

## Emerging infectious diseases

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#### Abstract

The spectrum of human pathogens and the infectious diseases they cause is continuously changing through evolution, selection and changes in the way human populations interact with their environment and each other. New human pathogens often emerge or re-emerge from an animal reservoir, emphasizing the central role that non-human reservoirs play in human infectious diseases. Pathogens can also re-emerge with new characteristics, such as multidrug resistance, or in different places, such as Ebola virus in West Africa in 2013 and Zika virus in Brazil in 2015, to cause new epidemics. Most human pathogens have a history of evolution in which they first emerge and cause epidemics, become unstably adapted, re-emerge periodically and then – without intervention – eventually become endemic, with the potential for future outbreaks.

#### Keywords

Drivers of emergence; emerging infections; hotspots for emergence; species jump; zoonosis

#### Key points

- Infectious diseases are continuously emerging
- Most known human pathogens are zoonoses, and most that are not have zoonotic origins
- Globalization and human invasiveness creates more opportunities for emergence
- Global surveillance and research consortia and novel technologies will allow for more frequent and more rapid detection of novel pathogens
- A more proactive approach to mitigation of emergence events is required

## Introduction

In the 1970s, with antibiotics and vaccines at hand and the eradication of smallpox within reach, there was a general optimism that infectious diseases would soon be a thing of the past. In 1972 the Nobel laureate Macfarlane Burnet concluded that: 'If ... we retain a basic optimism and assume no major catastrophes occur and that any wars are kept at the 'brush fire' level, the most likely forecast about the future of infectious disease is that it will be very dull'. The pandemic of HIV crushed this optimism, and infectious diseases were put back on the global health agenda, of which the 1992 publication *Emerging Infections: Microbial Threats to Health in the United States*<sup>1</sup> has been a landmark. Since then, the emergence of antimicrobial resistance among many different pathogens, including against last-resort antibiotics, the continuous emergence of (mostly) viruses with potential for human-to-human or pandemic spread, and the intentional release of pathogens as terrorist weapons are continuously reminding us that infectious diseases are actually far from dull.

## Definitions

'Emerging infectious diseases' are defined as 'those whose incidence in humans has increased within the past two decades or threatens to increase in the near future. Emergence can be from the spread of a new agent (including known agents with a new resistance mechanism), from recognition of an infection that has been present but undetected in the population, or from the realization that an established disease has

an infectious origin. Emergence can also be used to describe the reappearance (or re-emergence) of a known infection after a decline in incidence.<sup>1</sup>

## Zoonotic emergence

### Pathogen

There are >1400 known human pathogens, most (60%) of which are transmitted to humans zoonotically and depend on an animal reservoir for survival. An additional smaller proportion (5–10%) is environmentally transmitted, and the remainder consists of pathogens that can be maintained by an exclusively human-to-human transmission cycle. Among emerging infections, the proportion of zoonotic infections is even higher (73%), indicating that the human–animal interface presents a risk for emergence.<sup>2</sup> In addition, almost all (now) established strictly human pathogens have zoonotic origins:<sup>2,3</sup> these pathogens have moved from animals into humans and fully adapted to them during many millennia of human and pathogen evolution.

### Human

Because most human pathogens rely on an animal or environmental reservoir, the interactions between human populations and their surrounding ecosystem determine the local pathogen spectrum, and the interpopulation interactions determine the spread of these pathogens. Historically, there have been several profound and distinct transitions in human environmental and interpopulation interactions that have radically changed the spectrum and causes of infectious disease in human populations (Table 1). Today, we are living through the fourth great historical transition. The invasiveness of human activity into all geographical areas of the world, the globalization of economic activities and culture, the speed and accessibility of distant contact, the spread and intensification of urbanization, and our increasing reliance on either intricate or massive technology, are reshaping the relations between humans and microbes.<sup>4</sup>

### The species jump

The jump between species that initiates a first human infection by a new agent is often brought about by a novel or unusual physical contact between potential pathogen and human. Such contacts usually occur because of cultural, social, behavioural or technological change on the part of humans that affects the human–animal interface. The potential for subsequent spread of this ‘new’ infectious disease depends on many different factors, including environmental or social factors. These changes and factors (Table 2) are the drivers of emergence.<sup>1</sup>

Rather than being a single event, biologically the species jump is often more a transition process involving several stages (Figure 1). The pathogen has to overcome various biological barriers (interspecies, intrahuman, interhuman) to move from one stage to the next, to be able finally to cause sustained human-to-human transmission. Based on data from 1940 onwards, the hotspots for emergence of infectious diseases were mapped for zoonotic infections from wildlife and domestic animals, and for drug-resistant and vector-borne organisms. Figure 2 shows that these hotspots are primarily located in South and South-East Asia, South and Central America and Sub-Saharan Africa.<sup>5</sup>

Various international consortia and large research programmes have been established in an attempt to predict and prevent, or prepare for and mitigate, these novel emergence events. Technical advances enable us to detect, characterize and trace these agents much more rapidly than ever before. However, experience shows us that we have not been able to appropriately predict, anticipate or tackle emergences of unknown pathogens such as Middle East respiratory syndrome coronavirus, known pathogens such as Ebola and Zika virus, or even the annual reappearance of H7N9 influenza in China. A more proactive approach, for example using platform technologies to develop libraries of vaccines and monoclonal agents that can be mass-produced when needed, is therefore warranted.

## Non-zoonotic emergence

The emergence of novel zoonotic pathogens is appealing to the imagination and draws plenty of popular and scientific media attention, but does not necessarily represent the largest threat from infectious diseases. There is a rapid and increasing spread of antimicrobial drug resistance among bacteria and other pathogens. Drug resistance is a threat to the successful treatment of not only HIV, malaria and tuberculosis, but also hospital- and community-acquired infections caused by ‘normal’ Gram-positive and

Gram-negative bacteria; these have been predicted to have a major economic impact if not addressed. This has been recognized as a global public health emergency, requiring a global effort to raise awareness, implement regulation and develop novel antibiotics or alternative approaches to prevention and treatment.

Failure of vaccination programmes because of bad press or religious conviction in developed countries can within years cause re-emergence of highly infectious viruses, such as those causing measles or rubella, as has happened in the USA and Europe. Global food production and distribution processes can give rise to widely disseminated foodborne infections that are hard to tackle, and to rapid spread of bacteria with novel resistance mechanisms. Finally, in the Asia-Pacific region, although avian influenza viruses attract most international attention, hand, foot and mouth disease, caused by a fluid spectrum of non-polio enteroviruses, is associated with hundreds of thousands of hospitalizations of children < 5 every year; this includes with neurological and cardiopulmonary complications and a mortality of around 0.1%, showing that humans can also be a source of emerging infections (Table 3).

### The role of the doctor

In daily medical practice, it is important that doctors, especially infectious disease physicians, are aware of emergence events and countries where processes of emergence and species-jumping are occurring (e.g. by subscribing to ProMED, the World Health Organization influenza update, International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) or others). It is crucial that each patient's history should include a travel history, which involves more than asking for the countries the patient has visited. In the end, despite sophisticated surveillance programmes, it is usually an astute clinician who, after having seen or heard one or two extraordinary patient histories, makes the connection and sees the first signs of an event of emergence.

### Transitions in human environmental and interpopulation interactions through time

Transition, time	Major change
Prehistoric transition, millions of years ago	From tree-dwelling to savannah, hunter-gatherer
Historic transitions	
•First (local), 5000–10,000 years ago	Settlements, crop and livestock domestication
•Second (continental), 1000–3000 years ago	Intracontinental military and commercial contacts
•Third (intercontinental), from AD 1500	European exploration and imperialism
•Fourth (global), today	Globalization, urbanization, climate change

**Table 1**

## **Biological, social and environmental drivers of emergence of infectious disease**

- Microbial adaptation and change
- Susceptibility to infection
- Climate, weather and the environment
- Economic development and land use
- Human demographics and behaviour
- Technology and industry
- International travel and commerce
- Breakdown in public health
- Poverty and social inequality
- War and conflict
- Urban decay
- Lack of political will
- Intentional biological attacks

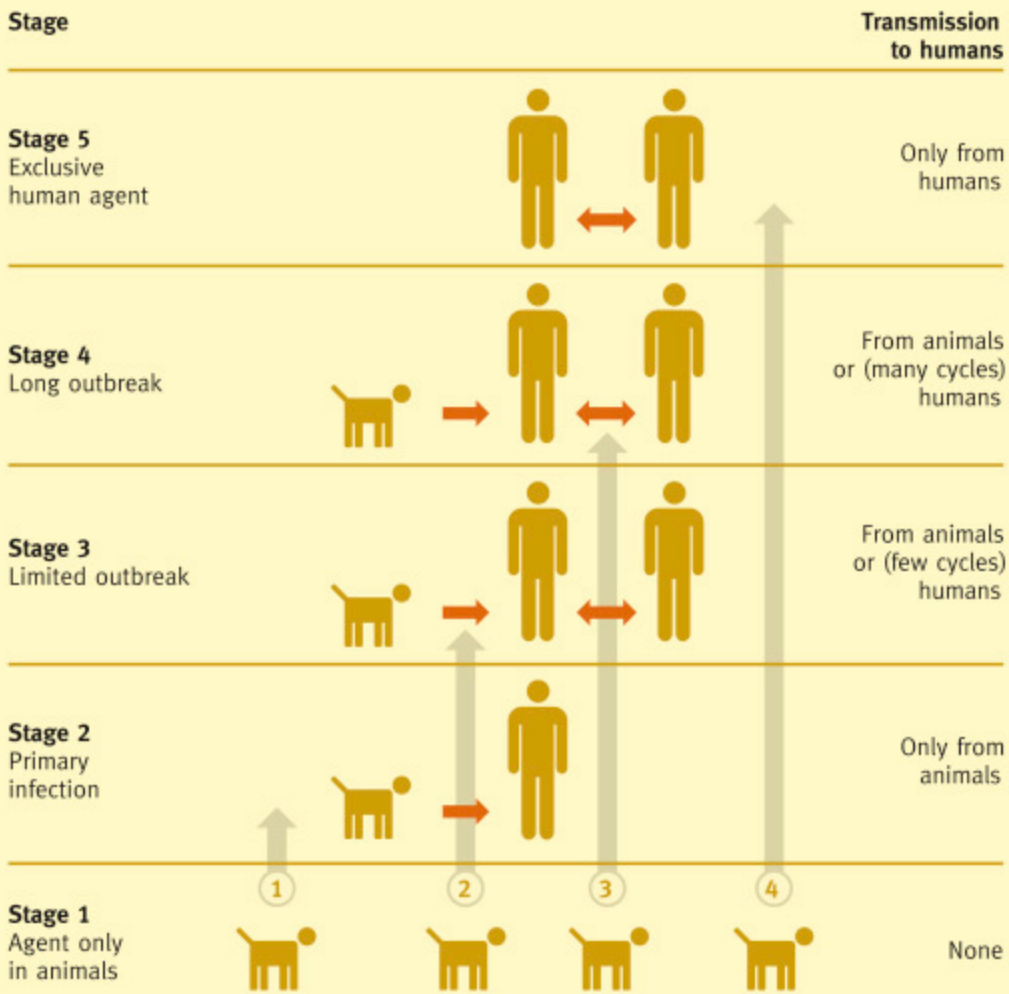
**Table 2**

### Selection of important emerging infectious diseases since 2003

2016	Plasmid-mediated colistin resistance in Enterobacteriaceae
2015	Zika virus
2013	Ebola virus in West Africa
	Influenza virus A/H7N9
2012	Middle East respiratory syndrome coronavirus
2011	<i>Escherichia coli</i> O104:H4
2010	New Delhi metalloprotease-associated carbapenem resistance in Enterobacteriaceae
	Huaiyangshan virus, associated with severe fever and thrombocytopenia syndrome
2009	Influenza virus A/H1N1pdm09
2008	Artemisinin-resistant <i>Plasmodium falciparum</i>
	<i>Plasmodium knowlesi</i>
	Lujo virus
2006	Extensively drug-resistant <i>Mycobacterium tuberculosis</i>
2005	Human retroviruses HTLV3 and HTLV4
2004	Re-emergence of influenza virus A/H5N1
2003	Severe acute respiratory syndrome coronavirus

**Table 3**

**The five stages through which pathogens of animals evolve to cause diseases confined to humans<sup>6</sup>**



Vertical grey arrows represent (from left to right): (1) rabies (dead-end transmission to human through bites of infected dogs or bats); (2) Ebola virus (transmission to humans through contact of hunters with infected gorillas or chimpanzees followed by several cycles of human-to-human transmission that suddenly stop); (3) yellow fever (mosquito-borne transmission from monkeys to humans that can be maintained from human to (mosquito) to human for many cycles (in contrast to Japanese encephalitis virus, which is transmitted by mosquitoes from an avian or porcine reservoir to humans but is – due to low viral load in blood – not transmitted from human to mosquito)); and (4) HIV (several transmission events of related viruses from apes and monkeys to humans followed by sustained local and pandemic human to human transmission).

Figure 1

Source: Adapted from Wolfe ND et al. Origins of major human infectious diseases. Nature 2007; 447(7142): 279–83.

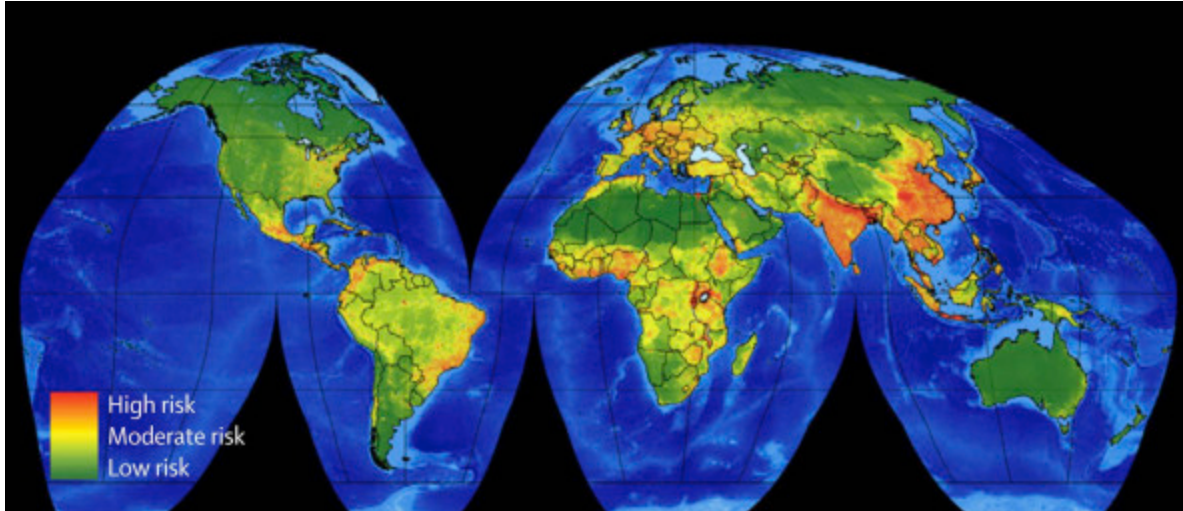


Figure 2  
Global hotspots for emerging diseases originating in wildlife.

Source: From Morse SS, Mazet JA, Woolhouse M, Parrish CR, Carroll D, Karesh WB et al. Prediction and prevention of the next pandemic zoonosis. *Lancet*. 2012 Dec 1; **380**: 1956–65. With permission from Elsevier.

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