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Overviews of Pathogen Emergence: Which Pathogens Emerge, When and Why?

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Abstract An emerging pathogen has been defined as the causative agent of an infectious disease whose incidence is increasing following its appearance in a new host population or whose incidence is increasing in an existing population as a result of long-term changes in its underlying epidemiology (Woolhouse and Dye 2001). Although we appear to be in a period where novel diseases are appearing and old diseases are spreading at an unprecedented rate, disease emergence *per se* is not a new phenomenon. It is almost certain that disease emergence is a routine event in the evolutionary ecology of

pathogens, and part of a ubiquitous response of pathogen populations to shifting arrays of host species. While our knowledge of emerging diseases is, for the most part, limited to the time span of the human lineage, this history provides us with a modern reflection of these deeper evolutionary processes, and it is clear from this record that at many times throughout human history, demographic and behavioural changes in society have provided opportunities for pathogens to emerge.

1 Introduction

Over recent years, many reviews have been undertaken that survey emergence events and factors associated with recently emerging diseases. In this chapter, we discuss whether, and how, these surveys can improve our understanding of the mechanisms of emergence and influence our ability to predict, detect or control emerging diseases. To address the question of which pathogens emerge, we first review what can be learnt from the history of emerging diseases. We then consider surveys that characterise emerging pathogens in terms of taxonomy, host range and transmission routes, drawing on examples from both emerging human and emerging animal diseases to illustrate general patterns in disease emergence. Finally, we present an alternative framework for analysing why different pathogens emerge, attempting to identify high-risk situations and environments that might be of practical relevance for targeting disease surveillance and control measures.

2 Emerging Zoonoses and Human Population History: When Have Human Pathogens Emerged in the Past?

Pathogens can persist in host populations only if each infected host, on average, infects one or more susceptible hosts. If the average number of new hosts infected per case (which in the event that the rest of the population is entirely susceptible is the basic reproduction number, R_0,) falls below 1, then the pathogen will ultimately die out (Anderson and May 1991). Pathogen persistence requires a supply of susceptible hosts, generated through birth, immigration or loss of immunity. If a pathogen with an $R_0 < 1$ is introduced into a naïve population, there may be a small trickle of cases, but the introduction will ultimately fail. If $R_0 > 1$, then there remains a probability that simply by chance the outbreak may only number a handful of cases, but the probability of a major outbreak is much larger. As the epidemic spreads through the host population, the pool of remaining susceptibles will diminish (as more of the population becomes immune or infected

individuals die) and the rate of spread will slow. If the population is smaller than an identifiable critical community size (Bartlett 1966; Keeling and Grenfell 1997), the pathogen is unlikely to persist and the outbreak will fade-out. This is particularly true for infections with short infectious periods and those that either cause high mortality or generate prolonged host immunity.

From a historical perspective, early hunter-gatherer communities would have been too small to generate sufficient susceptible hosts to maintain species-specific pathogens. At this stage of human history, outbreaks of infectious diseases would have required repeated introduction of the pathogen from other host populations and most were likely to have been zoonotic. Human-specific pathogens probably comprised only the heirloom species, such as pinworm, that were carried over from hominid ancestors (Sprent 1969).

The history of human emerging infectious diseases (EIDs) has been described with reference to key transitions (Barrett et al. 1998; McMichael 2004). The first key transition in human societies is likely to have been the domestication of livestock 10,000–15,000 years ago, which provided multiple opportunities for disease emergence, first by facilitating cross-species (zoonotic) transmission and, second by allowing the expansion of human settlements large enough for virulent pathogens, such as measles and smallpox, to persist (Diamond 2002). As settlements became cities, a second transition point was reached: the problems of sanitation and pest control increased, allowing huge epidemics of infections, such as the black death and cholera. Migration, trade, exploration and conquest gave rise to the third major transition during which human infections established in one area were brought to highly susceptible populations in another, often with catastrophic consequences. The Age of Discovery, starting in the fifteenth century, with an estimated 10–15 million deaths in 1520–1521, and other Amerindian and Pacific civilisations were destroyed by imported smallpox and measles. In return, treponemal infections were introduced into Europe.

The past history of human infectious diseases can therefore be described by major epidemiological transitions that have been associated with large-scale changes in human demography, behaviour and technology (Barrett et al. 1998; McMichael 2004). Anthropogenic factors have always been the driving force behind human epidemiological change and this situation still applies today. What makes the recent emerging and re-emerging disease trends different to those over the rest of human history is the number of diseases which are increasing and the potential scale of outbreaks (McNeill 1976, Barrett et al. 1998). New diseases are currently being detected at a rate of about one new disease per year, with more than 30 new pathogens identified over the past 30 years (CDC http://www.cdc.gov; WHO http://www.who.int; Woolhouse 2002). Given that a total of only 1,415 human pathogens have been identified (Taylor et al. 2001), it is possible that the current rate at which humans are acquiring new infections

is unprecedented, although data from other major transitions are not available for comparison. Although some new pathogens, such as *Helicobacter pylori* and *Legionella pneumophila* have turned out to be newly recognised causes of old diseases, the global impact of entirely new human diseases (such as HIV/AIDS and SARS), and the increasing incidence and spread of pre-existing infectious diseases (such as tuberculosis) cannot be denied.

The recurring theme throughout reviews of historical and recent disease emergence is the importance of changes in host ecology and contact patterns. Anthropogenic impacts that have affected human demographics and contact patterns between different host populations have almost invariably resulted in disease emergence. The current rate of increase in the human population, the scale of human and animal movements and the rate of environmental change creates a situation of unprecedented global contact between people and between different human and animal populations, a clear harbinger of future risk. As we look into the future, the lessons of the past become increasingly resonant.

3
Zoonotic Origins of Human Diseases

Zoonoses have been defined as "diseases and infections that are naturally transmitted between vertebrate hosts and man" (WHO 1959; Palmer et al. 1998). Zoonotic infections have long been considered an important category of emerging diseases, with animal reservoirs providing a source of new infections for humans throughout evolutionary history.

In the past, as today, two distinct mechanisms of zoonotic disease emergence can be recognised. Some pathogens have their origins as zoonoses but appear to have evolved as predominantly or exclusively human infections, having adapted to human-to-human transmission after jumping from animals to humans (R_0 in humans >1). Others require continued re-introduction from animal reservoirs (obligate zoonoses) and have never taken off in the human population as self-sustaining epidemics (R_0 in humans < 1).

Hart et al. (1999) proposed a system of classifying zoonoses based on these distinct mechanisms and the time-scale of emergence events. In the former category, human-specific infections that have their origins in an animal host were defined as either old or recent. Many of these old diseases are thought to have originated from domestic animal pathogens at the time of animal domestication (Bennet and Begon 1997; Diamond 2002). It is suggested, for example, that measles originated from closely-related morbilliviruses of cattle (rinderpest), and smallpox from poxviruses of either camels or cattle. Examples

of recent zoonoses include HIV-1 and HIV-2, which have appeared as new human diseases after jumping the species barrier from primates to humans (Gao et al. 1999; Hahn et al. 2000) and SARS, which is thought have had its origins as a zoonosis (Song et al. 2005) but has now adapted to human-to-human transmission.

While genetic analyses have provided important evidence for these recent animal-to-human species jumps, they have also cast doubt on the historic zoonotic origins of other human pathogens. For example, the conventional wisdom that *Mycobacterium tuberculosis* (the cause of human tuberculosis) originated as a zoonosis from *M. bovis* (the cause of bovine tuberculosis) now appears unlikely in the light of sequence data analysis, which shows that the genome of *M. bovis* has lost a number of genes that are present in *M. tuberculosis* and that *M. tuberculosis* evolved from the common progenitor of the tuberculosis complex earlier than *M. bovis* (Garnier et al. 2003).

Within the second broad category of zoonoses are the obligate zoonoses, which include those that are established (e.g. Q-fever, brucellosis) and those that are newly recognised (e.g. Nipah and Hendra viruses) (Hart et al. 1999). These pathogens can only be sustained in human populations by continued re-introduction from animal reservoirs

4
Which Pathogens Have Recently Emerged?

The literature on recent emerging human diseases contains accounts of many pathogens that are zoonotic (e.g. vCJD, *Escherichia coli* 0157) and many that involve wildlife hosts (e.g. Ebola virus, West Nile virus), suggesting that transmission from an animal host to humans is an important component of human disease emergence. However, most of these accounts have been largely descriptive (e.g. Morse 1995; Osburn 1996, Murphy 1998; Palmer et al. 1998; Chomel 1998; Daszak et al. 2000) and quantifying risk factors has only been possible with the construction of a database that contains all known human pathogens and thus allows the characteristics of emerging and nonemerging human pathogens to be compared (Taylor et al. 2001). A similar database has been constructed for domestic carnivore and livestock pathogens allowing features of both human and animal emerging pathogens to be identified (Cleaveland et al. 2001). The most important finding of these quantitative analyses is that emerging pathogens are not a random selection of all pathogens, but that host range and pathogen taxonomy are important risk factors for disease emergence.

5
Host Range

Links between human emerging diseases and animal hosts have been noted in several emerging infectious disease (EID) reviews (Morse 1995; Murphy 1998; Osburn 1996; Palmer et al. 1998, Chomel 1998; Daszak et al. 2000). Of the 1,415 pathogens identified in the human pathogen database, 61% pathogens from 313 different genera are known to be zoonotic and therefore infect multiple hosts (Taylor et al. 2001). Overall, 175 (12.4%) human pathogens from 96 genera were identified as the cause of emerging diseases and, of these, 133 (76%) were zoonotic (Taylor et al. 2001). In this study, zoonoses did not include those which are known to have their origin in animal hosts, but for which infection now occurs exclusively through human-to-human transmission (e.g. HIV-1 and HIV-2). Multi-host pathogens also predominate among animal EIDs, with 90% of emerging livestock diseases and 100% of emerging domestic carnivore diseases caused by multi-host pathogens (Cleaveland et al. 2001).

From these surveys, it is clear that generalist pathogens are over-represented in both human and animal emerging diseases. Thus, pathogens that have the ability to infect more than one host (which, for human diseases, includes all zoonoses), pathogens that have the ability to infect more than one taxonomic order (Fig. 1), and pathogens infecting wildlife hosts all have a higher relative risk for emergence than pathogens with more restricted host ranges (Cleaveland et al. 2001) (Table 1; Fig. 1). A broad host range is also a feature of many recent disease outbreaks in wildlife hosts, particularly endangered populations (Cleaveland et al. 2002).

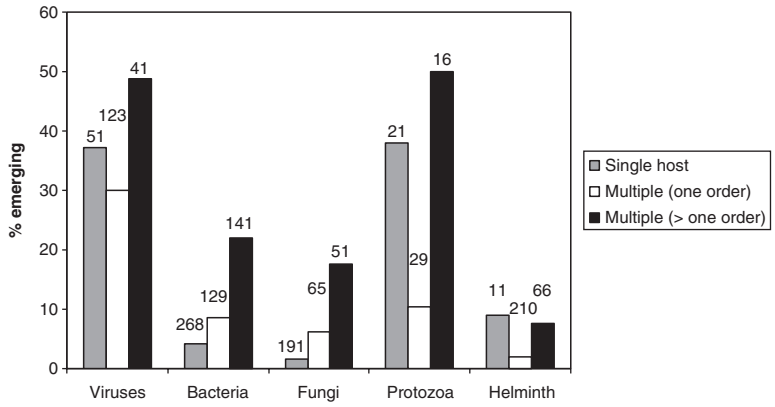

Fig. 1 The proportion of emerging pathogens in different taxonomic groups in relation to host range. The numbers shown above each column indicate the total number of human pathogens in each category

Table 1 The relative risk of emergence for different categories of pathogen in relation to host range of pathogens. Diseases for which the identity of animal hosts was unknown were excluded, hence the number of zoonoses given here (n = 800) is lower than the total number of human pathogens identified as zoonoses (n = 872)

Categories of host infected by pathogen	Number of zoonotic diseases (n = 800)	Number of emerging zoonotic diseases (n = 125)	Relative risk
Wildlife	619 (77.4%)	113 (90.4%)	2.75
Birds	82 (10.3%)	23 (18.4%)	1.97
Nonmammalian hosts	109 (13.6%)	30 (24.0%)	2.0
Ungulates	315 (39.3%)	72 (57.6%)	2.09
Carnivores	344 (43.0%)	64 (51.2%)	1.39
Primates	103 (12.9%)	31 (24.8%)	2.23
Rodents	180 (22.5%)	43 (34.4%)	1.81
Marine mammals	41 (5.1%)	6 (4.8%)	0.93
Bats	15 (1.9%)	6 (4.8)	2.64

Here, parallels can be drawn with early human communities; endangered wildlife populations are too small to maintain species-specific pathogens and the risk of emergence invariably arises as a result of cross-species transmission.

6 Pathogen Taxonomy

Although all taxonomic groups are represented within the group of human emerging pathogens, viruses appear disproportionately among emerging pathogens. For viruses, the proportion of pathogens that are emerging is four times higher than other taxonomic groups (relative risk of emergence [RR] = 4.3), with viruses comprising 15% (n = 215) of all human pathogens and 35% (n = 76) of emerging pathogens. This applies also to emerging pathogens of domestic animals (Cleaveland et al. 2001). Conversely, parasitic helminths are underrepresented in the emerging disease category (RR < 0.25). Although quantitative baseline data are lacking for wildlife diseases (and hence RR cannot be calculated), viral pathogens have also been the cause of most recent wildlife disease outbreaks (Murray et al. 1999; Dobson and Foufopoulos 2001; Funk et al. 2001). Among the viruses, RNA viruses have only a slightly higher RR of emergence (RR = 2.8) than DNA viruses (RR = 2.5), but are disproportionately represented among those pathogens that have emerged as new human and animal diseases after jumping from other host species (Table 2).

Table 2 Examples of viruses thought to have emerged as a result of species jumps A. in the historical past (5000–10,000 years ago) and B. in the recent past

A. Historical past				
Disease/pathogen	Proposed original host	New host		Reference
Measles	Cattle/dogs?	Human		Bennett and Begon 1997; Diamond 2002
Smallpox	Cattle/camels?	Human		Bennett and Begon 1997; Diamond 2002
Common cold	Cattle?	Human		Bennett and Begon 1997; Diamond 2002
B. Recent past				
Disease/pathogen	Original Host	New host	Year first observed in new host	
FPLV/CPV	Cats	Dogs	1978	Parrish 1994
SIVcpz/HIV-1	Chimpanzee	Human	1983	Gao et al. 1999; Hahn et al. 2000
SIVmac/HIV-2	Macaques	Human	1986	Hahn et al. 2000
Canine/Phocine	Canids	Harp seals	Harp seals?	
distemper virus	Harp seals	Harbour seals	Harbour seals 1988	Mahy 1993
Hendra virus	Fruit bats	Humans/horses	1994	Mackenzie et al. 2001
Australian bat lyssavirus	Fruit bats	Humans	1996	Mackenzie et al. 2001
Menangle virus	Fruit bats	Pigs, human	1997	Mackenzie et al. 2001
Nipah virus	Fruit bats	Humans/pigs	1999	Mackenzie et al. 2001
Canine distemper virus	Dogs	Lions	1994	Roelke-Parker et al. 1996
	Sledge dogs?	Crab-eating seals	1955	Bengston et al. 1991
	Dogs/wild canids?	Lake Baikal seals	1987/1988	Grachev et al. 1989
	Dogs/wild canids?	Caspian sea seals	2000 (disease)	Kennedy et al. 2000
H5N1 Influenza A	Chickens	Humans	1997	Li et al. 2004
Hepatitis E virus	Deer	Humans	2003	Tei et al. 2003
SARS coronavirus	Palm civets?	Human	2003	He et al. 2004; Song et al. 2005

7
Does Knowing Which Pathogens Emerge Help Us Understand How Diseases Emerge?

What does the preponderance of viral pathogens among emerging diseases tell us about mechanisms of disease emergence? Several factors has been proposed to explain this observation, such as the relative difficulty of treating viral diseases, improved detection rates, short generation and higher mutation rates (Domingo and Holland 1994). That RNA viruses are over-represented in instances of pathogens jumping into new host species is consistent with the view that mutation rates may play a role in emergence. High mutation rates in RNA viruses (Drake 1993; Domingo and Holland 1994), and the existence of multiple variants within strains of RNA viruses, provide an enormous capacity for RNA viruses to adapt to changing host environments and to overcome barriers to spread of virus both within hosts and between species. For example, it has been suggested that the spread of rabies virus within different host tissues and between host species may only be possible as a result of the combined action of virus variants with diverse tissue tropism, with multiple strain variants compensating for the simplicity and lack of regulatory elements within the rabies virus genome (Morimoto et al. 1998).

However, it has also been argued that the limitations of a very small genome act as an important constraint to the adaptability and evolution of RNA viruses. As specific sequences are required to encode multiple functions, there may be little flexibility for mutations to confer any adaptive advantage (Holmes 2003; see the chapter by Holmes and Drummond, this volume). Understanding the mechanistic basis of genomic constraints to RNA virus evolution may help explain why some RNA viruses are more able to cross species boundaries than others (Holmes and Rambaut 2004; see chapter by Holmes and Drummond, this volume).

The ability to undergo recombination, which is seen in a wide range of RNA viruses (Worobey and Holmes 1999), may also be a factor. Recombination plays a key role in the emergence of highly pathogenic strains of influenza A (Shu et al. 1996), and may contribute to the burgeoning diversity and emergence of Dengue viruses (Holmes and Burch 2000). If recombination is an important mechanism in emergence, then understanding how the genetic organisation of viral genomes influences recombination rates is an important question. For example, rates in segmented viral genomes, like influenza A, may be higher than in nonsegmented genomes, while in negative stranded RNA viruses, such as rhabdoviruses, recombination rates are likely to be lower than in positive stranded viruses.

In terms of mechanisms of disease emergence, most attention has focussed on the question of host-switching and the appearance of new pathogens, such as HIV and SARS, in the human populations. Parallels are also seen in animal EIDs, with host-switching an important feature of several new disease outbreaks, such as canine distemper virus (CDV) jumping from domestic dogs to lions (Roelke-Parker et al. 1996), Lake Baikal seals (Grachev et al. 1986; Mamaev et al. 1996) and Caspian seals (Kennedy et al. 2000), phocine distemper virus (PDV) jumping from harp seals to common seals (Goodhart 1988; Barrett 1999) and feline panleucopaenia virus in cats evolving into canine parvovirus in dogs (Hueffer et al. 2003).

Evolutionary ecologists studying adaptive radiations have long suggested that they arise from generalist ancestors, and develop through adaptive diversification into ever more specialised niches (Simpson 1953; Mayr 1942; Thompson 1994; Schluter 2000). Many taxonomic groups of pathogen fit comfortably into the paradigm of adaptive radiation, but it is not clear whether the phenomenon of emergence corresponds to a process of increasing ecological generalism or simply host-switching followed by subsequent further specialism (for example, HIV). Host-switching events are indicated throughout the evolutionary record by the frequent topological discordancies in paired host-pathogen phylogenies (Jackson and Charleston 2004), and it is reasonable to suppose that these switches corresponded to periods of pathogen emergence. But following a host switch, the outcome of opposing selective forces for further adaptation to the new host, or maintaining a broader spectrum of host species use remains unclear.

A broad host range may be a more important predictor of the potential for novel host use than close taxonomic relatedness, which is not invariably required for either pathogens that undergo species jumps (Table 2; Woolhouse et al. 2005) or for established zoonotic pathogens. Emerging zoonoses originate from a broad spectrum of different animal hosts (Table 1), with the greatest number of emerging zoonoses caused by ungulates (58%), followed by carnivores (51%) and rodents (34%). However, only relatively few zoonoses overall (13%) are known to infect primates under natural conditions, so this may simply reflect a lack of data on natural populations (Wolfe et al. 1998). Perhaps a better measure of the potential for emergence is given by the relative risk, which is greater in primates and bats than ungulates and carnivores (Table 1).

The determinants of a broad host range are poorly understood. It has been suggested that the use of host-cell receptors that are highly conserved across host species may facilitate infection in a wide range of hosts (Woolhouse 2002). For example, the rabies virus, which has the potential to infect all mammal species, gains entry to peripheral nerves via the highly conserved nicotinic acetylcholine receptor, and the foot-and-mouth disease virus (FMDV) uses the

conserved vitronectin receptor (Baranowski et al. 2001). While appropriate receptors are clearly a prerequisite for entry in to the cell lines of any potentially permissive host, it is becoming increasingly clear that downstream intracellular events can also restrict host range (McFadden 2005), and much remains to be learned about these processes.

8
What Practical Lessons Can Be Learnt from Emerging Disease Surveys?

Characterising the features of emerging pathogens highlights several key issues in the approach towards human and animal EIDs. First, these surveys all demonstrate the importance of zoonotic transmission in past and current emerging human diseases, emphasising the need to understand the infection dynamics of zoonotic pathogens in both animal and human populations and to broaden the single-species focus of human medicine to incorporate knowledge available within veterinary and wildlife disciplines. It was notable that during the construction of the human infectious disease database, a substantial number of human pathogens were identified as zoonoses from veterinary reference texts, but not from medical texts. Many emerging zoonotic diseases of the future may be infections that are currently recognised by veterinarians or wildlife biologists, and their involvement is likely to be an important element in the early detection of emerging zoonoses. For example, veterinary pathologists at the Bronx zoo played a major role in the detection and identification of West Nile Virus (McNamara 2002). A granulocytic *Ehrlichia* described from meadow voles on Martha's Vineyard in the 1930s (Tyzzer 1938) is now believed to be the agent causing human granulocytic ehrlichiosis (Telford 2002), and archived veterinary material is likely to provide an important source of data for identifying potential reservoirs of new or emerging zoonotic infections.

The predominance of viral pathogens among human and animal EIDs highlights the need for maintaining expertise in virological techniques, for improved anti-viral treatments and for enhanced collaboration between medical and veterinary virologists. Prior to the emergence of SARS, human coronaviruses had been of little interest in medical virology and much of the knowledge about coronavirus biology was available only from studies of animal coronaviruses in the context of important veterinary diseases (Cavanagh 2000). This expertise was effectively harnessed in the rapid international response to SARS, contributing to the rapid isolation, diagnosis and characterisation of the SARS virus and to an understanding of aspects of pathogenesis and immune response (Cavanagh 2003; Berger et al. 2004). Similarly, insights from research on coronavirus vaccines for animals are likely to assist the development of a SARS vaccine.

In general, relatively little is still known about the infection dynamics of emerging zoonoses in animal host populations, and this is particularly true when wildlife hosts are involved. The epidemiology of generalist pathogens in multi-host populations is often complex and identifying reservoirs of infection invariably a challenging task (Haydon et al. 2001). The enduring uncertainties about the role of badgers as reservoirs and/or sources of bovine tuberculosis for cattle in the UK typify these difficulties (Krebs et al. 1998). For zoonotic diseases, integration and collaboration between disciplines is clearly important. Public health researchers and veterinarians require some understanding of ecological processes and the links between the environment, ecology and disease. Conversely, ecologists and population biologists need to understand the dynamics of pathogens at individual, population and community levels (Daszak and Cunningham 2002).

From these surveys, we know which pathogens have emerged and we are beginning to understand how they are able to do so. An important lesson is the breadth of pathogens that *can* emerge. The fact that many recent emergence events have taken us by surprise is, in itself, surprising, given the historical patterns of disease emergence and the evidence that many pathogens have the potential to emerge under favourable ecological and environmental conditions. In the next section, we therefore explore the question of why certain pathogens emerge, attempting to identify circumstances and situations where disease emergence might be expected, so that surveillance and control measures can be targeted to high-risk settings. We consider whether an appraisal of risk factors provides a useful way of reviewing past emergence events and attempt to address the question of which pathogens emerge with reference to particular environmental or demographic settings rather than a particular pathogen type.

9
Which Pathogens Emerge: Where and Why?

Many reviews have emphasised the importance of anthropogenic social and environmental factors in disease emergence (e.g. Institute of Medicine 1992; Schrag and Wiener 1995; Kuiken et al. 2003). Indeed all the six factors identified by the Institute of Medicine (1992) as contributing to EIDs are considered anthropogenic (i.e. human demographics and behaviour, technology and industry, economic development and land use, international trade and commerce, microbial adaptation and change, breakdown of public health measures). Recognition of the importance of human-related impacts has dispelled some of the early complacency about infectious diseases and suggests that the EIDs are likely to increase as the human ecological footprint continues to grow. In theory, it also suggests that counter measures to mitigate the effects of anthropogenic change might be

possible. However, risk factors are often cited only in terms of broad categories, such as climate change, human population increase, urbanisation or habitat destruction. Unless we can link these factors to specific effects on the underlying dynamics of a disease, it will be difficult to design effective control measures or target surveillance to the appropriate steps of different transmission pathways.

As an example, land-use change is often suggested as a risk factor for emerging zoonoses, but there are multiple ways in which changes in land use and habitat might affect the infection dynamics of zoonotic pathogens, including (1) an increase in the number of reservoir hosts, (2) an increase in the incidence of infection in reservoir hosts, or (3) a change in the pattern, rate or frequency of contact between reservoir and human hosts. Understanding which of these factors are operating will determine how and where control measures can be targeted for optimum effect. However, identifying critical pathways may not be simple; the ecological processes that can lead to changes in zoonotic infection dynamics are often very specific (Box 1), requiring a detailed understanding of host population ecology.

Box 1: Potential mechanisms by which land-use changes can affect pathogen dynamics and emergence

The complexity of mechanisms by which changes in host-pathogen dynamics can result in emergence is illustrated here with respect to land-use change as a risk factor for disease emergence. Land-use change could result in pathogen emergence by any of the following factors, which may affect reservoir dynamics or host-reservoir contact patterns: (1) demographic host release arising from reduction of competitor and/or predator species, resulting in competitive release and an increased density of the most competent host for a pathogen (Rosenblatt et al. 1999), (2) the fence effect, whereby habitat fragmentation restricts dispersal and leads to unnaturally high densities and hence infection rates (Dobson and May 1986), (3) reduction of species diversity leading to a relative increase in alternative, more competent hosts (Ostfeld and Keesing 2000), (4) a reduction in the genetic diversity, which may increase opportunities for EIDs (Acevedo-Whitehouse et al. 2003; Keller et al. 2002) with knock-on effects on the equitability of higher trophic levels, (5) enrichment of nutrient status (by pollution or agricultural crop presence, or fertiliser), which may favour certain species that specialise on such resources, (6) elimination of biodiversity creating vacant niches for invasive species, which has been suggested as a factor in the emergence of non-polio enteroviruses following elimination of polio (Delpeyroux et al. 2000) and (7) the establishment of secondary contact zones, in which pathogens introduced into novel environments have the opportunity to come into contact with closely related but previously geographically isolated pathogens. This concept has been explored mainly in the context of plant EIDs and identified as the cause of emergence of diseases, such as Dutch elm disease (*Ophiostome novo-ulmi*) (Brasier 2001) and novel fungal diseases of alder trees (*Alnus spp.*) (Brasier et al. 1999). However, pathogen recombination in secondary animal contact zones may prove to be a rich source of novel zoonotic pathogens (e.g. Waterfield et al. 2004).

We focus on ecological risk factors for zoonotic disease emergence and propose a framework that identifies three steps for zoonotic disease emergence: (1) transmission from animal host to human samplers (individuals with a high risk of acquiring novel infections), (2) transmission from samplers to spreaders (individuals with a high potential for transmitting novel infection onwards within the new host population) and (3) transmission from spreaders to the general population. The risk of transmission at each of these steps is a function of the number of infections in the source population (*I*), the per capita rate of contact between populations (*C*), the number of individuals engaging in this type of contact behaviour (*N*) and the susceptibility of the host population (*S*) (Fig. 2). The number of cases in the source population, *I*, reflects both the number of hosts and the incidence/prevalence of infection in the population, and may therefore incorporate enormous complexity (as illustrated by the multiple factors outlined in Box 1 that can affect reservoir infection dynamics). Transmission between host populations is encapsulated by the terms describing both contact and host susceptibility. This framework does not specifically consider the genetic mechanisms by which pathogens acquire or increase their ability to infect humans, but assumes that a pathogen is competent to infect humans.

As in the earlier discussion of zoonotic disease classification, this framework also needs to distinguish obligate zoonoses, which can only be transmitted to humans from animals (i.e. there is no or virtually no human-to-human transmission), from human diseases that originate in animal hosts but have the potential to spread within the human population. For obligate zoonoses, such as rabies, brucellosis, and West Nile virus, there is no human spreader population and all victims are essentially samplers. Mechanisms and risk factors for disease emergence in this group are therefore concerned only with the transmission step between animal host and human samplers (Fig. 2b). To explore the value of this framework for providing insights into the mechanisms of zoonotic disease emergence and identifying key gaps in current knowledge, we examined several well-studied emerging diseases, attempting to allocate risk factors to specific components of the emergence pathway.

We chose ten relatively well-studied pathogens, or pathogen groups, in order to attempt a preliminary analysis of the epidemiological relevance of factors suggested for their emergence. These were *Borrelia burgdorferi*, Ebola virus, Hantaviruses, human immunodeficiency viruses, influenza virus, *Mycobacterium tuberculosis*, Nipah virus, severe acute respiratory syndrome coronavirus, variant CJD and *Yersinia pestis*.

A literature search using the terms "factor", "emergence" and the pathogen name identified 18 references that listed 157 risk factors, many being repeated across different references (Table 3). These were summarised into both the conventional categories such as land-use changes and urbanisation effects, and the

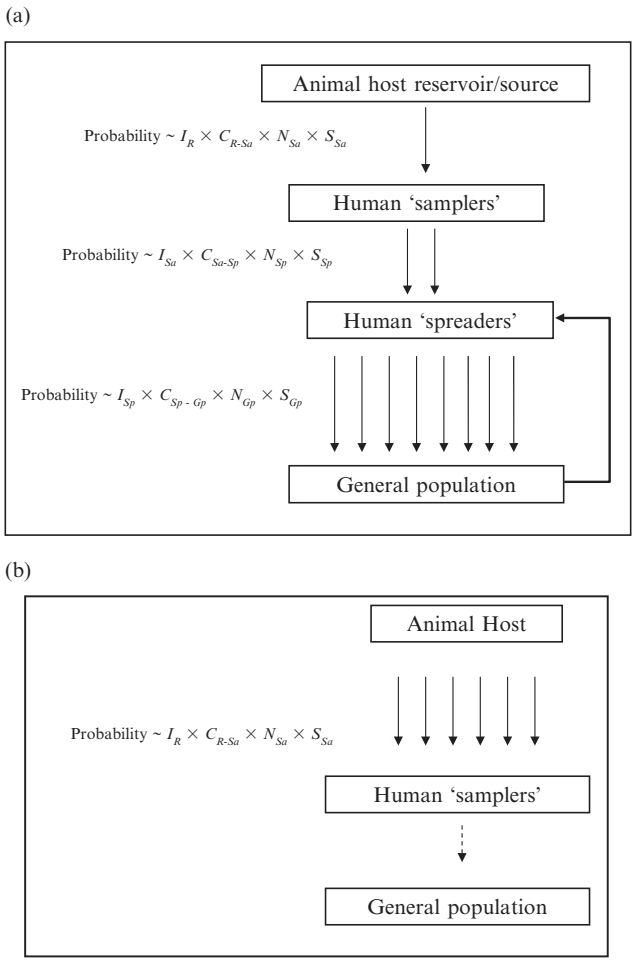

Fig. 2a, b Steps in the emergence of a zoonotic pathogen with the associated risk function. *I* is the number of infections in the source population, *C* a function of per capita contact rate between populations, *N* the number of hosts engaging in that contact activity and *S* the susceptibility of the host population. The subscripts refer to the following populations: *R*, animal reservoir or source population, *Sa*, human samplers, *Sp*, human spreaders, *Gp*, the general human population. **a** Zoonotic pathogens which have the capacity for human-to-human transmission. **b** Obligate zoonotic pathogens for which human-to-human transmission is limited

Table 3 Risk factors associated with the emergence of selected zoonotic diseases showing the elements of emergence pathways potentially affected by each factor. Key: Green = Land-use changes, Red = Bush meat trade, Blue = Hospital/medical practices, Yellow = Farming, food production and marketing, Grey = Urbanisation, Pale Blue = Local and long-distance travel

	Infection			Contact			Number			Susceptibility		
Pathogen	Reservoir	Samplers	Spreaders	Reservoir-Samplers	Samplers-Spreaders	Spreaders-Population	Samplers	Spreaders	General Population	Samplers	Spreaders	General Population
Borrelia burgdorferi	Forest fragmentation Reforestation Land-use changes			Intrusion into country Reforestation			Intrusion into country					
Ebola virus			Poor hospital hygiene	Bush-meat trade Intrusion into countryside	Contaminated needles	Long-distance travel	Bush-meat trade					
Hantaviruses	Increase in rodent density Land-use changes Weather changes			Logging Land-use changes Importation of exotic animals Intrusion into countryside Transport of rats with trade	Long-distance travel	Long-distance travel	Land-use changes					

	Infection			Contact			Number			Susceptibility		
Pathogen	Reservoir	Samplers	Spreaders	Reservoir-Samplers	Samplers-Spreaders	Spreaders-Population	Samplers	Spreaders	General Population	Samplers	Spreaders	General Population
HIV				Bush-meat trade	Promiscuous sex	Medical technology	Bush-meat trade, poverty	Poverty				
				Intrusion in country	Migration	Long-distance travel	Intrusion in country					
					Lack of control measures	Promiscuous sex						
						Medical technology						
						Lack of control measures						
Influenza A virus	Intensive farming Livestock movement Mixed livestock farming/markets			Livestock movement	Long-distance travel	Long-distance travel						
Mycobacterium tuberculosis			Public health breakdown		Migration	Public health breakdown		Public health breakdown			Co-infection with HIV Poverty	Co-infection with HIV Poverty
						High population densities						
						Long-distance travel						

(*Continued*)

Table 3 —cont'd.

	Infection			Contact			Number			Susceptibility		
Pathogen	Reservoir	Samplers	Spreaders	Reservoir-Samplers	Samplers-Spreaders	Spreaders-Population	Samplers	Spreaders	General Population	Samplers	Spreaders	General Population
Nipah virus	Intensive farming Livestock movements Weather changes Habitat destruction Farming practices			Livestock movements								
SARS-Coronavirus			Poor hygiene Poor hospital hygiene	Bush-meat trade Lab-acquired infections Mixed livestock markets	Local travel Lab-acquired infections Eating out	Dense populations Long-distance travel	Bush-meat trade			Chronic health problems Other health problems		
Variant CJD	Cattle-feeding practices BSE epidemic			Butchering practices	Blood transfusion							
Yersinia pestis	Weather Domestic animal infections rising			Intrusion into country	Travel, trade Migration	Travel, migration, trade Poor hygiene						

model parameters from our epidemiological framework that would be affected by those factors (Table 3). Obviously in an emerging disease context, there is a knock-on effect between our epidemiological parameters. For example, if contact between a reservoir and sampler population increases, so too does the infection level in the sampler population. We attempted to identify the root effect of the factor in question as the earliest point in the transmission pathway at which the factor operates. For example, we could consider that poor hospital hygiene, which increases transmission of Ebola virus through contact with infected bodily fluids, might influence contact between spreaders and samplers as well as increase infection rates in spreaders. Clearly there would be many ways of organizing this information and variability in the way that categories are assigned but we suggest that the broad patterns are robust to these alternative arrangements.

As a first step, we have adopted this simple approach for qualitative exploration of emergence risk factors, but the general methodology could be developed in more detail for further quantitative analyses. Using our selected examples, several issues come to light. For all the diseases selected here, emergence has been associated with multiple risk factors, which need to be operating simultaneously or sequentially for a disease to emerge or re-emerge. None of the major categories of risk factor, as they are generally summarised in the literature, operate at a single specific step in the epidemiological framework but have the potential for multiple impacts on infection dynamics. Thus, changes in farming practices can affect zoonotic disease emergence through changing infection rates in animal reservoirs, and/or by increasing contact between reservoirs and samplers.

A striking feature of Table 3 is the predominance of risk factors that affect the contact rate, with local and long-distance movements acting to increase both human-to-human and animal-to-human contact. This is perhaps unsurprising given the unprecedented speed, volume and extent of travel and international trade today. More than 1.4 million people cross international borders on flights everyday and cruise ships now have the capacity to carry 47 million passengers per year (Wilson 2003). Although long-distance movements tend to be associated with transmission by spreaders to the general population, some types of long-distance travel, such as tourism, provide travellers with the potential to act as both samplers and spreaders, and some long-distance trade movements have been associated with increased contact between animal reservoirs (e.g. rats) and humans. Wildlife and livestock movements clearly also play an important role in the emergence of zoonotic diseases, with the potential both to increase the incidence of disease in reservoir or source populations and increase reservoir-to-human contact. While limiting human contacts is often difficult, particularly with ease of travel, restricting the scale of legal and illegal

movements of domestic animals (livestock and pet animals) and wildlife presents a real opportunity to minimise emergence risks.

With respect to sampler-to-spreader transmission, or dissemination from spreaders to the general population, relatively few mechanisms may be involved (e.g. international airline travel, food contamination, hospital care). Some of these contact networks, and therefore emergence risks, may be relatively simple to predict. For example, a simulation model of SARS that used global aviation routes to predict contact and transmission networks was able to provide close estimates of the number of cases occurring in different countries (Hufnagel et al. 2004). In practice, SARS cases were contained more effectively by simple hygienic precautions, such as wearing masks, than airport surveillance and detection strategies (e.g. thermal imagery) (Bell 2004; John et al. 2005). However, the benefits of targeting control and surveillance efforts to high-risk travellers may still be considerable.

While compiling the table, the difficulty of pinning down the exact epidemiological components affected by the risk factor became clear and drew attention to gaps in our knowledge. For example, urbanisation actually summarises a large number of different factors, each of which affects the underlying epidemiology of a particular pathogen in different ways. Urbanisation could lead to disease emergence as a result of poverty (which could increase susceptibility of human populations), high population densities, crowded housing, poor sanitation (which could all affect contact rates and the number of spreaders), and/or a breakdown in social values and public health (which could affect both infection rates and contact rates). The table also highlights the complete absence of information about reservoir infection dynamics for several zoonoses (Ebola virus and SARS).

10
Prediction and Surveillance of Emerging Zoonoses

It is often stated that it is impossible to predict where and when the next emerging zoonosis will appear (e.g. Murphy 1998). If the exact timing of species jumps is likely to be difficult, if not impossible to predict, early detection of emergence events is likely to be the best hope of controlling outbreaks and minimising the impact of disease.

Given the amplification effect of spreaders in the population, both the probability of transmission and the consequences (costs) of an emergence event increase with progression down the pathway from animal-to-human to human-to-human transmission. An important question is therefore to determine the point in the transmission chain at which resources are best directed. Is it better to try to detect transmission events from animal reservoirs to samplers, which may

occur relatively rarely but may allow large and costly outbreaks to be prevented, or to focus surveillance on transmission events in spreader populations, which may occur more frequently, but may result in delayed control of epidemics. How important is it to understand infection dynamics in animal reservoirs, which may be costly and demanding to achieve, particularly for wildlife populations (Haydon et al. 2000)? For prevention of Nipah virus, for example, is it better to focus efforts on surveillance of fruit-bat reservoir populations, on enhancing the capacity for disease detection in high-risk pig farms (e.g. in areas with recent conversion from mangrove to oil palm plantations), on improving case surveillance in hospitals in these areas, or some combination of these three?

Factors that increase I_R or $C_{R\text{-}Sa}$ and therefore increase the probability of spill-over from animal populations into humans may be easier to predict than rare cases of species jumps. At this stage in the emergence of zoonoses, it may indeed be possible to identify sentinel (i.e. sampler) populations associated with high-risk situations (Table 4). For example, increased bushmeat consumption is cited as a risk factor for the emergence of several zoonoses and novel pathogens, and could be caused by an increase in the number of hunters/consumers (increased N_{Sa}) and/or increased contact between hunters/consumers and wildlife reservoirs (increased $C_{R\text{-}Sa}$). Improved surveillance of a sampler population of bushmeat hunters or butchers may detect host-switching and emergence events, possibly before dissemination to the general population. Similarly, farmers and market traders may be suitable sentinels for diseases

Table 4 Suggested high-risk environments and human sentinels that could be targeted for surveillance of emerging zoonoses

Risky environments/situations	Potential human sentinel population
Travel hubs	Airline crews, airport staff, frequent flyers, cruise ship staff, international conferences
Urban shanty towns	Impoverished communities, urban livestock keepers, prostitutes
Hospitals	Nurses, doctors, immunosuppressed and elderly patients
Farms and markets	Farmers, market traders, abattoir workers, vets, peri-urban livestock keepers
Interface habitats	Bush-meat hunters and butchers, market traders, consumers
Changing habitats, e.g. dam construction, logging, reforestation	New settler communities
New technologies	Transplant and blood transfusion recipients

affected by changes in farming practice, and may allow early detection of new outbreaks of SARS or Nipah virus. The potential value of high-risk human sentinels has been demonstrated, with detection of simian foamy viruses (retroviruses) in villagers in Cameroon that have direct contact with blood and body fluids of non-human primates (Wolfe et al. 2004). However, host-switching events appear to be occurring frequently and, since most outbreaks are small and may never take off (Woolhouse et al. 2001), the appropriate response to detecting new microbial agents in human populations remains very uncertain. An alternative approach would be the improvement of medical diagnostics and communication in remote communities (such as at the tropical forest interface), which might provide a more cost-effective approach to preventing large outbreaks of emerging pathogens (Shears 2000a, 2000b).

Land-use changes that affect reservoir infection rates are often associated with emerging zoonoses transmitted from wildlife reservoirs (e.g. *Borrelia burgdorferi*, Hantaviruses, Nipah viruses). While the emergence of a specific pathogen may be hard to predict, it is certainly predictable that changes in land use carry a risk of zoonotic disease emergence. Can we identify high-risk environments in which accelerating land-use changes raise particular concerns?

In summary, pathogen emergence is not an ecologically novel phenomenon, rather an inevitable consequence of changes in the abundance of host populations and the contact networks that exist between them. Throughout human history, pathogens have always exploited ecological change. Some pathogens, such as viruses and generalists, may be better at doing this than others, but many different pathogens have emerged. While there are several features that characterise many emerging pathogens and these may be combined into a profile of an emerging disease, most emerging pathogens will not fit this profile exactly. The objective perhaps should not be to predict which pathogens emerge but to plan for the inevitability of emergence events and prepare to detect and deal with them quickly. However, planning an effective response requires an understanding of their epidemiology, and once an emergence event is detected, efforts must be directed to the rapid acquisition of this information. The response to SARS provides encouragement that a flexible, integrated global strategy can be developed. SARS also highlights our inability to predict where and when the next outbreak might occur. Increasing our knowledge about the identity or infection dynamics of animal reservoirs must be a key priority that requires contributions from many different disciplines.

Over the past decade, there has been clear recognition of the problems that emerging infectious diseases pose to health care professionals throughout the world. The next decade will reveal whether solutions to these problems lie in the development of a general theory of infectious disease emergence or whether they will require case-specific approaches.

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