



The first step in the success or failure of emerging pathogens

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"In order to understand the dynamics of infectious disease outbreaks in humans, we really need to understand the dynamics of the pathogen in nature."* Over the last decade, I have heard one particular gray-haired ecologist repeat this every chance he gets, for one good reason: It is true. Understanding how pathogens work in natural settings can inform us what consequences may lie ahead if a particular pathogen jumps from one species to another. Outbreaks start with the first or index case in a species. The pathology of the disease agent in that case will determine the fate of that pathogen in its new host species. Mollentze et al. (1) use a meta-analysis of infection challenge data to predict the likely significance, in terms of pathology, of a transspecies infection. This study has particular relevance for rabies and may highlight general implications for other infectious diseases jumping species. At the very least, beyond rabies, it provides an excellent framework for predicting transspecies pathologies for infectious diseases.

Successful establishment of the index infection is reliant on complementary host and pathogen attributes. Pathogens have a finite, often streamlined, genetic code, which has evolved to take advantage by evading, attacking, or hijacking the host's immune system. Coevolution hones the pathogen's phenotype toward sustainable exploitation of its host's population. When a pathogen jumps into a new host species, the outcome of that infection and its significance to the new host species is largely cryptic, ranging from benign to disastrous. Some of these outcomes can be predicted using laboratory infection studies across species. Moreover, larger studies or meta-analyses across studies can help us predict and assess risks involving transspecies infections (1). I will discuss some of the other aspects of pathogen biology, ecology, and evolution which precede and follow a pathogen jumping species.

Novel Pathogens Are Often Derived from Other Species

Pathogens do jump around between species. In fact, the majority of infectious diseases circulating

in humans around the globe have zoonotic origins. If there is an infectious disease going around, there is a good chance it derived from a wild or domestic animal population. For emerging infectious diseases an estimated 60.3% of these are zoonotic in origin, and most of these are from wildlife (2). With over 7.5 billion people on Earth and increasing, it stands to reason that more people will mean more contact with wildlife reservoirs, which may lead to more emerging infectious diseases entering the human population.

Pathogens Are Not Equal across Species

A pathogen entering a new host species may not follow the same pathology it expressed in its former host. Pathogens and their attributes like virulence, duration of infection, symptomology, and so on are the cumulative products of their genome where selection has taken place through past infection and transmission cycles. A given pathogen, which has a specific reservoir species, will have a phenotype that optimizes its chance for transmission within the context of its host species and greater ecology. When a pathogen jumps into a new species there are often mismatches simply because the pathogen and host are novel to one another. Mismatches can result in longer or shorter infections, higher or lower rates of transmission, and so forth, ultimately affecting the success of the pathogen in its new host species.

Pathogen Success and Failure

Culturally, pathogens tend to evoke the fear of unknown outcomes on personal and societal levels. Zoonotic diseases with high mortality like bubonic plague, Ebola, Middle East respiratory syndrome, and so on have spilled over into human populations through the human/wildlife interface with explosive results. Most likely, pathogens moving across from one species to another are very often failed transmission events. Perhaps these start index infections,

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but onward transmission is likely often thwarted by unfavorable pathologies.

Plague is caused by the bacterium *Yersinia pestis* and likely first evolved from its ancestor *Yersinia pseudotuberculosis* into a new species during the Bronze Age (3). Today, despite a high degree of genetic similarity, marked differences in pathology (mortality) appear among strains isolated from different species of rodents (4). In part this can be due to host physiology, yet factors like sociality, population density, and dynamics can play an important role in transmission and hence will have selective effects on the agent's phenotype and greater pathology (5).

Pathology can even change on much smaller time scales. For instance, outbreaks of Ebola viruses have demonstrated significantly different mortality rates among lineages during a single outbreak. Interestingly, in one single outbreak in Sierra Leone, lineages of Ebola virus had evolved to be less lethal (6). Whether or not this was an adaptive process will remain cryptic as public health has a large effect on preventing new diseases from establishing.

Obligate pathogens (those which rely on a host to perpetuate) tend to evolve to be less virulent, reducing morbidity and mortality to optimize transmission, which often is realized with longer infection periods to maximize contact and transmission to new hosts. Yet, the process of a pathogen becoming less harmful to its host can be a very morbid process.

Take the introduction of myxomatosis virus into the feral rabbit population in Australia, where the first waves of the disease had a greater than 99% mortality, decimating a population of some 500 million rabbits (7). At this point highly virulent strains could spread easily because of large, dense populations of rabbits and ample insect vectors (mosquitoes). As a result of the population crash, fewer hosts meant lower chance of the virus transmitting to its next host. Highly virulent strains had short infections, allowing little time for transmission. Highly virulent strains basically burned out, while concurrently the pathogen selected for hosts with more resistance to the infection (8).

Similarly, initial waves of a new disease can be devastating to human society. Unknown pathologies, disease outcomes, and routes of transmission can paralyze the flow of everyday life, regardless of realized morbidity and mortality. Yet, in the circumstances where highly virulent infectious diseases meet dense, highly connective populations the impact can be dramatic. When plague swept through Europe with the Black Death in the 14th century it killed somewhere between 75 and 200 million people. While it persisted in Europe and the Middle East over the next 300 y the frequency and magnitude of plague epidemics diminished. Subsequent waves of infectious diseases tend to have less of an impact; some of this is at least partly attributed to coevolution.

The spectrum between parasitism and commensalism is not necessarily two species living in some sort of laissez-faire relationship, but rather that the host–pathogen relationship evolves toward a state where the pathogen exerts little or no evolutionary pressure on the

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host, and vice versa. This does not necessarily end up with a pathogen that is more of nuisance than a threat, like the common cold. For instance, *Bacillus anthracis*, the etiological agent of anthrax, may be close, if not a true commensalist, despite being obligately lethal. This is due to its long transmission cycles between infections as a mostly enzootic pathogen. Long periods of dormancy and typically low case basic reproductive numbers (9) result in a pathogen that is deadly but may not exert much stress on host populations.

Prediction through Surveillance

One Health has become the catch-all framework for emerging infectious diseases that are coming from livestock and wildlife. Within this framework public health has increased the demand for understanding which infectious diseases are out on the landscape and what type of risk they pose to humans (10). Plague control has enacted some large-scale attempts to curtail spillover of this disease into human populations. In the former Soviet Union and in China where plague is endemic several strategies have been used to prevent plague, including removal of fleas (the main sylvatic vector of *Y. pestis*) and the removal of rodents around human settlements (11). China at one point had removed marmots from an entire mountain range in an attempt to remove plague from the area. There has been an increasingly greater focus on surveilling wildlife for reemerging and novel pathogens as greater interconnectedness through the globalization process has made the world more vulnerable to infectious disease (12). The current COVID-19 pandemic has highlighted how quickly infectious diseases can wreak havoc in our daily lives on a global scale.

Pandemics starting from zoonotic reservoirs all go through this single bottleneck in their transition from one species to the next. Predicting how the pathogen will behave in a new host species is the first step to assessing the risk potential of preemerging infectious diseases. Hopefully, a better understanding will lead to better mitigation strategies.

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