Anatomy of a pandemic

For millennia, human beings have been plagued by pathogens originating in other animal species. Pathogens that are now endemic in human beings, such as measles and smallpox, evolved from wildlife microbes that exploited our successful development for their own global spread.[1] Zoonotic diseases have had a substantial effect on our social, cultural, and economic development. When these diseases first began to emerge is unknown,[2] but causal factors include large-scale ecological and demographic changes, such as the domestication of livestock[3] and the formation of dense human populations around 10 000 years ago.[4] As human societies have developed, pathogens from animal hosts have continued to spill over into our population: the Justinian Plague (541–542 AD), the Black Death (first introduced into Europe in 1347), yellow fever in South America in the 16th century, the global influenza pandemic in 1918, and modern pandemics such as HIV/AIDS, severe acute respiratory syndrome (SARS), and triple-reassortant A H1N1 influenza. The *Lancet* Series on zoonoses[5–7] reassesses our relationship with zoonoses, and the human societal developments that drive their emergence. This Series addresses key questions about zoonotic pathogens. What factors underpin their ecology and transmission? How can we predict their emergence? What is our global strategy to prevent the next zoonotic pandemic? To answer these questions, we must dissect the anatomy of a pandemic to identify its origins and the causes of its emergence.

Emerging zoonoses are the product of socioeconomic and anthropogenic environmental changes. For example, the domestication of livestock that led to the emergence of measles is paralleled by more recent intensification of global food production that contributed to the emergence of variant Creutzfeldt-Jakob disease and other zoonoses.[8] Expansion of road networks, development of agricultural land, and intensification of wildlife trade have caused novel pathogens to emerge from wildlife (eg, Nipah virus, SARS, and HIV). Furthermore, the expansion of trade routes, which contributed to the spread of Black Death in the 14th century and the emergence of smallpox in the Americas in the 16th century, has continued in the era of globalisation, with the concomitant spread of SARS, West Nile virus, influenza A H5N1, and monkeypox. We have become a dense globally connected network of human beings vulnerable to the rapid spread of new zoonoses.

To dissect the origins of a pandemic, we need ecological methods that can be used to explain how populations of host species and their microbes are altered by social and environmental changes. These methods model disease spillover from wildlife,[9] retrace the origins of infectious disease,[10] classify and analyse their causes,[11] and measure how social networks affect the spread of disease.[12] The field of disease ecology provides a way to predict the risk of spillover and spread of known zoonotic disease, but can it be adapted to anticipate future pandemic zoonoses, which are usually caused by unknown vertebrate pathogens? In *The Lancet*, Stephen Morse and colleagues[7] outline the new science of predicting pandemics. Meta-analyses can be used to identify pandemic hotspots by first establishing the geographical origins of the 400 diseases that have emerged in human beings in the past few decades. These data are then corrected for observer bias to account for differences in the capacity of countries to conduct disease surveillance. Data on disease origin can then be correlated with key socioeconomic and ecological drivers. Hotspots identified so far include areas of the tropics with high wildlife diversity and dense populations, and parts of Europe and North America.[13] One part of our solution to the next pandemic is therefore to focus global resources for surveillance and pathogen discovery to hotspots, as the US Agency for International Development PREDICT programme now does.[14] To identify future pandemics, targeted surveillance programmes should screen the wildlife species that

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Fruit bat (*Pteropus vampyrus*), a host for Nipah virus

are known to harbour pathogens that have previously emerged and focus efforts on the regions where most contact between wildlife and humans occurs.

A microbe in a primate population is more likely to become zoonotic than is a microbe from a rodent, because we are more likely to have similar cell surface receptors to the primate owing to our shared evolutionary history. But at what point does contact override phylogeny? If a hunter catches a primate once a year, but the staple diet in his village is bush rats, which of these is the high-risk species? These are the questions that disease ecologists can answer, and that are being applied to the new science of pandemic prediction. However, the prediction and prevention of a pandemic is not straightforward. Although molecular techniques exist that can identify novel microbes carried by these high-value wildlife targets, our predictive ability can be overwhelmed by the many novel microbial sequences discovered. For example, how can we identify, from the genetic sequences of ten new paramyxoviruses from bats, which one is most likely to be a virulent pathogen of human beings, capable of spillover and sustained human-to-human transmission? This is the biggest of the grand challenges for pandemic prevention, and one that I believe we are not strategically addressing. Morse and colleagues[7] describe a strategy for the so-called known unknowns—novel microbes closely related to known agents. But what of the unknown unknowns—novel microbes that have no known close relative? This challenge, of prediction of viral virulence from a sequence, for example, should be a major focus of basic virology research in every developed country.

A global programme for pandemic prevention based on improved risk forecasting, surveillance, and pathogen discovery will be expensive. Who should pay and how would it work? The answer might lie in the underlying socioeconomic drivers of disease emergence. Pandemics are a product of our economic development—they emerge when we domesticate new species, open up new trade routes, build roads into forests, or expand air travel networks. Perhaps these industries should insure themselves against the rare but devastating pandemics their activities can sometimes cause. Additionally, health-impact assessments, already used in many large development projects, could calculate and assess the pandemic risk of a project. The ultimate public health programme would work with, and be funded by, high-risk development projects to develop better clinics, pathogen discovery, and surveillance programmes that prevent pandemics at their source.

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I declare that I have no conflicts of interest.

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