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Source: *Philosophical Transactions: Biological Sciences*, Vol. 356, No. 1411, Population Biology of Emerging and Re-emerging Pathogens (Jul. 29, 2001), pp. 983-989
Published by: The Royal Society
Stable URL: http://www.jstor.org/stable/3066689
Accessed: 14/11/2008 04:05

THE ROYAL SOCIETY

doi 10.1098/rstb.2001.0888

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 & Schluederberg 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.* 1998*a*,*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 1*a*. Overall, 15% are viruses or prions, 38% are bacteria or rickettsia, 22% are fungi, 5% are protozoa

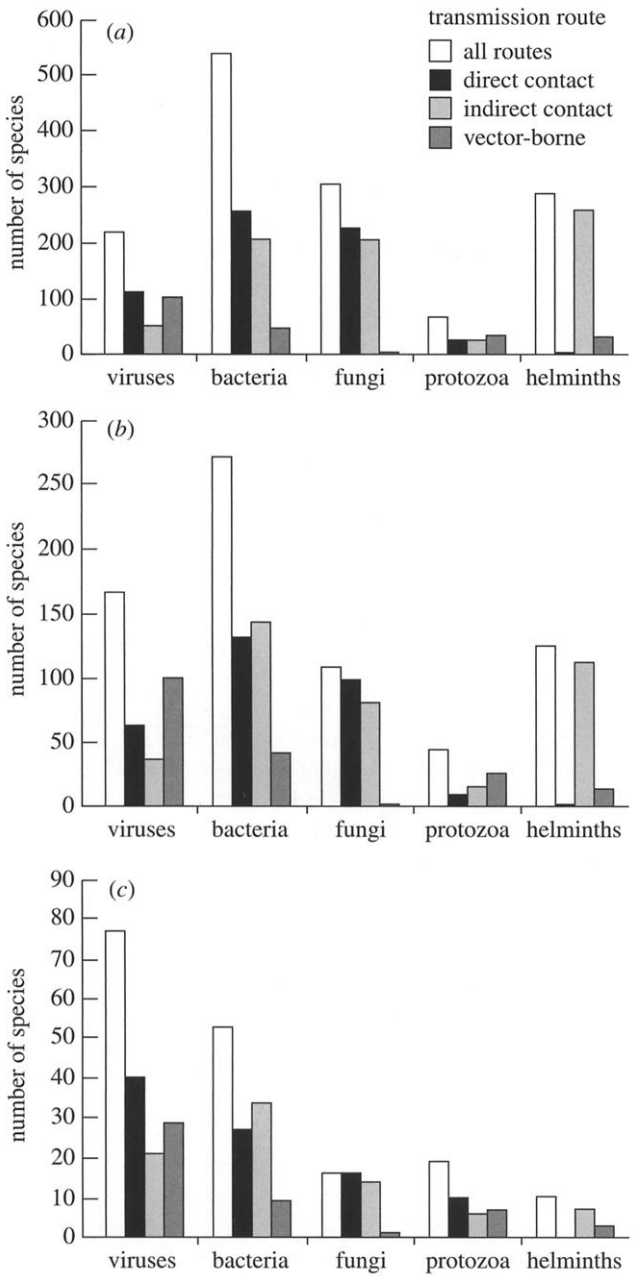

Figure 1. Numbers of species of infectious agent causing human disease, by taxonomic division and transmission route (noting that some species have more than one transmission route and for some the transmission route is unknown). (*a*) All infectious organisms ($n = 1415$). (*b*) Zoonotic organisms ($n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

Table 2. Ranking of categories according to the proportion of species associated with emerging diseases.

(Species in the database fell into 26 categories, seven of which were excluded as they contained less than ten species.)

transmission route	zoonotic status	taxonomic division	total number of species	number of emerging species	proportion of species emerging
indirect contact	zoonotic	viruses	37	17	0.459
indirect contact	zoonotic	protozoa	14	6	0.429
direct contact	zoonotic	viruses	63	26	0.413
direct contact	non-zoonotic	protozoa	15	6	0.400
indirect contact	non-zoonotic	viruses	13	4	0.308
direct contact	non-zoonotic	viruses	47	14	0.298
vector borne	zoonotic	viruses	99	29	0.293
vector borne	zoonotic	bacteria	40	9	0.225
indirect contact	zoonotic	bacteria	143	31	0.217
vector borne	zoonotic	protozoa	26	5	0.192
direct contact	zoonotic	bacteria	130	20	0.154
indirect contact	zoonotic	fungi	85	11	0.129
direct contact	zoonotic	fungi	105	13	0.124
vector borne	zoonotic	helminths	23	2	0.087
direct contact	non-zoonotic	bacteria	125	7	0.056
indirect contact	non-zoonotic	bacteria	63	3	0.048
indirect contact	non-zoonotic	fungi	120	3	0.025
direct contact	non-zoonotic	fungi	123	3	0.024
indirect contact	zoonotic	helminths	250	6	0.024

indirect contact, 28% by vectors, and for 6% the transmission route is not known.

Risk factors for emergence were first analysed separately and the relative risks are presented in table 1*a*. One hundred and thirty-two emerging pathogen species (75%) are zoonotic (electronic Appendix A). This is substantially more than expected if zoonotic and non-zoonotic species were equally likely to emerge, and corresponds to a relative risk of 1.93. This result is retained when the analyses are repeated at the genus rather than the species level; 78 out of 96 emerging genera are zoonotic (81%), compared with 235 out of 376 non-emerging genera (62%). This corresponds to a relative risk of 2.20, similar to that for species, suggesting that the result is robust. However, different risks of emergence are also associated with different taxonomic divisions; viruses and protozoa are overrepresented and fungi and helminths are underrepresented among emerging species (electronic Appendix A). A higher risk of emergence is also associated with vector-borne transmission. These analyses suggest that zoonotic pathogens are more likely to emerge than non-zoonotic pathogens, but that the strength of the effect may be affected by pathogen taxonomy and transmission routes.

Pathogen taxonomy, zoonotic status, and transmission routes are not independent (figure 1). For example, virtually all helminths are zoonotic and transmitted by indirect contact and there are very few vector-borne fungi. To investigate how these different risk factors combine to affect the likelihood of pathogen emergence, two approaches were taken. First, the effect of zoonotic status within individual taxonomic and transmission route categories was investigated (table 1*b*). The effect of zoonotic status varies markedly among the taxonomic groups. Zoonotic bacteria and fungi were more than three times as likely to emerge than non-zoonotic bacteria and fungi (relative risks of 3.79 and 7.14, respectively). However, the opposite was true for helminths with zoonotic species far less likely to emerge than non-zoonotic ones (relative risk of 0.19). For viruses and protozoa, zoonotic status appears to make little difference to the risk of emergence (relative risks of 0.96 and 0.74, respectively). Zoonotic pathogens show a higher probability of emerging if they are transmitted by direct or indirect contact (relative risks of 2.13 and 2.60, respectively), but among vector-borne pathogens zoonotic status made virtually no difference (relative risk of 0.97). Second, all species were divided into categories based on taxonomic division, transmission route and zoonotic status (table 2). Categories with less than ten species were excluded and the rest ranked by the percentage of species emerging. The most striking result is that viruses and protozoa account for all of the top seven categories, all with more than 29% of the species emerging. The next strongest pattern was that zoonotic pathogens tended to rank above non-zoonotic pathogens, although zoonotic helminths transmitted by indirect contact showed a very low proportion of emerging pathogens (2%). No obvious pattern was seen associated with route of transmission.

4. DISCUSSION

The majority of pathogen species causing disease in humans are zoonotic (868 species, i.e. 61% of the total; electronic Appendix A). In agreement with the original hypothesis, zoonotic species are overall twice as likely to be associated with emerging diseases than non-zoonotic species. However, more detailed analysis shows that there are also very strong effects of taxonomy on the probability that a pathogen will be classed as emerging. Viruses and protozoa are especially likely to emerge and helminths

very unlikely to emerge irrespective of their transmission routes or zoonotic status. Our attempt to identify risk factors for emergence points strongly towards taxonomic and zoonotic status effects.

Interpretation of these results is complicated by uneven distributions of organisms across the taxonomic divisions, transmission routes and zoonotic status, and non-independence between these variables. Helminths are especially likely to be associated with zoonoses: 95% of helminth species pathogenic to humans are known to be zoonotic, compared with 76% of viruses and prions, 65% of protozoa, 50% of bacteria and rickettsia, and just 38% of fungi. In addition, zoonoses are relatively likely to be transmitted indirectly (including transmission by intermediate hosts) or by vectors, suggesting that these transmission routes may be associated with lower host specificity (Woolhouse *et al.* 2001). These two observations are not independent; for example, almost all helminths are transmitted by these routes. The observation that the route of transmission of over 200 human pathogens (both zoonotic and non-zoonotic) remains unknown emphasizes the need for improved understanding of the biology of infectious agents in general.

An additional factor that may be involved in emergence is transmissibility between humans, because the incidence of new infections can also be highly sensitive to small changes in transmission rates within a local human population. Rigorous analysis is precluded by the absence of data: for 620 species of infectious agents (44%) the cited references contain no information on whether they are transmissible between humans. However, for species where information is available, the pattern is highly suggestive. Human-to-human transmissibility is a risk factor for emergence across all pathogens, with a relative risk of 2.60.

The most important finding reported here is that emerging pathogens are not a random selection of all human pathogens. The next challenge is to explain why some kinds of pathogen—such as zoonotic viruses and protozoa transmitted by indirect contact (table 2)—are likely to emerge while others are not. It must be emphasized that disease emergence is to some extent subjectively defined and so any analysis is prone to biases in reporting, recognition and the availability of information, as may be associated with different taxa or different geographical regions. Indeed it is sometimes suggested that emerging disease trends at least partly reflect biases among the research community. Nonetheless, we anticipate that pathogen biology also contributes to the likelihood of emergence, including such factors as genetic diversity, generation time and existence of a reservoir (whether zoonotic or environmental).

This study considers the diversity of pathogens causing disease in humans, and not the public health burden imposed by these diseases. Although mortality and morbidity estimates are now available for some common infectious diseases (Murray *et al.* 1994; Murray & Lopez 1996), such data cannot always be attributed to individual species of pathogen and the health burden for the vast majority of human pathogens remains completely unquantified. Moreover, the importance of zoonoses is often to be found in the origins rather than the severity of disease outbreaks. While direct transmission from animals is important for some zoonotic pathogens, such as rabies, *Brucella melitensis* and *Mycobacterium bovis*, for others, such as influenza A and Dengue, transmission from animals is important mainly in the origin of outbreaks; the majority of humans are infected by other humans. This argument is well illustrated by the HIVs: these viruses emerged into humans from a primate reservoir, but rapidly evolved and are no longer regarded as zoonotic. Nonetheless, animal and human diseases can be closely associated; recent examples include Rift Valley fever in Kenya and Somalia (WHO Press Release 1998), Nipah virus in Malaysia and Singapore (Chua *et al.* 2000), West Nile virus in the United States (Lanciotti *et al.* 1999) and Hendra virus in Australia (Westbury 2000). The management of these pathogens poses challenges outside the scope of traditional medical practice and demands a much closer collaboration between medical and veterinary researchers than has tended to occur in the past.

In conclusion, this study is, as far as we are aware, the first to identify risk factors for human disease emergence. This type of analysis, which, hopefully, will be refined and improved in the future, is essential if emerging diseases are not always to be regarded as a set of individual case studies with no underlying general principles.

We are very grateful to Professor R. W. Ashford (Liverpool School of Tropical Medicine, UK) for access to data on human parasites prior to publication and to Dr M. K. Laurenson, Dr L. Matthews and Professor R. W. Ashford for discussions and comments on the manuscript. Dr C. Büchen-Osmond (now at Biosphere 2 centre, Columbia University, USA) provided valuable clarification on virus nomenclature and access to data prior to publication on the Web. Two anonymous referees provided very helpful comments. L.H.T. holds a UK Wellcome Trust Veterinary Research Fellowship.

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