Population biology of emerging and re-emerging pathogens

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Emerging and re-emerging pathogens present a huge challenge to human and veterinary medicine. Emergence is most commonly associated with ecological change, and specific risk factors are related to the type of pathogen, route of transmission and host range. The biological determinants of host range remain poorly understood but most pathogens can infect multiple hosts, and three-quarters of emerging human pathogens are zoonotic. Surveillance is a key defence against emerging pathogens but will often need to be integrated across human, domestic animal and wildlife populations.

There are 1415 species of endoparasitic infectious organisms known to be pathogenic in humans [1], many of which have only recently been recognized (Table 1). These pathogens are responsible for an enormous global burden of disease and cause 14 million human deaths per year [2]. The incidence of many infectious diseases is increasing, and this is true not only of new diseases, such as acquired immunodeficiency virus (AIDS), but also of diseases previously regarded as being in decline, such as tuberculosis (TB). Similarly, pathogens affecting domestic animals are responsible for huge economic losses and welfare problems, and pathogens affecting wildlife can be a threat to conservation. Both novel and resurgent pathogens, such as bovine spongiform encephalopathy (BSE) in cattle and phocine distemper in seals, are having an increasing impact on animal health [3–5].

This situation presents a major challenge for the development of diagnostics and therapeutics and their use in effective surveillance and intervention strategies. The huge diversity of pathogen species represents an equally huge diversity of life cycles, transmission routes, biochemistries, pathogenicities and epidemiologies. For the most part, biomedical science has responded to this challenge on a case-by-case basis, with each pathogen species or variant being treated as a separate problem. By contrast, this article reviews some of the generalities underlying the biology of pathogens of medical and veterinary importance, especially those regarded as emerging or re-emerging, and identifies some general lessons for combating them.

Emerging pathogens

An emerging pathogen can be defined as an infectious agent whose incidence is increasing following its first introduction into a new host population; a re-emerging pathogen is one whose incidence is increasing in an existing host population as a result of long-term changes in its underlying epidemiology [6]. These definitions are intended to differentiate the short-term, local increases in incidence that characterize the epidemiologies of many infectious diseases, from the long-term, global trends that constitute 'true' emergence. In practice, however, pathogens are usually designated as emerging based on subjective criteria, which can reflect increased awareness, improved diagnosis, discovery of previously unrecognized aetiological agents, and the interests of the researcher, as much as any objective epidemiological data. Reporting bias must therefore always be considered as a possible explanation for any apparent patterns.

A recent review [1] listed 175 human pathogen species (12% of the total) that could be regarded as emerging or re-emerging. Many of these pathogens have only recently been identified and some might genuinely be novel (Table 1), for example, human immunodeficiency virus (HIV) and the agent causing variant Creutzfeldt–Jakob disease (vCJD) (the review excluded newly recognized aetiological agents if there was no evidence that disease incidence was increasing). There are also dozens of pathogen species regarded as emerging or re-emerging in livestock, domestic animals and wildlife [3–5], although data for non-human hosts are likely to be far less comprehensive than those for human.

Broadly, there are three sources of emerging and re-emerging pathogens: (1) from within the host population itself, for example, *Mycobacterium tuberculosis* in humans or chronic wasting disease in cervids; (2) from the external environment, for example, *Legionella pneumophila* in humans; or (3) from populations of other host species, for example, HIV and vCJD in humans, and the rabies virus in wild dogs. Several (not mutually exclusive) factors have been linked with pathogen emergence from these sources, including: (1) genetic changes in the pathogen, for example, the evolution of HIV from simian immunodeficiency virus, or canine parvovirus from feline panleukopenia virus, or the emergence of multidrug-resistant *Staphylococcus aureus* and drug-resistant *Plasmodium falciparum*

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Table 1. Pathogens recognized since 1973*

Year	Pathogen	Disease
1973	Rotavirus	Infant diarrhoea
1976	*Cryptosporidium parvum*	Acute and chronic diarrhoea
1977	Ebola virus	Ebola haemorrhagic fever
	Legionella pneumophila	Legionnaires disease
	Hantaan virus	Haemorrhagic fever with renal syndrome
	Campylobacter jejuni	Enteric diseases
1980	Human T-lymphotropic virus (HTLV)-1	T-cell lymphoma-leukemia
1981	Exotoxin-producing *Staphylococcus aureus*	Toxic shock syndrome
1982	*Escherichia coli* O157:H7	Haemorrhagic colitis; haemolytic uraemic syndrome
	HTLV-2	Hairy cell leukemia
	Borrelia burgdorferi	Lyme disease
1983	Human immunodeficiency virus (HIV)-1	AIDS
	Helicobacter pylori	Peptic ulcer disease
1985	*Enterocytozoon bieneusi*	Chronic diarrhoea
1986	HIV-2	AIDS
	Cyclospora cayetanensis	Chronic diarrhoea
1988	Hepatitis E virus	Enterically transmitted non-A, non-B hepatitis
	Human herpesvirus 6	Roseola infantum
1990	Guanarito virus	Venezuelan haemorrhagic fever
1991	*Encephalitozoon hellem*	Conjunctivitis, disseminated disease
1992	*Vibrio cholerae* O139	New strain associated with epidemic cholera
	Bartonella henselae	Cat-scratch disease; bacillary angiomatosis
1993	Sin Nombre virus	Hantavirus pulmonary syndrome
	Encephalitozoon cuniculi	Microsporidiosis
1994	Sabia virus	Brazilian haemorrhagic fever
	Hendra virus	Viral encephalitis
1995	Hepatitis G virus	Parenterally transmitted non-A, non-B hepatitis
	Human herpesvirus 8	Associated with Kaposi sarcoma in AIDS patients
1996	TSE causing agent	Variant Creutzfeldt–Jakob disease
	Australian bat lyssavirus	Viral encephalitis
1997	Avian influenza virus [Type A (H5N1)]	Influenza
1999	Nipah virus	Viral encephalitis

*Data taken from: The World Health Organization (WHO) (http://www.who.int/); Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/); and ProMED (http://www.fas.org/promed/).

in humans; (2) immunocompromised hosts, for example, *Haemophilus ducreyi* and *M. tuberculosis* in AIDS patients or, possibly, phocine distemper virus in seals; and (3) changes in host–pathogen ecology, for example, *Borrelia burgdoferi* in humans or *Myxobolus cerebralis* in salmonids. The last category includes changes in: host demography, movement or behaviour; climate, natural environment or land use; and the use of technology (e.g. food production). The common feature of these changes is their effect on transmission – altering the ways and the degree to which susceptible hosts are exposed to potential pathogens. In practice, ecological changes affecting opportunities for transmission are associated with the great majority of instances of emergence.

Risk factors for emergence

Recent studies have suggested that emergence could be associated with some taxa of pathogens more than others, with certain transmission routes and with a broad host-range [1–5].

Viruses are disproportionately likely to be regarded as emerging, both in humans and in domestic animals [1,4], with relative risk (RR) greater than 4 (RR is the proportion of species *with* a risk factor that are emerging, relative to the proportion of species *without* that risk factor that are emerging). Conversely, parasitic helminths are unlikely to be considered emerging (RR<0.25); protozoa, bacteria and fungi are intermediate. There is a similar trend among emerging wildlife pathogens [5].

The major categories of transmission route are: (1) direct contact (including inhalation, via wounds, sexual contact, transmission *in utero* and iatrogenic transmission); (2) indirect contact (via food or an environmental reservoir, including free-living infective stages); and (3) vector-borne (biting or mechanical transmission by arthropods). In fact, transmission of many pathogens falls into more than one of these categories, for example, *Yersinia pestis* or the flaviviruses. Among human pathogens, vector-borne pathogens are most likely to be regarded as emerging, followed by those transmitted by direct contact and those transmitted by indirect contact [1].

The majority (75%) of emerging and re-emerging human pathogens are known to be zoonotic [1]; that is, they are naturally transmitted between humans and other vertebrates (excluding those where other vertebrates are involved only as intermediate hosts in a complex life cycle) [7]. Zoonotic pathogens are almost twice as likely as non-zoonotic pathogens to be regarded as emerging [1]. They are not strongly associated with any particular reservoir species but can be associated with both taxonomic and ecological breadth of host range; zoonotic pathogens that can infect both domestic animal and wildlife hosts are most likely to emerge [4]. There is some evidence (data from [1]) that, as might be anticipated, transmissibility between humans is a risk factor for the emergence of zoonotic pathogens. This is indicated by comparing: (1) pathogens not known to be transmissible between humans (e.g. *Fasciola hepatica*); (2) pathogens occasionally transmitted between humans but with most infections acquired from animal reservoirs (e.g. *Trypanosoma brucei rhodesiense*); and (3) pathogens that are usually transmitted between humans with animal reservoirs playing a minor role (the so-called anthroponoses, e.g. the measles virus). In these three categories the fractions regarded as emerging are 9%, 24% and 48%, respectively. There is less information for non-human hosts, but having multiple-host species is a risk factor for the emergence of livestock pathogens [4], and there are indications that the same applies to emerging wildlife pathogens [5].

The three factors discussed here – taxonomy, transmission route and host range – are highly confounded. Multifactorial analyses indicate that taxonomic division has the greatest effect but that host range is also important, although these two factors interact; that is, host range is more important for some taxonomic divisions than for others [1,4]. It is less clear whether the route of transmission has a significant independent effect overall, although it might be important within certain pathogen categories, for example, human arboviruses that are transmitted by dipterans which are more likely to emerge than those transmitted by acarids (J. Robertson, unpublished results).

This kind of analysis is at a very early stage and the robust identification of underlying risk factors for emergence is far from straightforward. In addition to the problem of confounding, data on transmission routes and host range might be unavailable or incomplete (especially for rare pathogens), comparisons across species might be biased by phylogenetic relatedness, and there might also be biases in designating pathogens as emerging. Even so, it is clear that the pathogens regarded as emerging are not a random subset of all pathogens. The challenge is to understand the biological and epidemiological factors underlying differences in the relative risk of emergence. One of the variables (host range) that influences the risk of emergence is now considered in more detail.

Box 1. Receptor usage by viruses

Cell receptors have been identified for only 88 species of virus known to be pathogenic in mammals [a–c], although these include members of most recognized families as defined by the *Index Virum* (http://life.anu.edu.au/viruses/Ictv/index.html). The receptors include immunoglobulin-like molecules (e.g. major histocompatibility complex I), integrins and adhesins, chemokine receptors (e.g. CXCR4), transport proteins (e.g. cationic amino acid receptors), signalling proteins (e.g. the acetylcholine receptor), complement control proteins (e.g. decay accelerating factor), components of the extracellular matrix (e.g. sialic acid, heparan sulfate) and many others (including α-dystroglycan). Using data held in GenBank (http://www.psc.edu/general/software/packages/genbank/genbank.html) it is possible to identify which protein receptors are 'conserved', crudely defined here as ≥85% homology between human and mouse amino-acid sequences. Examples of conserved receptors include the vitronectin, coxsackie–adenovirus and epidermal-growth-factor receptors. Viruses with a host range encompassing different taxonomic orders are statistically significantly more likely to use conserved receptors than those with narrower host ranges ($X^2 = 7.4$, df = 1, one-tailed $p = 0.0032$), although this result must be interpreted cautiously because of the incompleteness of the data and the possibility of phylogenetic confounding (J. Robertson, unpublished results).

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Host range

Most human pathogens (868 species; 61% of the total) are zoonotic. The majority of these is associated with

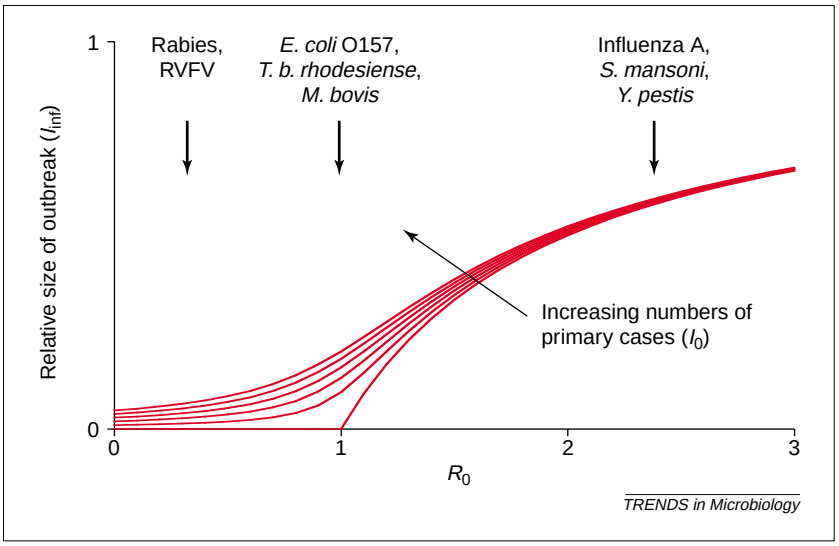

Figure 1. Determinants of outbreak size

Relationship between expected final outbreak size (I_{inf}, as fraction of total population) and basic reproduction ratio (R_0) for increasing numbers of primary cases (I_0, increasing from 0 to 5% total population, shown by arrow). The model is the recursive equation $I_{inf} = 1 - (1 - I_0)\exp[-R_0 I_{inf}]$ (adapted from [17]). The limiting cases are: (1) $R_0 << 1$, where outbreak size is determined largely by the number of primary cases; (2) $R_0 >> 1$, where outbreak size is determined largely by the size of the susceptible host population. In the range $R_0 \approx 1$, outbreak size is very sensitive to changes in either the number of primary cases or the basic reproduction ratio. Suggested examples of zoonotic pathogens whose dynamics lie in different parts of this spectrum are shown. Species names: *M. bovis*, *Mycobacterium bovis*; RVFV, Rift Valley fever virus; *S. mansoni*, *Schistosoma mansoni*; *T. b. rhodesiense*, *Trypanosoma brucei rhodesiense*; *Y. pestis*, *Yersinia pestis*.

Box 2. Profile of an emerging pathogen

Based on this review, the profile of a 'typical' emerging human pathogen might be:

- an RNA virus;
- zoonotic, with a reservoir host-range that is both taxonomically and ecologically broad;
- transmitted by vectors, especially by biting flies that are generalist feeders;
- able to use a cell receptor that is conserved across host species;
- potentially transmissible between humans, but currently rare;
- found in areas that are experiencing ecological, demographic or social change.

Recognized examples meeting most of these criteria include St Louis encephalitis virus (a flavivirus), Venezuelan equine encephalitis virus (an alphavirus) and Oropouche virus (a bunyavirus).

ungulate, carnivore and/or rodent reservoirs, although a substantial minority is associated with primates, bats, marine mammals, birds and other vertebrates [4]. The proportion of human pathogens known to be zoonotic varies widely between taxonomic divisions, from 95% of helminths to 38% of fungi [1]. There are some interesting contrasts: RNA viruses are much more likely to be zoonotic than DNA viruses (84% versus 36%, respectively) and rickettsia than bacteria (100% versus 48%, respectively). Yet host range can differ greatly, even between very closely related pathogens, for example, *Schistosoma haematobium* versus *Schistosoma japonicum*, or *T. b. rhodesiense* versus *T. b. gambiense*.

Among human viruses, bacteria and protozoa, those transmitted by direct contact are less likely to be zoonotic than those transmitted by indirect contact, and those transmitted by vectors are most likely to be zoonotic (few fungi are transmitted by vectors and helminths are very rarely transmitted by direct contact) [8]. One explanation for this is that transmission route affects both the opportunities for, and the benefits of, a broad host range. Indirect contact transmission (often involving widespread contamination of the environment) might provide more opportunities to infect different hosts than direct contact. Transmission by generalist vectors might do the same, noting that non-zoonotic vector-borne human pathogens are often transmitted via anthropophilic vectors [8]. Vector-borne pathogens suffer an additional constraint in that they have much more limited transmission opportunities: a blood meal taken on one host means a blood meal not taken on another. This provides powerful selection for pathogens transmitted by generalist vectors to themselves be generalists [8].

There is also some evidence among viruses that a broad host-range is associated with the use of host-cell receptors that are highly conserved across host species (Box 1). Examples include the rabies virus and foot-and-mouth disease virus.

The population dynamics of multihost pathogens remains relatively poorly understood in comparison to single host–single pathogen systems [9]. An important aspect is the size of an infectious disease outbreak derived from an outside source, such as a reservoir host. Outbreak size is related to the initial number of infections, the basic reproduction number (R_0) and the size of the susceptible population. If R_0 is close to 1, small changes in R_0 (reflecting small changes in the biology or ecology of host and/or pathogen) can readily lead to the large increases in incidence of infection that constitute emergence (Fig. 1).

Lessons for control

Emerging and re-emerging pathogens are opportunists responding to changing host and/or pathogen ecologies; they have been likened to weeds [5]. Given that ecological changes are continuing apace, mostly as a result of human activities, there is every reason to suppose that emerging disease problems will also continue (Table 1 and Box 2). Detailed information on molecular biology and pathogenesis is becoming available for only a minority of these pathogens (e.g. HIV) and, for some (e.g. Ebola virus), even basic knowledge (such as transmission route and host range) is lacking.

From a public health perspective, a key defence against emerging pathogens is surveillance, which requires: (1) adequate diagnostic tools; (2) well-designed surveillance systems; (3) adequate infrastructure and human resources; and (4) effective coordination on regional, national and global scales. Although there have been numerous recent advances in diagnostics, such as PCR for *T. b. rhodesiense* [10], and immunomagnetic separation for verocytotoxin-producing *Escherichia coli* (VTEC) [11], many pathogen taxa (e.g. mycobacteria) remain problematic. The design of monitoring and surveillance systems (MOSS) for rare diseases has also improved recently, partly prompted by legislative requirements to screen for BSE [12]. However, the provision of adequate resources and infrastructure requires political will and sustained investment. The same applies to coordination, which is the remit mainly of government and international agencies, supplemented by informal reporting services such as Pro-MED (http://www.fas.org/promed/). Most emerging human pathogens are zoonotic [1,13], so medical and veterinary surveillance must be integrated effectively, as illustrated recently by West Nile virus in the US, Rift Valley fever virus (RVFV) in east Africa, Nipah virus in south-east Asia, and Hendra virus in Australia. Such integration has been important for the monitoring and management of vCJD in the UK where, in response to the BSE epidemic in cattle, measures were put in place to reduce possible transmission of infection to humans several years before the first vCJD cases were detected [14,15] (see http://www.bseinquiry.gov.uk/report/index.htm).

Globalization – the widespread and rapid movement of people, livestock or other animals, and agricultural or other biological products – heightens the importance of effective surveillance systems. An example is the UK's recent epidemic of foot-and-mouth disease: the index case is thought to have been caused by imported meat products, and extensive trading of sheep allowed widespread dissemination of infection nationally and internationally before the disease was known to be present [16]. Gauging the potential for events of this kind requires a much better understanding of the demographies and movements of humans, livestock and other animals than exists at present.

In conclusion, better management of emerging diseases demands a multidisciplinary research effort extending well beyond the traditional confines of human and veterinary medicine.

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