

Risk factors for human disease emergence

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A comprehensive literature review identifies 1415 species of infectious organism known to be pathogenic to humans, including 217 viruses and prions, 538 bacteria and rickettsia, 307 fungi, 66 protozoa and 287 helminths. Out of these, 868 (61%) are zoonotic, that is, they can be transmitted between humans and animals, and 175 pathogenic species are associated with diseases considered to be 'emerging'. We test the hypothesis that zoonotic pathogens are more likely to be associated with emerging diseases than non-emerging ones. Out of the emerging pathogens, 132 (75%) are zoonotic, and overall, zoonotic pathogens are twice as likely to be associated with emerging diseases than non-zoonotic pathogens. However, the result varies among taxa, with protozoa and viruses particularly likely to emerge, and helminths particularly unlikely to do so, irrespective of their zoonotic status. No association between transmission route and emergence was found. This study represents the first quantitative analysis identifying risk factors for human disease emergence.

Keywords: emerging diseases; zoonoses; epidemiology; public health; risk factors

1. INTRODUCTION

Infectious diseases account for 29 out of the 96 major causes of human morbidity and mortality listed by the World Health Organization and the World Bank (Murray & Lopez 1996) and 25% of global deaths (over 14 million deaths annually) (WHO 2000). The publication of *Emerging infections: microbial threats to health in the United States* by the Institute of Medicine in 1992 (Institute of Medicine 1992) highlighted the fact that numbers of cases of many infectious diseases, e.g. tuberculosis, cholera and acquired immune deficiency syndrome, are currently increasing and, over the last few years, there has been a great deal of discussion of the reasons underlying the 'emergence' of these diseases (e.g. Satcher 1995; Ebel & Spielman 1997; Greenwood & de Cock 1998; Scheld *et al.* 1998*a,b*; Binder *et al.* 1999). It has been noted (Institute of Medicine 1992; Morse 1995; Murphy 1998; Palmer *et al.* 1998) that many emerging diseases are zoonoses, infectious diseases which are transmitted between humans and animals. Emerging zoonoses include new variant Creutzfeldt–Jakob disease (The Lancet 1999; Will *et al.* 1999) and *Escherichia coli* O157 (Featherstone 1997; *Veterinary Record* 1997) in Britain, influenza A strains H5N1 and H9N2 in Hong Kong (de Jong *et al.* 1997; CDC Press Release 1999), Hantaviruses in the USA (Schmaljohn & Hjelle 1997) and human sleeping sickness across Africa (Barrett 1999). These and other issues, such as the possibility of infections associated with xenotransplantation (Murphy 1996; Stoye 1998), have increased concern about the impact of animal pathogens on human health. However, most studies of disease emergence have been essentially descriptive and more formal

analysis has been hampered by the absence of quantitative data.

Here, we seek to identify aspects of the epidemiology of pathogenic species that are associated with increased risk of disease emergence in humans. Of particular interest is the hypothesis that zoonotic pathogens are especially likely to be associated with emerging diseases, which has not previously been formally tested. We carry out such a test using the published literature to compile a list of organisms known to be pathogenic to humans, together with available information on whether they are zoonotic, whether they are regarded as emerging, and on their transmission routes and epidemiologies. Our approach differs from previous surveys (Murray & Lopez 1996; WHO 1998) as the focus is the species of pathogen rather than the disease; many diseases, such as infant diarrhoea, can be caused by many different pathogens. At this stage we consider simply numbers of species, treating both common and rare pathogens equally, without reference to the human disease burden they currently impose.

2. METHODS

(a) *Species database construction*

The database of pathogens infectious to humans was compiled from texts of human infectious diseases (Ajello & Hay 1998; Ashford & Crewe 1998; Balows & Duerden 1998; Cox *et al.* 1998; Gorbach *et al.* 1998; Hausler & Sussman 1998; Mahy & Collier 1998), texts of zoonoses (Hubbert 1975; Andrewes & Walton 1977; Acha & Szyfres 1987; Bell & Palmer 1988; Beran 1994*a,b*; Palmer *et al.* 1998), and, so as to include very recently identified human pathogens, reviews of the emerging disease literature (Morse & Schluenderberg 1990; Institute of Medicine 1992; CDC 1994; Wilson *et al.* 1994; Morse 1995; Roizman 1995; Schrag & Wiener 1995; Wilson 1995; Osburn 1996; WHO 1996, 1997; Henderson 1997; Meslin 1997; Schwartz 1997; Childs *et al.*

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1998; Greenwood & de Cock 1998; Gubler 1998; Scheld *et al.* 1998a,b; Dobos *et al.* 1999; Mackenzie 1999; Cohen 2000; Mahy & Brown 2000; Meslin *et al.* 2000; Pollard & Dobson 2000). Each entry was a separate species known to be infectious and capable of causing disease in humans under natural transmission conditions. Although the definition of species is difficult for some infectious organisms, this is the most appropriate level of classification for the vast majority of pathogens and avoids biases that would otherwise be introduced by organisms that exhibit a large amount of subspecific variation (e.g. some species of *Salmonella* and *Listeria*).

Ectoparasites (e.g. Arthropoda, Hirudinea) were not included in the database. Natural transmission was taken to include all routes (e.g. vector-borne, food-borne, accidental laboratory infections) apart from deliberate experimental infection. Infectious pathogenic species only known to cause disease in immunocompromised patients were included. Species for which only a single case of human disease has been documented were included, but this information was noted. Additional references (Soulsby 1982; Greene 1984; Anderson 1992; Quinn 1994; Radostits *et al.* 1994; Carter *et al.* 1995; Roberts & Janovy 1996; Urquhart *et al.* 1996; Aiello 1998) were used to provide additional information about transmission routes and zoonotic status.

The following information was collected.

- (i) Genus and species name of the pathogen. Nomenclature followed standard references currently available (*Bacterial nomenclature up-to-date* (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH), *Index virum* (International Committee on Taxonomy of Viruses), and *The CABI bioscience database of fungal names (Funindex)* (CABI Bioscience) (see publishers' entries in References for Web addresses)). To appear in the database a species name must first have appeared in an up-to-date source text (published within the last ten years), and second appeared in an up-to-date nomenclatural reference source, where available (see above), or appeared in a second up-to-date source text, or appeared in an ISI Web of Science Citation Index search of the last 10 years. Where a genus is known to cause disease in humans, but no species name was given, the genus name appears in the database once followed by 'sp.'. Diseases caused by prions were grouped according to the species of host which is the source of infection. For three species of parasites (*Trypanosoma brucei*, *Strongyloides fuelleborni* and *Nanophyetus salmincola*) distinct subspecies are sometimes given species status. For this study, these species are included only once in order to maintain consistency across the database.
- (ii) Taxonomic division. Five major divisions were recognized: viruses (including prions), bacteria (including rickettsia), fungi, protozoa and helminths (cestodes, nematodes, trematodes and acanthocephalans).
- (iii) Transmission routes to humans. Three categories were distinguished: direct contact (including via wounds, sexual contact, vertical transmission or by inhalation), indirect contact (via food or an environmental reservoir), and vector borne (by biting or mechanical transfer by arthropods). Where an organism could be transmitted by more than one route, all were included with equal weighting. Where no transmission route was documented, this information was assumed to be unknown. It was also noted if the species was known to be transmissible between humans (by any of the routes listed above).
- (iv) Whether or not the species is zoonotic. Zoonoses are defined, following the World Health Organization (WHO 1959; Palmer *et al.* 1998), as diseases and infections that are naturally transmitted between vertebrate animals and man. Species, such as HIV, which recently evolved from animal pathogens, but are no longer transmitted between the animals and humans were not regarded as zoonotic. Given this definition, the main reservoir hosts for zoonotic organisms could be either animal or human, but for diseases where animals played only a minor role in the epidemiology (so called 'zooanthroponoses' (WHO 1959; Palmer *et al.* 1998)) this information was noted. Organisms with complex life cycles where vertebrate animals are involved as intermediate hosts, but humans are the only known definitive host, were defined as non-zoonotic; this applied to two species of protozoa and two species of helminths.
- (v) Whether or not the species is emerging. Emerging pathogens are those that have appeared in a human population for the first time, or have occurred previously but are increasing in incidence or expanding into areas where they had not previously been reported (WHO 1997), usually over the last 20 years (Institute of Medicine 1992). Some definitions of emerging also include recently discovered aetiological agents of already-described diseases. However, if there was no evidence that such a pathogen was increasing in incidence, it was not regarded in this database as emerging.

A second database was constructed from the first to allow investigation of the patterns at the level of genus rather than species. This was intended to make some allowance for the potential biases introduced by certain species-rich genera, e.g. *Flavivirus*. A genus was considered to be zoonotic, and/or emerging, and/or transmissible by a particular route if at least one species in it had that characteristic. Twenty-one species (all viruses) have not been assigned to any genus and were excluded from this database.

(b) Analysis

Taxonomic division, transmission route and zoonotic status were considered as potential risk factors. Analyses were performed comparing emerging and non-emerging species by taxonomic division, transmission route and zoonotic status and by combinations of these characteristics. The analyses were performed at both species and genus level. Results were expressed as relative risks, which measure the multiplicative risk relative to species lacking the risk factor. It was assumed throughout that the lists of all pathogens, zoonotic pathogens and emerging pathogens were complete, hence further statistical analyses were not appropriate.

3. RESULTS

A total of 1415 species of infectious agent in 472 different genera have been reported to cause disease in humans according to the criteria used here (electronic Appendix A, available on The Royal Society's Web site). The number of species in each of the major taxonomic divisions and their routes of transmission are shown in figure 1a. Overall, 15% are viruses or prions, 38% are bacteria or rickettsia, 22% are fungi, 5% are protozoa

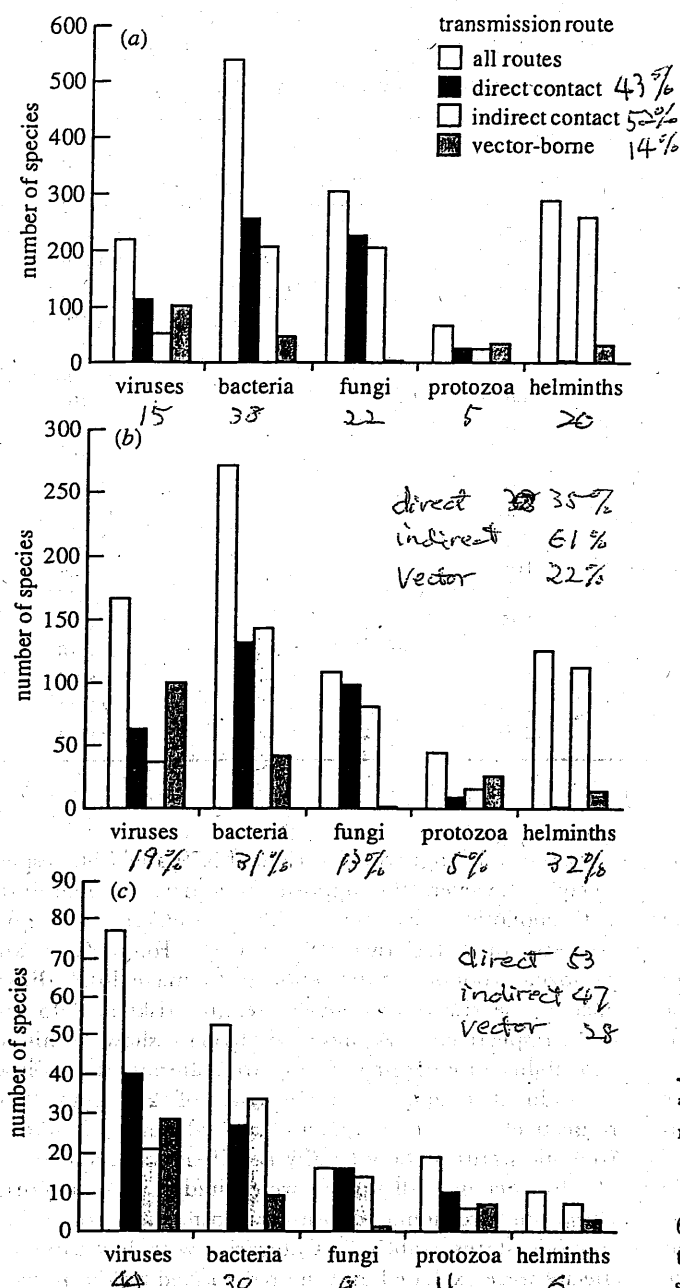


Figure 1. Numbers of species of infectious agent causing human disease, by taxonomic division and transmission route (noting that some species have more than one transmission route and for some the transmission route is unknown). (a) All infectious organisms (n = 1415). (b) Zoonotic organisms (n = 868). (c) Emerging organisms (n = 175).

and 20% are helminths. Three hundred and fifty-seven species are known to be transmitted by more than one route but, overall, 43% can be transmitted by direct contact, 52% by indirect contact, 14% by vectors, and for 16% the transmission route is not known.

Out of these species, 868 (61%) from 313 different genera are known to be zoonotic (electronic Appendix A). The number of zoonotic species in each of the major taxonomic divisions and their routes of transmission is shown in figure 1b. Overall, 19% are viruses or prions, 31% are bacteria or rickettsia, 13% are fungi, 5% are protozoa, and 32% are helminths. Thirty-five per cent of zoonotic pathogens can be transmitted by direct contact,

Table 1. Risk factors for emergence.

((a) Effect of taxonomic division, transmission route and zoonotic status individually. Relative risk for a particular category is the proportion of species in that category which are emerging, divided by the proportion of species not in that category which are emerging. (b) Effect of zoonotic status within taxonomic and transmission route categories. Within each category, relative risk refers to the proportion of species emerging among the zoonotic pathogens divided by the proportion of species emerging among the non-zoonotic pathogens.)

category	relative risk
(a) Effect of taxonomic division, transmission route and zoonotic status individually	
zoonotic status	non-zoonotic 0.52
	zoonotic 1.93
taxonomic division	viruses 4.33
	bacteria 0.71
	fungi 0.33
	protozoa 2.49
	helminths 0.24
transmission route ^a	direct contact 1.47
	indirect contact 0.80
	vector borne 2.35
(b) Effect of zoonotic status within taxonomic and transmission route categories	
overall	all species 1.93
taxonomic division	viruses only 0.96
	bacteria only 3.79
	fungi only 7.14
	protozoa only 0.74
	helminths only 0.19
transmission route ^a	direct contact only 2.13
	indirect contact only 2.60
	vector-borne only 0.97

^a Excludes 222 species (53 zoonotic) with unknown transmission routes.

61% by indirect contact, 22% by vectors, and for 6% the transmission route is not known. Only 33% of zoonotic species are known to be transmissible between humans and only 3% of all the zoonotic species are considered to have their main reservoir in human populations; the remainder have their main reservoir in animal populations. The clearest patterns are that helminths are overrepresented among zoonoses and that fungi are underrepresented. Also, zoonoses are more likely to be transmitted by indirect contact or by vectors, and are less likely to be transmitted by direct contact when compared with all pathogens (figure 1).

A total of 175 species of infectious agents from 96 different genera are associated with emerging diseases according to the criteria used here (electronic Appendix A). The number of emerging species in each of the major taxonomic divisions and their routes of transmission are shown in figure 1c. Overall, 44% of emerging species are viruses or prions, 30% are bacteria or rickettsia, 9% are fungi, 11% are protozoa and 6% are helminths. Some of these pathogens can be transmitted by more than one route, but overall 53% of emerging pathogens can be transmitted by direct contact, 47% by