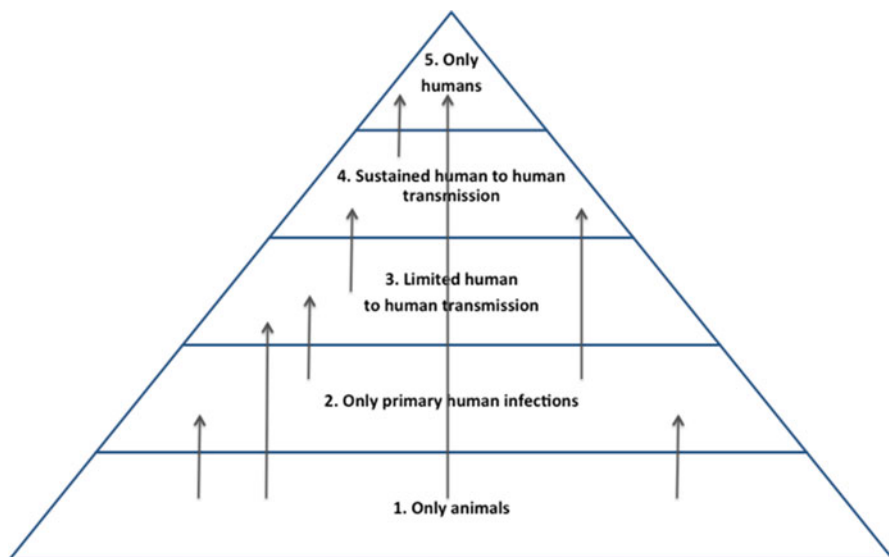
Fig. 2.1 Five stages of how exclusive animal pathogens can adapt to and infect humans (Wolfe et al. 2007). Stage 1: The pathogen is still exclusively infecting animals. Stage 2: The pathogen has been transmitted from animals to humans under natural conditions but not yet from human to human. Stage 3: 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
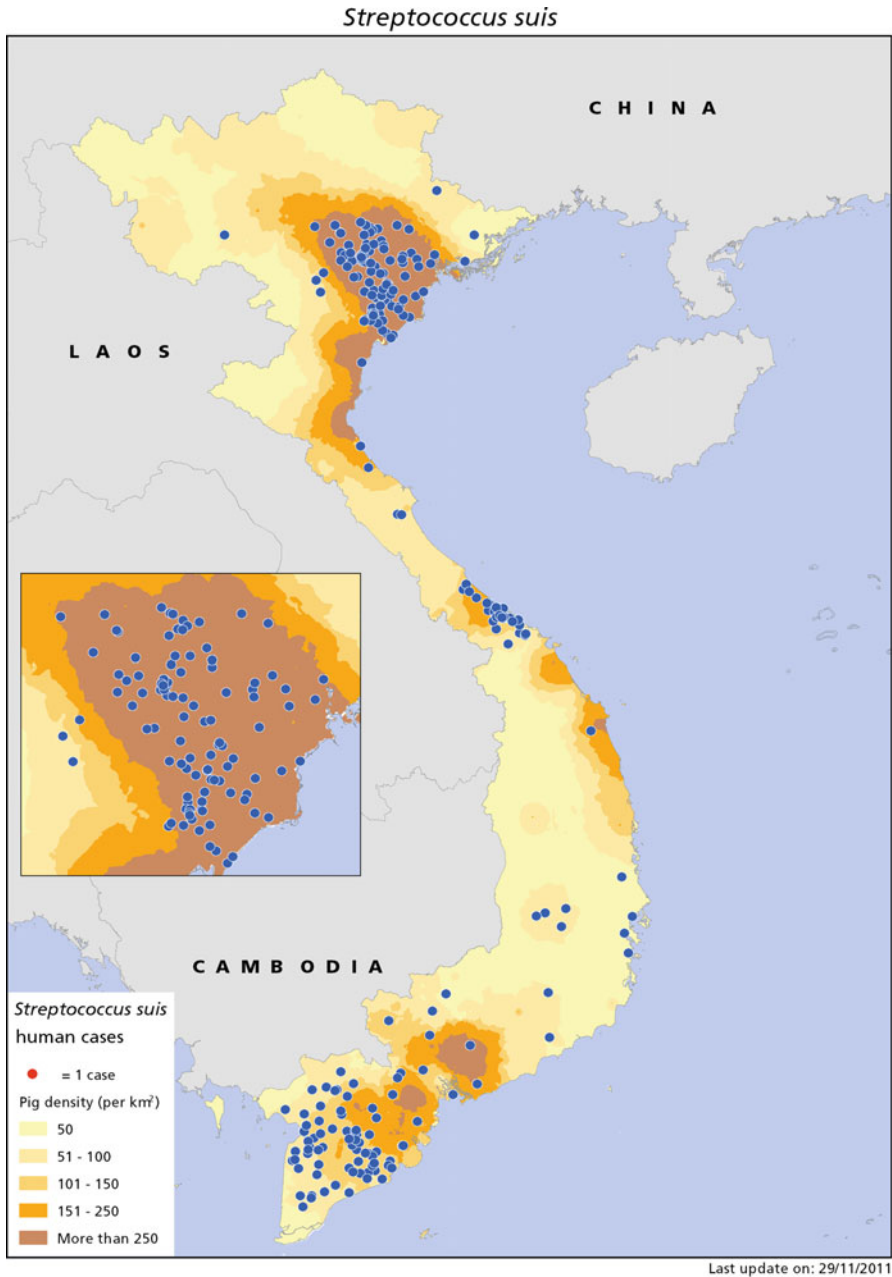
Fig. 2.2 Number of swine per km² and human *Streptococcus suis* infections in Vietnam from 2005–2011. Pig density data are based on Vietnam Government Statistics Office data 2006

highly intensive poultry production with poultry processing systems facilitating cross-contamination of meat (Moore et al. 2005; Nyachuba 2010). It is notable that some foodborne pathogens cause subclinical infections in their animal hosts (e.g., *Campylobacter* in poultry); therefore there is no direct incentive for farmers to control them. In addition, subsequent attribution of the source of foodborne disease in an affected human is notoriously difficult. It is likely that the global incidence of foodborne illness will rise as a result of increased industrial production of poultry in the emerging economies. The situation will be exacerbated by the emergence of antimicrobial resistant pathogens of foodborne pathogens (Sahin et al. 2012; Luangtongkum et al. 2009; Altekruse and Tollefson 2003).

Despite the examples above, the intensification of livestock farming often entails more effective separation of domestic and wild animals, improved standards of animal health and welfare, reduced movement and species mixing: all of which reduce the risk of EIDs. Reducing contact between domestic and wild animals, whether the wild animals are in their natural habitat or captive, is a key strategy of the Food and Agriculture Organization (FAO) to reduce risk to human health, and is part of the wider FAO strategy of enhancing 'biosecurity'. Improving biosecurity in farms is a major challenge since a large proportion of farming in Asia is based on small-scale backyard production, and there is often a mix of commercial and backyard farming in any one location. Achieving improvements in biosecurity without adversely affecting the livelihoods of small-scale farmers requires an approach to risk management that is adapted to their socio-economic context. The longer-term vision is to restructure the livestock production sector towards a more commercialised and controlled system, where controls benefit animal health, human health, and commercial profitability. But it has also been recognised that small-scale producers will continue to have a key role in providing food security in developing economies, and in fact their importance may increase due to their more efficient use of natural resources compared with large-scale industrial production (Sjauw-Koen-Fa 2012; Quan 2011).

2.6.2 Intensity and Complexity of Animal Markets

Food production has become a complex national, regional and global network of food value chains (Ercsey-Ravasz et al. 2012; Dickson-Hoyle and Reenberg 2009). Many countries have begun to more tightly regulate live animal trade in the wake of Bovine Spongiform Encephalopathy (BSE), SARS and avian influenza A/H5N1, but complex and poorly regulated food manufacturing and distribution chains still offer ample opportunities for disease outbreaks. In endemic regions, live bird markets are frequently contaminated with highly pathogenic avian influenza A subtype H5N1 (Davis et al. 2010; Samaan et al. 2011; Wan et al. 2011). Contaminated markets can become reservoirs and the source of infection for poultry and humans.

Measures to reduce the risk in live animal markets include the separation of species, not allowing animals to remain in the market more than 24 h, not allowing poultry to exit the market alive, improved cleaning and disinfection, and weekly rest-days, when all animals are removed and the market is thoroughly cleaned. The re-emergence of brucellosis, one of the world's most common zoonoses, is thought to be the result of higher risk of transmission through increased within- and between country trade of susceptible livestock and their products (Seleem et al. 2010). The development of denser regional road transport networks may be especially important since, compared to air travel, roads offer a more egalitarian form of connectivity that includes animals and goods as well as humans. This provides opportunities for pathogens to disperse beyond their traditional niche by increasing opportunities for informal trade in live animals and their products (Eisenberg et al. 2006).

Veterinary medical authorities often struggle to enforce compliance with regulations, and it is common practice for farmers and traders to adapt their production and trading behaviors to avoid adverse economic consequences of regulations aimed at controlling zoonotic diseases. As a result, informal trade networks may intensify and re-structure in unpredictable ways during disease outbreaks.

Increasing intensification of animal husbandry in Asia may be a trade-off between a lower risk of emergence events, as animals will be 'healthier' and better isolated, but should an EID event occur, an increased risk of massive amplification in large, naïve monocultures. Perhaps the greatest risk arises when a limited number of intensive livestock production units are surrounded by substantial backyard farming with little or no biosecurity, thereby linking extensive and weakly regulated value chains with global food systems.

2.6.3 Antibiotics and Other Practices

Livestock production practices can have major unintended and unanticipated impacts on the risk of zoonotic infections. Perhaps the most notable example is BSE. The feeding of ruminant-derived meat and bone meal to cattle, and possibly changes in practices for rendering animal tissue, led to an epidemic of BSE in cattle, that was followed by an epidemic of a fatal neurological disease (variant Creutzfeldt-Jacob Disease) in humans (Taylor and Woodgate 2003).

In contemporary livestock production, the use of antibiotics is a significant concern. Almost 40 % (23/59) of EIDs identified in Asia since 1940 represent the emergence of a new pattern of antimicrobial resistance (Jones et al. 2008). Bacteria in some areas show alarmingly high rates of resistance to anti-bacterial agents, and the recent emergence of the New-Delhi Metallo-beta-lactamase-1 (NDM-1) resistance gene, conferring resistance to a last resort antibiotic, and its rapid dissemination to other regions highlights the serious threat to human health of antimicrobial resistance (Khan and Nordmann 2012). Antibiotics are used extensively in the livestock and aquaculture sector to treat or prevent infections, or as

growth promoters. Non-therapeutic use of antibiotics as growth promoters involves the prolonged administration of sub-therapeutic doses. This practise has a demonstrable effect on the emergence and prevalence of resistant microorganisms in food animals and their environment, as well as resulting in the excretion of antibiotics into the environment, where environmental bacteria may be subject to antibiotic selection pressures (Marshall and Levy 2011).

Synthetic antibiotics such as quinolones are quite stable in the environment over long periods of time. Heavy metal contamination of animal food may also play a role in selection of antimicrobial resistance. Whilst there remains some debate about the overall impact of these findings on human health, it is clear that the continued use of non-therapeutic antibiotics in an agriculture industry that is rapidly increasing in scale and intensity, has potential for becoming a very real threat through the inability to prevent/cure disease in production animals and the consequences for human food security as well as the transmission, for example, of resistant food-borne bacterial pathogens to humans.

Some recent examples concern transmission of methicillin resistant *Staphylococcus aureus* (MRSA) from pigs to humans and ESBL (extended spectrum beta-lactamase, an important resistance mechanism against most beta-lactam antibiotics) positive *E. coli* on chicken meat for human consumption (Verkade et al. 2012; Kluytmans et al. 2013). Swine-associated MRSA is now contributing significantly to invasive disease in patients in the Netherlands (Verkade et al. 2012).

Antibiotic production and consumption continues to increase, often in an uncontrolled way, accelerating the evolution of antibiotic resistance, which then spreads rapidly across the globe. Since the 1990s few new antibiotics have been developed and we are on the cusp of returning to an era of untreatable infections. The consequences of antibiotic use in animals therefore require better surveillance, research and regulation.

2.7 Conclusions

Infectious diseases continue to be an important cause of human and animal morbidity and mortality worldwide. Whilst important health advances (e.g. hygiene and vaccination) have been made, infectious diseases are dynamic and resilient, and continue to challenge local, national and global public health systems (Fauci and Morens 2012).

The recognition of the linkage between anthropogenic changes, animals, and disease emergence has resulted in repeated calls for a more holistic, interdisciplinary, and integrated approach to the study of infectious diseases. The One Health approach is one initiative aimed at realizing this aspiration. The task ahead is to understand how social, economic, and environmental changes are altering the landscape of infectious disease risks for both animals and humans, and how future emerging risks may be mitigated. A more analytical approach to these emergence

events requires characterisation of the attributes of natural and artificial ecological systems before and after disturbance, and the functional relationship between changes in system attributes and pathogen emergence (Woolhouse 2011).

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