



Five Major Challenges for Pandemic Prediction and Prevention

By Peter Daszak

Dissecting the Anatomy of a Pandemic

Pandemics (diseases that spread globally) are rare events that are often devastating, causing substantial mortality and economic damage. Just like hurricanes or earthquakes, efforts to understand the origins of pandemics and predict their emergence would help reduce their impact and ultimately prevent them. However, unlike earthquakes or hurricanes, our efforts to understand the causes, patterns, and origins of pandemics are only just beginning. Here I highlight recent advances in disease ecology, virology, and biogeography that move us towards these goals. I also identify five critical questions that, if answered, will greatly enhance our ability to predict and prevent pandemics.

Predicting pandemics first requires analyzing trends and common themes in their emergence

Over the past few decades we have learned a great deal about the anatomy of a pandemic. Most pandemics originate as zoonoses (diseases from animals, mainly wildlife). In fact, every one of the true pandemics of the last 50 years has either originated entirely within a wild animal species (e.g., SARS originating in bats) or contains genes derived from wild animal viruses (e.g., pandemic influenza A H1N1/09 virus).¹ Because most pandemics

are caused by viruses, this article will focus on them. Pandemics emerge through a complex interplay among socioeconomic, ecological, and biological factors. This process contains at least three distinct stages.²

- First, potentially pandemic pathogens exist in their natural wildlife reservoir. Changes to land use or other environmental changes bring people into increased contact with wild animal hosts, or perturb natural host-pathogen dynamics to increase the risk of viral transmission from wildlife to people (i.e., "spillover").³
- Second, spillover to human occurs repeatedly, either directly from a wildlife host or via domesticated animals. Some spillover events cause small chains of human-to-human transmission.
- Third, the virus achieves sustained human-to-human transmission, expands its geographical range, and moves internationally via travel and trade networks. This stage is pandemic emergence: international spread with sustained transmission across large swathes of the planet.

Each stage of emergence is driven by different socioeconomic, ecological, and biological factors that push pathogen dynamics through emergence,

amplification, and spread. However, these processes are poorly understood because they are complex; elucidating their mechanisms requires collaboration across many disciplines (e.g., demographers, virologists, and wildlife biologists). However, general trends can be identified.

Emerging infectious diseases are increasing in frequency, pandemic potential, and impact

The literature on emerging infectious diseases (EIDs) is growing. Does this growth reflect an actual increased threat of pandemics, or simply better reporting of outbreaks? To test this, we developed a database of EID events (expanded from a published list of EIDs) which we define as the first temporal emergence of a pathogen in a human population or the point at which a previously known disease became classified as emerging due to increased incidence or other factors.^{4,5} We collected and analyzed data on the location and time at which all EIDs since 1960 emerged, and a series of associated ecological, biological, and socio-demographic drivers of disease emergence. Our spatial and temporal regression analyses showed that the frequency of EID events has increased over time, peaking between 1980 and 1990. This peak was associated with increased susceptibility to infection due to the HIV/AIDS pandemic. Like Taylor et al. (2001), we found that zoonoses comprised the majority of EID events (60.3 percent), and that almost 71.8 percent of zoonotic EIDs were from wildlife (43.3 percent of all EID events).⁴ Furthermore, zoonoses from wildlife were increasing as a proportion of all EID events — between 1990 and 2000, 52 percent of EID events were zoonoses with a known wildlife origin. We attempted to correct for increasing infectious disease reporting by including in our regression model the number of articles published in the *Journal of Infectious Diseases* (which gives a crude measure of research effort for infectious diseases generally, not just EIDs). Controlling for the frequency of reporting further supported our conclusions that EID events are becoming more common, that zoonoses comprise the majority of EID events, and that zoonoses are rising significantly faster as a proportion of all EID events.

Identifying hotspots for pandemic disease emergence

Using geographic data in our EID database, we tested associations between subsets of EID events

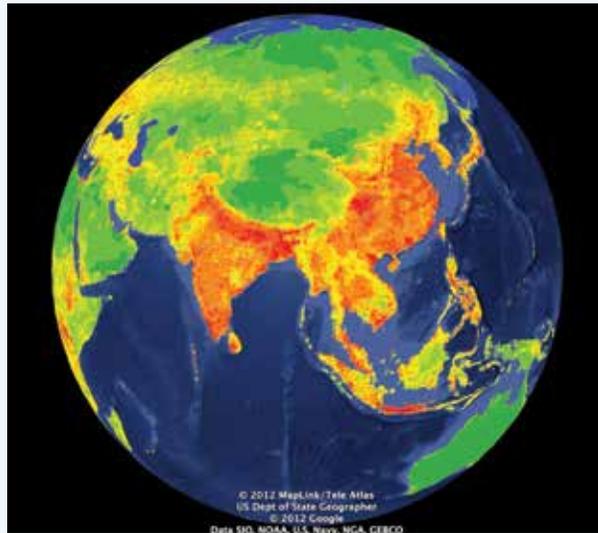


Figure 1 | Heat map of risk of a zoonotic disease of wildlife origin emerging in people; warmer colors reflect increased risk of EID events (EID hotspots). Because pandemics are mainly zoonotic in origin, this map acts as a potential basis for future targeted surveillance and the pre-empting of potential pandemics.

(drug-resistant and vector-borne pathogens, and zoonoses with wildlife and non-wildlife origins) and a few hypothesized drivers. While each category of EID event was associated with different outbreak drivers and geographic patterns of origin, all were strongly associated with human population density. This finding suggests that the presence and number of people and the changes they make to a landscape are key risk factors for emerging diseases. We also found that land use (e.g., urbanization, change in land cover) correlates significantly with EID event distribution. Zoonoses from wildlife also correlate significantly with mammal species richness; more animal species in a given location host a greater diversity of microbes. This approach provides a way to identify the relative risk of EID events (through their correlated drivers) globally. These EID hotspots tend to be lower-latitude, developing countries with high populations of people, high wildlife diversity, and lots of land use change.⁵ Our hotspot maps (Figure 1) provide a first crude attempt at pandemic prediction — they identify regions likely to propagate the next EID event or Stage 1 spillover. This spatial and temporal analysis of EID events can provide a simple but powerful way to prioritize resources for global disease surveillance. The goal of this surveillance would be identifying pathogens likely

to become the next EID, or pathogens in the process of emerging. However, they also raise critical questions we need to address in our quest to prevent pandemics.

Five Critical Questions

1. How many unknown viruses are waiting to emerge?

The first step in a global program to prevent pandemics might be to survey the extent of microbial diversity in hotspot regions. Sampling wildlife and identifying all the viruses they harbor would generate a pool of potential pandemic pathogens from which to develop vaccines and other medical countermeasures. This approach is exactly the basis for a number of new programs, including the USAID Emerging Pandemic Threat (EPT) program, and research programs that target pathogen discovery in bats and other zoonotic disease reservoirs.^{2,6} However, scale is critical. If there are 30 million unknown viruses in wildlife, it will be extremely costly to identify them all, and difficult to assess which pose the greatest threats.

So far, only one systematic attempt has been undertaken to predict the unknown viral diversity in a single animal host species.⁷ We used samples collected and tested through the USAID EPT PREDICT program, in which animals were captured, tagged, and released, and the number of recaptures of tagged individuals relative to the number of untagged individuals yielded a statistical prediction of the total number of individuals in a region. For pathogen discovery, we repeatedly sampled a large population of *Pteropus giganteus*, a bat species known to carry zoonotic viruses. From high quality samples collected from around 2,000 unique bats, we discovered 55 viruses from 9 viral families known to harbor zoonoses.⁷ We estimated the total viral richness of these 9 families in *P. giganteus* to be 58 viruses (i.e., 3 not-yet discovered). Extrapolating to all 5,517 known mammal species, we estimated that there are at least 320,000 mammalian viruses awaiting discovery in these 9 viral families. Using field and lab expenses of the PREDICT program, the cost to uncover 100 percent of virodiversity in all mammalian reservoirs will be \$6.8 billion, and to uncover 85 percent of virodiversity will be \$1.4 billion, considering the diminishing returns of continued sampling. The latter figure is less than the cost of a single SARS-scale pandemic and, if spread over a decade, a small portion

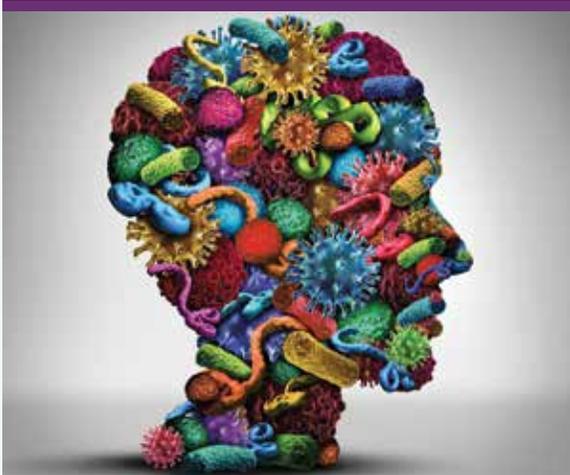
of current global pandemic prevention spending. This first attempt at estimating pathogen diversity is crude and has a number of significant assumptions. Further work on other species is critical to assess its validity.

2. In which wildlife species will the next pandemic pathogen originate?

The cost of surveying pathogens in mammalian species may be reduced by prioritizing those wild species most likely to harbor viruses that could cause a pandemic. One criterion might be close genetic relatedness to humans (e.g., non-human primates). Such animals are more likely to share with humans similar host cell receptors and viral defense mechanisms. Potentially, viruses that can infect animals related to humans are more likely to be able to infect our cells, and less likely to be quashed by our innate immunity. While the genetic, behavioral, and ecological rules that underpin these relationships are poorly understood, recent work shows that closely-related mammals are more likely to share virus species.⁸ However, many mammalian genera and families have been too poorly sampled to assess their risk. Furthermore, for reasons not well-understood, this rule can break down when two unrelated species have extensive, intimate contact over long periods of time (e.g., humans and domesticated mammals). Expanding trade in wildlife may also bring more animal species from different regions into close contact with people; creating opportunities for pathogens to emerge that would normally have difficulty infecting people.

3. Can we predict the pandemic potential of a newly discovered pathogen?

Even if we increase the rate of virus discovery, how can we identify which viruses will be able to infect humans? Testing in animals or cultured human cells can predict host range and potential pathogenicity to humans, but these methods are not definitive. Other factors which may suggest disease-causing potential include the relatedness of the host species to humans, the relatedness of a virus to known human viruses, known host range, and evolutionary capacity.² A few heuristics can help us prioritize certain pathogens: those existing at an interface of human-wildlife contact, those closely related to known human pathogens, and whose hosts are closely related to humans are likely to pose greater risks. For close neighbors of known pathogens,



The rising frequency of emerging infectious disease events, their increasing geographic spread, and their expanding impact should make overcoming pandemic disease an international priority.

sequencing their receptor binding domains may provide a rudimentary strategy to assess potential virulence. For example, the SARS-like coronaviruses (SL-CoV) identified by our group in bats in China have varying degrees of sequence homology to the SARS coronavirus (SARS-CoV).^{1,9} We have shown that some SL-CoVs can bind directly to the human cell surface receptor for SARS-CoV, ACE2. Others have now demonstrated that chimeric viruses (SARS-CoV backbone expressing SL-CoV spike protein) can infect human cells and cause clinical signs in humanized mice.¹⁰ Importantly, there appears to be a lack of immune cross-reactivity between SARS-CoV and our SL-CoV, suggesting that our SL-CoV has significant pandemic potential. These studies provide proof-of-concept for predictive approaches.

4. Can we predict how, and where, a new EID will spread?

The emergence of A/H1N1 influenza in 2009 highlighted how rapidly diseases can spread once they have achieved capacity for transmission. Analyses of travel and trade data have shown that modeling disease spread is relatively straightforward, and can provide accurate estimates of spread and case numbers when applied to prior outbreaks, e.g. of SARS and A/H1N1 influenza.^{11,12} This approach has been used to analyze the spread of disease vectors via shipping and likely routes of spread via airplane, and to predict the spread of ongoing events such as the MERS-CoV outbreak in Saudi Arabia.^{13,14} Models of disease spread have been used to examine the likely cause of past spreading events for A/H5N1 influenza, and predict and set policy

for its likely route of introduction to the New World.¹⁵ Finally, modeling has reduced the risk of West Nile introduction to Hawaii and the Galapagos Islands (the most likely vector is mosquitoes transported via air travel).¹⁶

The predictive power of such models improves with the quality of data available. For example, accurate predictions about disease spread require countries to identify and report outbreaks early once a pandemic has begun. During the 2009 H1N1 influenza pandemic, two key factors influenced the pandemic's arrival date in a given country: the country's accessibility via air travel, and the percentage of GDP per capita spent on healthcare (a proxy for testing and reporting capacity).¹² Less well-understood is the role of intra-country human movement in disease spread. New data on roads, migration, and human network connectivity will increasingly illuminate this area.

5. How do we prevent pandemics from emerging?

Even if we can identify the capacity of a novel virus for human-to-human transmission and predict how it will spread, we still lack strategies to prevent evolution of an epidemic into a pandemic. One positive development is a change in how pandemic prevention programs are funded and managed. Traditionally, outbreaks were handled by state and national agencies, which fund the World Health Organization and field laboratory networks. H5N1 influenza emerged in several small-scale outbreaks, which suggested chronic persistence

in backyard poultry farms. In response, a systems approach to pandemic prevention was developed, as well as a “One Health” collaboration of animal health, public health, and environmental agencies.^{17,18} International development agencies, which had set up programs targeting individual infectious diseases, are now actively involved in this systems approach to pandemic prevention, including support for crucial infrastructure investments, and a specific focus on collaborative One Health programs.¹⁷ With most EID events occurring in the developing world, disease-based programs for HIV/AIDS, malaria, TB, and polio do not address the underlying flaws in public health systems that predispose locations to outbreaks of emerging infectious diseases.¹⁹

Future work may target the underlying drivers of disease emergence, providing economic incentives to improve practices and reduce the EID threat. For example, promoting the farming of wildlife species for consumption in place of wild-caught animals would likely reduce EID risk. This support, including better regulation and stronger agricultural institutions, should reduce the inflow of wild-caught animals and simultaneously help manage biosecurity.

Similarly, 43 percent of past EID events are attributable to changes in land use and agriculture, including logging, oil and gas, mining, and plantations. The economic impact of EIDs from land-use change is estimated to be \$10-40 billion over the next 10 years, which could be considered a potential liability

to extractive industries. Industrialized mining and plantation operations in EID hotspot countries are likely to be on the frontline of disease outbreaks, and are often under pressure to improve their environmental impacts. Incentives could be built into World Bank loans or concession agreements to run emerging disease impact assessments (e.g., surveillance in wildlife at a mining development site), or to mandate the building of clinics and diagnostic labs that conduct surveillance for novel EIDs at extractive sites.

Conclusion

Predicting pandemic disease emergence is difficult and complex. Overcoming pandemics will require new technological solutions, better interdisciplinary collaboration, and significant funding. However, a simple economic assessment suggests they are likely to have a substantial return on investment. With the costs of pandemics rising (between \$10 and \$30 billion for SARS), the relatively moderate cost (less than \$10 billion) of conducting targeted surveillance, identifying novel pathogens from key wildlife species, and analyzing their potential risk becomes more attractive. There is a critical, urgent time window of around 20 years within which a global strategy to prevent pandemics needs to be implemented before the rate and cost of disease emergence expands to swamp out any possibility of control. The rising frequency of EID events, their increasing geographic spread, and their expanding impact should make overcoming pandemic disease an international priority. **Q**

Peter Daszak, Ph.D., is President of EcoHealth Alliance, a global organization dedicated to innovative conservation science linking ecology and the health of humans and wildlife. Daszak has also consulted for other non-profit organizations and governmental agencies such as the OIE ad hoc working group on amphibian diseases, the National Academy of Sciences, U.S. Department of the Interior, International Union for the Conservation of Nature, National Institutes of Health, Australian Biosecurity CRC, DIVERSITAS, Society for Conservation Biology, and the Millennium Ecosystem Assessment. He is a recipient of the 2000 CSIRO medal for collaborative research, and his work has been the focus of extensive media coverage, including articles in *The New York Times*, *The Wall Street Journal*, *The Economist*, *The Washington Post*, *U.S. News & World Report*, and broadcast appearances on *60 Minutes II*, *CNN*, *ABC*, *NPR's Talk of the Nation, Morning Edition*, and *Fresh Air with Terry Gross*.

ACKNOWLEDGMENTS

This article is based, in part, on talks given to a meeting of the IOM Forum on Microbial Threats, September 24–25, 2013 and at In-Q-Tel, October 2015. Funding was provided by USAID-EPT-PREDICT, NIAID, NSF/NIH EEID, and core funding from EcoHealth Alliance.

BIBLIOGRAPHY

- ¹ Ge, X.-Y. *et al.* Isolation and characterization of a bat SARS-like Coronavirus that uses the ACE2 receptor. *Nature* 503, 535-538 (2013).
- ² Morse, S. S. *et al.* Prediction and prevention of the next pandemic zoonosis. *Lancet* 380, 1956-1965 (2012).
- ³ Murray, K. A. & Daszak, P. Human ecology in pathogenic landscapes: two hypotheses on how land use change drives viral emergence. *Current Opinion in Virology* 3, 79-83, doi:10.1016/j.coviro.2013.01.006 (2013).
- ⁴ Taylor, L. H., Latham, S. M. & Woolhouse, M. E. J. Risk factors for human disease emergence. *Philosophical Transactions of The Royal Society B-Biological Sciences* 356, 983-989 (2001).
- ⁵ Jones, K. E. *et al.* Global trends in emerging infectious diseases. *Nature* 451, 990-994 (2008).
- ⁶ Drexler, J. F. *et al.* Bats host major mammalian paramyxoviruses. *Nature Communications* 3, 796 (2012).
- ⁷ Anthony, S. J. *et al.* A strategy to estimate unknown viral diversity in mammals. *MBio* 4, doi:10.1128/mBio.00598-13 (2013).
- ⁸ Bogich, T. L. *et al.* in *New directions in conservation medicine* (eds A. A. Aguirre, R.S. Ostfeld, & P. Daszak) 607-618 (Oxford University Press, 2012).
- ⁹ Li, W. *et al.* Bats are natural reservoirs of SARS-like coronaviruses. *Science* 310, 676-679 (2005).
- ¹⁰ Menachery, V. D. *et al.* A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat Med* advance online publication, doi:10.1038/nm.3985 <http://www.nature.com/nm/journal/vaop/ncurrent/abs/nm.3985.html#supplementary-information> (2015).
- ¹¹ Hufnagel, L., Brockmann, D. & Geisel, T. Forecast and control of epidemics in a globalized world. *Proceedings of the National Academy of Sciences of the United States of America* 101, 15124-15129 (2004).
- ¹² Hosseini, P., Sokolow, S. H., Vandegrift, K. J., Kilpatrick, A. M. & Daszak, P. Predictive power of air travel and socio-economic data for early pandemic spread. *PLoS ONE* 5, e12763 (2010).
- ¹³ Tatem, A. J. The worldwide airline network and the dispersal of exotic species: 2007–2010. *Ecography* 34, 94-102 (2009).
- ¹⁴ Khan, K. *et al.* Global Public Health Implications of a Mass Gathering in Mecca, Saudi Arabia During the Midst of an Influenza Pandemic. *J. Travel Med.* 17, 75-81, doi:10.1111/j.1708-8305.2010.00397.x (2010).
- ¹⁵ Kilpatrick, A. M. *et al.* Predicting the global spread of H5N1 avian influenza. *Proceedings of the National Academy of Sciences of the United States of America* 103, 19368-19373 (2006).
- ¹⁶ Kilpatrick, A. M. Globalization, Land Use, and the Invasion of West Nile Virus. *Science* 334, 323-327, doi:10.1126/science.1201010 (2011).
- ¹⁷ Bogich, T. L. *et al.* Preventing Pandemics Via International Development: A Systems Approach. *Plos Medicine* 9, doi:10.1371/journal.pmed.1001354 (2012).
- ¹⁸ FAO *et al.* Contributing to One World, One Health: a strategic framework for reducing risks of infectious diseases at the animal-human-ecosystems interface. 1-67 (Food and Agriculture Organization; World Organisation for Animal Health; World Health Organization; United Nations System Influenza Coordinator; United Nations Children's Fund; World Bank, Rome, 2008).
- ¹⁹ Standley, C. J. & Bogich, T. L. International development, emerging diseases, and eco-health. *EcoHealth* 10, 1-3 (2013).