

## Where Do Emerging Pathogens Come from?

Understanding the origins of pathogens will help us to combat emerging infectious diseases

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**I**nfectious diseases continue to impose a huge global public health burden, accounting for more than one-quarter of all deaths annually and a similar fraction of morbidity. In addition to long-established infections such as malaria, tuberculosis, and measles, we are also seeing the frequent emergence of new infectious diseases: HIV/AIDS was unknown 25 years ago and is now one of the biggest killers; the virus responsible for severe acquired respiratory syndrome (SARS)

caused a minor public health problem but still had severe economic repercussions for affected countries; and there is considerable concern about the possible emergence of a new subtype of influenza A, with potentially devastating, global consequences.

The evolving nature of infectious disease problems is a challenge to microbiologists on several different levels. There are practical challenges, such as developing diagnostics, treatments, and vaccines, and of designing effective surveillance and intervention strategies. Plus, there are intellectual challenges, including understanding the complex and multifaceted causes of the emergence and spread of new pathogens and the reemergence of those previously thought to be in decline. Neither the practical nor intellectual challenges are likely to be met without developing more effective working partnerships among those in various disciplines, at different institutions, and living in different nations.

### Summary

- Emerging and re-emerging infectious diseases pose both practical and intellectual challenges, including understanding their complex causes; developing diagnostics, treatments, and vaccines; and designing effective surveillance and intervention strategies.
- Of the catalogued pathogen species that infect humans, 538 are bacteria, 317 are fungi, 287 are helminths, 208 are viruses, and 57 are protozoa; among those associated with emerging and re-emerging infectious disease, viruses are significantly over-represented, whereas helminths are under-represented.
- Species jumps by pathogens require both the opportunity and capacity to infect a new host species; recent species jumps have usually involved RNA viruses, perhaps because their genetic lability allows them to adapt quickly to a new host species.
- Recently emerging or re-emerging pathogens most often are RNA viruses having a taxonomically broad host range, using a phylogenetically conserved cell receptor, being transmissible between humans, and occurring in regions undergoing ecological, demographic or social change.

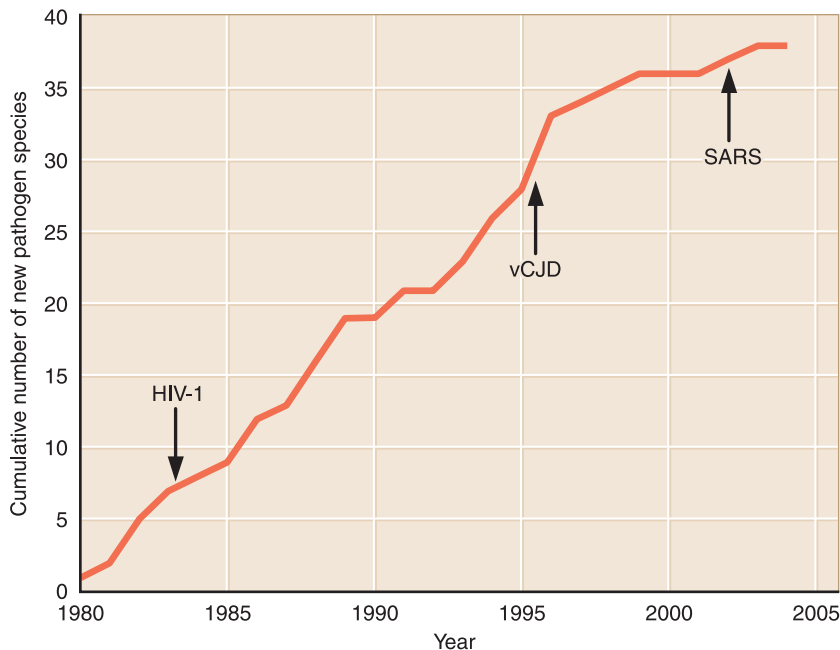
### Pathogen Diversity

A human pathogen can be defined as “a microbial or parasite species that can infect and is capable of causing disease in humans under natural transmission conditions.” Humans are affected by an impressive diversity of pathogens. My colleagues Sonya Gowtage-Sequeira, Ben Evans, and I recently surveyed the recent literature, building on earlier work by Louise Taylor and Sophie Latham, and found 1,407 currently recognized species of human pathogen.

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FIGURE 1



The accumulation of newly reported human pathogen species since 1980. The total of 38 species includes only those associated with emerging infectious disease problems; newly recognized etiological agents of existing disease problems (e.g. *Helicobacter pylori*, associated with peptic ulcers, or metapneumovirus, causing respiratory infections) are excluded. Also excluded are novel variants of known species, such as the O157:H7 serotype of *E. coli* and the H5N1 subtype of influenza A virus. The dates of emergence of some key examples discussed in the text are highlighted.

Of course, a species count provides only a simple measure of pathogen diversity. Much medically important variation—in traits such as virulence factors, immunogenicity, and drug resistance—occurs within pathogen species as well as between them. However, focusing on species proves revealing. Of the catalogued pathogen species that infect humans, 538 are bacteria, 317 are fungi, 287 are helminths, 208 are viruses, and 57 are protozoa. Within this taxonomic diversity, individual species manifest a wide variety of life cycles, transmission routes, pathogenicities, and epidemiologies.

We are particularly interested in pathogens associated with emerging and reemerging infectious diseases. These are defined by the Centers for Disease Control and Prevention (CDC) as “diseases of infectious origin whose incidence in humans has increased within the past two decades or threatens to increase in the near future.” Of the species in our survey, 177 cause diseases that are regarded as falling into this

category, with viruses significantly overrepresented and helminths underrepresented.

Within the scope of our survey, we found reports of 38 apparently novel human pathogen species associated with emerging diseases during the past 25 years (Fig. 1). Some species within this category likely were active before they were identified. For example, although HIV-1 was first reported in 1983, it is thought to have begun infecting humans several decades earlier. Two-thirds of these novel species are RNA viruses, a finding that may partly be due to ascertainment bias through improved viral diagnostics, especially PCR-based technologies. However, several inherent features of RNA virus biology may also help to explain why there are so many of them in this category.

### Importance of Animal Reservoirs

Relatively few pathogen species—perhaps no more than 100—do nothing other than infect and cause disease in humans. Many of them are commensals that do not ordinarily cause disease; many others are distributed in the wider environment such as water or soil; and yet others also infect host species other than humans.

The latter category constitutes the zoonoses, which the World Health Organization (WHO) defines as “diseases or infections which are naturally transmitted between vertebrate animals and humans.” Almost 60% of human pathogen species are zoonotic. A small minority of these, the “anthroponoses,” are mainly passed from humans to animals rather than the other way around: measles virus, for example, is essentially a human virus that also can infect great apes. But for hundreds of human pathogen species, an animal reservoir is an important feature of their biology.

The most striking feature of such animal reservoirs is their diversity. We share our pathogens with ungulates, carnivores, rodents, primates, sometimes other kinds of mammals such as bats, and also nonmammals, especially birds. Many of the reservoirs are domestic animals, but just as many are wildlife species. These pat-

terns apply to the whole range of pathogens from viruses to helminths.

Stephen Morse at Columbia University suggested more than 10 years ago that emerging and reemerging pathogens were disproportionately zoonotic, and subsequent research has confirmed his observation. Emerging and reemerging zoonoses are not associated with any particular animal reservoirs but they are associated with pathogens that can infect several different kinds of hosts.

Several recently emerged human pathogens illustrate these findings. Examples are the SARS coronavirus and the agent responsible for bovine spongiform encephalopathy (BSE), both of which are zoonotic and can infect a wide variety of animals and recently appeared in humans. Even some novel pathogens that are not now regarded as zoonotic, such as HIV-1, were acquired by humans from animals.

These are but a few recent examples of a process that has been going on for millennia. Jared Diamond of the University of California, Los Angeles, is among those who note that many of the most serious infectious diseases of humans, including measles, influenza, and smallpox, likely have animal origins.

### Invading New Host Populations

When a pathogen of one host species first invades a new one, it is called a “species jump” (see table). Successful species jumps require both the opportunity and capacity to infect new host species. Opportunity depends on the pathogen contacting the new host, perhaps through changes in the ecology or the behavior of either of the host species. The capacity to infect reflects whether the pathogen is compatible with its new host. Even so, the pathogen still may need to surmount a threshold, called the “species barrier,” generally meaning it cannot establish an infection unless the new host species is exposed to a higher dose than was required to infect its original host. For instance, this phenomenon holds for the rabies virus and the transmissible spongiform encephalopathies.

Those pathogens that already have a broad host range seem more likely to be successful at jumping into new host species than do pathogens with narrow host ranges. The determinants of host range, and so of a propensity for species

Pathogen	Original host	Year reported
Ebola virus	Bats(?)	1977
<i>Escherichia coli</i> O157:H7	Cattle	1982
<i>Borrelia burgdorferi</i>	Rodents(?)	1982
HIV-1	Chimpanzees	1983
HIV-2	Primates	1986
Hendra virus	Bats	1994
vCJD	Cattle	1996
Australian bat lyssavirus	Bats	1996
H5N1 influenza A virus	Chickens	1997
Nipah virus	Bats	1999
SARS coronavirus	Palm civets(?)	2003

jumps, are poorly understood. One key factor, at least for viral pathogens, appears to be their use of cell receptors that are phylogenetically conserved across a range of host species.

The ability to infect a host species is merely the first step; invading the new host species also depends on the ability to transmit between individual hosts within a species. Many emerging pathogens have no or very limited transmissibility between humans, including variant Creutzfeldt Jakob disease (vCJD), lyssavirus, influenza A subtype H5N1, and *Borrelia burgdorferi*, which causes Lyme disease. Other poorly transmitted pathogens cause self-limiting outbreaks, including Ebola virus and *Escherichia coli* O157:H7. Meanwhile, some pathogens such as the SARS coronavirus spread much more freely among their newly acquired human hosts.

The quantitative framework for evaluating the spread of infections through host populations is well developed. A key concept is the reproduction number,  $R_0$ , the average number of secondary infections generated by a single primary infection within a large population of previously unexposed hosts. Only if  $R_0$  is greater than 1—that is, if a primary infection generates more than one secondary infection—can a novel pathogen successfully invade a new host population. If  $R_0$  is close to 1, small changes in infection or transmission rates can lead to large changes in the potential for pathogen emergence.  $R_0$  could change if there were changes in the demography or behavior of the host population, changes in susceptibility of the host population due to decreased immunocompetence, failures of disease prevention or control programs, or changes to the pathogen itself.

Changes to the pathogens can prove critical,



according to Rustom Antia of Emory University in Atlanta, Ga. He argues that, even if  $R_0$  for a new pathogen in the human population is initially less than 1, each infection provides an opportunity for the pathogen to adapt to its new host and for  $R_0$  to increase. The likelihood of adaptation occurring is sensitive to the number of infections, the extent of genetic change required to affect susceptibility and transmissibility, and, especially, to the genetic lability of the pathogen. The importance of this last factor may help explain why so many recent species jumps (table) involve RNA viruses, which have mutation rates several orders of magnitude higher than other kinds of pathogen.

We are only beginning to understand the biological basis for pathogen adaptation to a new host. Several veterinary examples, including canine parvovirus, foot-and-mouth disease virus, and Venezuelan equine encephalitis virus, indicate that changes affecting only a small number of amino acids in, say, the viral proteins that determine cell receptor specificity may be all that is required for such viruses to gain a foothold in a new host species.

The most striking recent example of successful adaptation to humans is simian immunodeficiency virus. This pathogen, having entered the human population, rapidly evolved to become HIV-1. And the possibility of adaptation similarly underlies current concerns about H5N1 influenza A virus causing a pandemic.

### Drivers of Pathogen Emergence and Reemergence

A 2003 report by the Institute of Medicine, *Microbial Threats to Health: Emergence, Detection and Response*, lists three broad categories of factors that drive pathogen emergence and reemergence: those relating to hosts, those relating to pathogens, and those relating to the wider environment. Human factors include population growth, urbanization, population health, and hospitalization, travel, and migration patterns. Pathogen factors include capacities to adapt to humans and to acquire virulence factors and antibiotic resistance as well as failures of disease control programs. Environmental factors include land use, agricultural practices, production and supply of food and water, trade in animals or animal products, and climate change.

The diversity of these drivers is immediately

apparent, but it is striking how often pathogen emergence or reemergence is associated with human activity. For example, changes in feed production processes led to BSE in cattle and to vCJD in humans; the exotic pet trade led to monkeypox outbreaks in the United States; and harvesting bush meat is associated with early human cases of both HIV and SARS. The overall impression is that changes in the way humans interact with their environment, and particularly with animal populations both domestic and wild, can provide new opportunities for pathogens. Andrew Dobson of Princeton University in Princeton, New Jersey, likens emerging and reemerging pathogens to weeds because both are adaptable exploiters of unstable environments.

### Future Risks and Ways to Address Them

A recent report by the U.K. Office for Science and Innovation suggests that local and worldwide changes will continue to provide opportunities for pathogens to shift host species, meaning we can anticipate continued emergence and reemergence of infectious diseases. Perhaps the most striking feature of human pathogens is their diversity, making pathogen emergence extremely difficult to predict. The advent of BSE and vCJD is a good example of a completely unanticipated infectious disease problem. Even so, we have some idea of the most likely profile for emerging or reemerging pathogens:

- an RNA virus;
- a taxonomically broad host range;
- use of a phylogenetically conserved cell receptor;
- transmissible between humans but at first causing only small outbreaks; and
- occurring in regions undergoing ecological, demographic, or social change.

Refining our expectations of emerging pathogens will help us design effective surveillance programs. Surveillance is the first line of defense, making rapid detection and identification key priorities. Often, the single biggest factor affecting the scale of an epidemic is the speed with which initial events are detected and effective interventions are put in place. Because emerging and reemerging pathogens often have animal reservoirs, surveillance should be extended to

cover populations of livestock and wildlife. This strategy already proved appropriate for BSE as well as the West Nile, Rift Valley fever, and avian influenza viruses.

A particular concern is the impact of globalization on the spread of infectious diseases. This trend includes not only people but also the growing trade in livestock, bush meat, and exotic pets, all of which pose risks to human health. Effective international cooperation, including the timely sharing of data and biological specimens, is essential. The WHO global program to combat SARS indicates what can be achieved. However, many poorer regions of the world cannot contribute to this or similar programs without significant external investment in infrastructure, technology, and human capacity. We would all benefit from such investments.

Moreover, we need more effective communication and cooperation between those working in human and animal health. We tradition-

ally draw a sharp boundary between these sectors, but pathogens do not recognize that boundary. Indeed, humans share the majority of their pathogens with a wide range of other animals, and jumps by pathogens into human populations from animal reservoirs are frequent and natural. In many cases the expertise relevant to an emerging human infectious disease problem will be found not in the medical community but among veterinarians; this was the case for vCJD (a transmissible spongiform encephalopathy), HIV (a lentivirus) and SARS (a coronavirus). In the 1960s Calvin Schwabe, a veterinarian and epidemiologist at the University of California, Davis, coined the term “One Medicine,” to emphasize how much human and veterinary medicine have in common. Following a one-medicine philosophy will be essential if we are to deal effectively with future infectious disease challenges.

#### SUGGESTED READING

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