2012

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Published in *New Directions in Conservation Medicine: Applied Cases in Ecological Health,* edited by A. Alonso Aguirre, Richard S. Ostfield, and Peter Daszak (New York: Oxford University Press, 2012).

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USING MATHEMATICAL MODELS IN A UNIFIED APPROACH TO PREDICTING THE NEXT EMERGING INFECTIOUS DISEASE

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Emerging infectious diseases (EIDs) pose a significant threat to human health, global economies, and conservation (Smolinski et al. 2003). They are defined as diseases that have recently increased in incidence (rate of the development of new cases during a given time period), are caused by pathogens that recently moved from one host population to another, have recently evolved, or have recently exhibited a change in pathogenesis (Morse 1993; Krause 1994). Some EIDs threaten global public health through pandemics with large-scale mortality (e.g., HIV/AIDS). Others cause smaller outbreaks but have high case fatality ratios or lack effective therapies or vaccines (e.g. Ebola virus or methicillin-resistant *Staphylococcus aureus*). As a group, EIDs cause hundreds of thousands of deaths each year, and some outbreaks (e.g., SARS, H5N1) have cost the global economy tens of billions of dollars. Emerging diseases also affect plants, livestock, and wildlife and are recognized as a significant threat to the conservation of biodiversity (Daszak et al. 2000). Approximately 60% of emerging human disease events are zoonotic, and over 75% of these diseases originate in wildlife (Jones et al. 2008). The global response to such epidemics is frequently reactive, and the effectiveness of conventional disease control operations is often "too little, too late". With rising globalization, the ease with which diseases spread globally has increased dramatically in recent times. Also, interactions between humans and wildlife have intensified through trade markets, agricultural intensification, logging and mining, and other forms of development that encroach into wild areas. Rapid human population growth, land use change, and change in global trade and travel require a shift toward a proactive, predictive, and preventive approaches for the next zoonotic pandemic.

The key emergence event for most infectious diseases is a change in transmission dynamics within or between host populations. The interconnectedness of humans, domestic animals, and wildlife facilitates the spillover of pathogens between hosts (Daszak et al. 2000). External forces, such as agricultural

intensification, global travel, and the accidental translocation of pathogens, augment this interaction. The role of zoonotic pathogens in causing human disease may be particularly important because when these diseases first emerge, humans have no acquired immunity to novel pathogens, resulting in sometimes highly lethal infections (e.g., AIDS/HIV, Ebola virus disease).

Despite the huge social, demographic, and economic impact of EIDs, there has been little advancement in understanding how anthropogenic changes drive disease emergence and in developing proactive, predictive, and preventive approaches (Hufnagel et al. 2004; Weiss and McMichael 2004; Ferguson et al. 2005; Wolfe et al. 2005). In this chapter, we describe a strategy to create a unifying predictive model for the zoonotic and pandemic potential of a given region by integrating predictive models of each stage of the process of zoonotic disease emergence. The three stages of emergence that we address are (1) a "pre-emergence" phase, where anthropogenic changes cause animal populations to come into contact, leading to cross-species transmission of their pathogens, (2) a spillover stage, where animal pathogens enter human populations, and (3) pandemic emergence, where pathogens are able to exploit human travel and trade networks to emerge across international and regional boundaries. Each stage of the emergence process requires a different approach and analyses at different scales. Each of these modeling exercises is then linked to data collection on the ground. Models are then parameterized through effective active and passive surveillance of wildlife, monitoring of keywords in media, and analysis of published literature.

This modeling approach also helps to increase surveillance efficiency by facilitating spatial and species-specific (e.g., phylogenetic) targeting of wildlife to sample for likely zoonotic pathogens. Our strategy is designed for the early detection of novel pathogens with human pandemic potential, to allow animal and human health professionals the opportunity to predict emergence and prevent spread. It also provides the tools to target important sentinel species at active human interfaces to improve on the efficiencies of previous surveillance for rare pathogens of interest. Our vision is to expand on lessons learned in order to better assess local capacity, increase the value of infectious disease modeling, implement targeted and adaptive wildlife disease surveillance systems, develop and deliver new technologies to improve efforts in hotspots, and use cutting-edge information management and communication tools to bring the world closer to realizing an integrated, globalized approach to controlling emerging zoonotic diseases.

In this chapter, we focus in particular on three key steps in designing this integrated modeling and field surveillance approach: (1) the selection of geographic sites for surveillance, (2) the selection of target species for sampling, and (3) the construction of predictive models of spread and future emergence (Table 42.1).

DEFINITIONS, DRIVERS, AND BIASES

History and Debate over the Definition of an EID

In the introduction to this chapter, we defined EIDs as diseases that have recently increased in incidence, have moved from one host population to another, are caused by recently evolved strains, or exhibit a change in pathogenesis. We use this definition because, despite the widely accepted importance of EIDs, there is little agreement on the exact properties that classify a disease as "emerging." While the term has generally been used to emphasize the novelty of a given infectious disease, closer inspection reveals that there is no consensus on what defines this novelty. With an increasing number of studies investigating the phenomenon of emergence and the underlying environmental and anthropogenic drivers (e.g., Taylor et al. 2001; Jones et al. 2008), it is important to agree on a medically and biologically meaningful definition of emergence. Such a definition should, in principle, allow one to decide not only whether a given infectious disease can be called "emerging", but also when and where exactly it emerged, and to do so via rigorous and quantifiable criteria.

The first mention of EIDs that can be found on MEDLINE was provided by Oster (1961), who concentrated solely on animal diseases but supplied a definition that can be generalized to human diseases. He describes the "sudden invasion by epizootic diseases into countries where they have never before struck" and mentions that these "have been described as 'emerging diseases', a new term which would seem to indicate new infectious disease situations."

Table 42.1 Summary of Questions, Approaches, and Results Related to Three Components of EID Surveillance and Prediction

Objective	Questions	Approach	Result
1. Selecting geographic sites for surveillance	- What is the risk of transmission to humans? - What is the distribution of undiscovered pathogens? What areas have been undersampled? - What are the spatial drivers of disease emergence? - How will the risk of disease emergence change geographically?	Spatial and temporal general linear models	- Geographically refined surveillance strategies - Refined "hotspot" maps - Sub-regional "hotspot" maps
2. Selecting species for sampling	- Which wildlife species are the greatest risk of being the source for zoonotic disease emergence?	Spatial and temporal general linear models	- Refined surveillance strategies according to phylogenetic relatedness and contact opportunities
3. Predicting spread and future emergence events	- Can the potential of a region to produce pandemic pathogens be measured? - Can the vulnerability of a region to the spread of an EID be determined?	Matrix-based population simulation	- A global emerging infectious disease vulnerability map

There are two ways in which a disease can be considered new (Table 42.2). In the first instance, the definition can be relatively specific. A disease may be "emerging" in that it has crossed the species barrier to infect a novel host, or that its clinical signs or symptoms or pathogenicity has changed. In other words, the disease is genuinely new to a host. In this sense, every disease can emerge only once in each host. Some diseases, such as measles (Babbott and Gordon 1954), sleeping sickness (Steverding 2008), and bubonic plague (Hays 2006), emerged in prehistoric or ancient times, whereas others, such as Ebola virus (World Health Organization 1978), Nipah virus (Chua et al. 2000), and SARS (Guan et al. 2003), emerged in recent years.

Some authors, on the other hand, have proposed defining EIDs in the wider purview of all diseases that are increasing in incidence (Institute of Medicine 1992; Morse 1993; Levins et al. 1994; Morse 1995; Jones et al. 2008). This approach includes not only diseases that are genuinely new in a host and are increasing in incidence by virtue of being recognized in the first place, but also diseases that were previously present at a lower level or are expanding to new areas. In this sense, a disease can emerge and re-emerge multiple times and in different locations.

With increasing interest in emerging infectious diseases, it is important to agree on the meaning of the term, which has been used for a variety of different and sometimes seemingly unrelated phenomena. In previous definitions, it has been interpreted in two ways: as the appearance of a new pathogen in humans or as a disease becomes a growing concern. These two scenarios can be distinguished by differentiating between primary and secondary emergence. For this chapter, we limit our focus to those EIDs that can infect humans. On the basis of the distinction between primary and secondary emergence, the following definitions are proposed for an emerging infectious disease (Table 42.2):

- *Primary emergence:* A novel infectious disease appears in humans by means of transmission from

Table 42.2 Previous Definitions of EIDs

	Primary Emergence		*Secondary Emergence*		
	New host	**New symptoms**	**Detection**	**Increased incidence**	**Expansion**
Oster (1961)					•
Lederberg et al. (1992)				•	
Morse (1993)			•	•	•
Levins et al. (1994)	•	•	•	•	
Morse (1995)		•		•	•
Garnett and Holmes (1996)	•	•			
Kilbourne (1996)	•	•	•		

Included factors of primary emergence were crossing of the species barrier to adapt to a new host (humans), the appearance of new symptoms or new pathogenicity, and new detection of a disease. Included factors of secondary emergence were an increase in incidence and expansion to a new area. Morse (1995) lists the appearance of an infection "for the first time" as emergence, which fits all categories of primary emergence, without being explicit about the mechanisms.

animals or the environment and adaptation to infecting humans, or through evolution within human hosts to develop new pathogenicity or resistance to treatment. In this case the first recorded cluster in humans is taken as the EID event. If an earlier case than the previously earliest known case is found retrospectively (as has happened for HIV), the timing of the event should be corrected accordingly.

Secondary emergence: An existing infectious disease increases in incidence in a population in a way that constitutes a significant change with respect to a baseline incidence. This is the case when a disease occurs where it has never previously been reported (and the baseline incidence was zero), or when a disease displays a trend of increasing incidence with respect to a non-zero incidence. The timing of the emergence event, in this case, should be the beginning of the increase.

Characterizing the Drivers of Emergence

Despite the threat posed by EIDs, we still do not fully understand the mechanism of emergence; instead, we rely heavily on a reactive approach of responding to pathogens after they have emerged. We must first take a broad-scale, ecological approach to understanding the processes driving emergence. The process of disease emergence is complex and generally driven by factors that "provide conditions that allow for a select pathogen to expand and adapt to a new niche" (Smolinski et al. 2003). These factors are largely environmental, ecological, political, economic, and social forces, which function on a range of different scales. During the past two decades, numerous studies have classified emerging diseases according to the factors underlying their emergence, commonly referring to these factors or processes as *drivers* of emergence.

The first attempt to classify drivers of emergence was published by the Institute of Medicine (IOM) in 1992 (Lederberg et al. 1992). This report identified six factors in the emergence of infectious diseases: (1) human demographics and behavior; (2) technology and industry; (3) economic development and land use; (4) international travel and commerce; (5) microbial adaptation and change; and (6) breakdown of public health measures. These factors are not mutually exclusive and are relevant to different stages of emergence (e.g., spillover or an increase in incidence). Seven additional drivers were added in a follow-up IOM report in 2003 (Smolinski et al. 2003): "human susceptibility to infection," "climate and weather," "changing ecosystems," "poverty and social inequity," "war and famine," "lack of political will," and "intent to harm." Other studies have found that disease emergence from animal hosts to humans is driven mainly

by anthropogenic forces, such as land use change (Patz et al. 2004) or global trade and travel across ecological and environmental boundaries (Hufnagel et al. 2004). The classification of these "factors in emergence" paved the way for research with respect to the underlying drivers of infectious disease emergence.

At larger spatial scales, datasets are freely available for many of these drivers (e.g., human population density or land use change). Analyzing these datasets allows us to move beyond a correlative approach for testing drivers of disease to a predictive framework (Jones et al. 2008; Dunn et al. 2010). Datasets for each driver are often correlated, so it is important to check for independence among variables when using multiple driver datasets in a single analysis. Determining, quantifying, and ranking drivers of emergence at smaller spatial scales can be more complicated. Often an emergence event arises from multiple drivers interacting simultaneously or sequentially. Further, the time lag between the driver acting directly on a host, pathogen, or environment and the origin of the emergence event can vary. The duration of this time lag may scale with organism generation time; for example, a driver acting directly on pathogens (short generation time) would have a much smaller lag in effect than a driver acting on a mammalian host species (longer generation time).

The spread of genetically based resistance will always lag behind the emergence of a pathogen and may be affected by other drivers. One could estimate a probability curve for this, and estimate lag time based on the slope of the curve. While drivers of emergence are indeed complicated, we can still make inferences on the role of multiple drivers acting simultaneously or sequentially, the time lag between drivers and emergence, and the possibility of unintentional drivers, those that were originally thought to be mitigating forces.

Quantifying Missing Reports and Biases in Reporting

Existing datasets have identified over 350 infectious diseases that have emerged in the past 70 years (Woolhouse and Gaunt 2007; Jones et al. 2008; Dunn et al. 2010). It is likely, however, that there have been numerous unreported cases of novel diseases. Whether the numbers of emerging infectious diseases are on the rise or health officials have merely grown more aware of these events is debatable and can only be estimated against the backdrop of the highly uneven surveillance capabilities across the globe. EID surveillance has become a high-priority issue for both local and global health authorities, thereby making reporting more equitable. Thorough, accurate disease surveillance reporting relies on comprehensive, unbiased participation of all national and sub-national health agencies. This has been highlighted in recent years by the SARS epidemic, H5N1 highly pathogenic avian influenza, the global H1N1 influenza pandemic, and, most poignantly, the ongoing HIV pandemic.

These diseases, whose spread may have at one time been constrained locally, are increasingly transcending national boundaries (Institute of Medicine 2009). Local outbreaks are of concern to the global community because of their potential for pervasive spread. We rely on human reports of these types of local events to detect epidemics with pandemic potential that require global action. However, this type of participatory reporting is incomplete and biased due to an uneven distribution of health systems, detection mechanisms, and communication infrastructure. Disincentives to reporting, such as negative political and economic consequences of control measures, may also result in reporting bias. When trying to determine the underlying drivers for global disease emergence events, the source of biases in reporting must be accounted for to ensure that true differences are reported rather than artifacts of sampling or reporting.

A number of factors may affect the probability of detecting novel EIDs or influence the lag time between infection and detection of a novel pathogen. Factors intrinsic to both the pathogen and the exposed individual—such as the pathogen's virulence and the individual's socioeconomic status—will determine whether the individual seeks medical attention and whether the medical examiner identifies the infection as novel. Unusually infectious or virulent pathogens may have a greater chance of being reported due to large numbers of infected individuals or more detrimental health effects. Long latency periods, during which individuals are asymptomatic, lead to temporal biases due to the lag time between the initial case and detection, as was the case with variant Creutzfeldt–Jakob disease and HIV/AIDS, which is suspected to have emerged in the United States more than a

decade before it was identified in 1981 (Gilbert et al. 2007).

Socioeconomic factors also play a role both as a driver of disease emergence and as a source of reporting bias. Lower-income countries have higher rates of malnutrition and reduced access to potable drinking water, sanitation, immunizations, and health services (Ruger and Kim 2006; World Health Organization 2010). Furthermore, many low-income countries, particularly in sub-Saharan Africa, are faced with double-digit HIV infection rates. These populations are more susceptible to EIDs due to greater exposure to infective agents and depressed immunity. Whether or not infected individuals in low-income countries receive medical attention depends also on the availability, accessibility, and appropriateness of medical services and the individual overall ability to use them (Ensor and Cooper 2004). GDP and population density are the strongest correlates with the supply of qualified medical staff, healthcare facilities, diagnostics, and treatments (World Health Organization 2010).

The first step in correcting for this reporting bias of EIDs is to identify the sources for potential bias in the data. Then, proxies may be determined that help account for this non-random bias (i.e., distance to nearest hospital, use of traditional medicine, or per capita spending on healthcare). Reporting of disease is also non-random throughout the world because of local capacity to conduct and publish research, and the dearth of investigation taking place in underdeveloped and hard-to-reach areas. To control for this when building their model of global EID risk, Jones et al. (2008) constructed an index of sampling bias based on author addresses of publications in the *Journal of Infectious Disease* from 1973 to 2008.

Caution must be taken in choosing potential datasets to act as proxies for bias measures. There must be quantification or evidence supporting a mechanistic link between the proxy and the outcome. Using this approach, we posit that the number of infectious diseases to have emerged over the past half-century is likely much greater than we had previously anticipated. Others have also suggested that recent exposure events are more common, as a result of more suboptimal attempts by pathogens to invade novel populations in the past—sometimes termed "viral chatter" (Antia et al. 2003; Woolhouse et al. 2005; Wolfe et al. 2007).

SITE SELECTION, SPECIES SELECTION, AND PREDICTIVE MODELING

Select Geographic Sites for Surveillance

Jones et al. (2008) provided an example of a comprehensive approach to identifying sites as priority areas for sampling for the next EIDs. These sites have been dubbed "hotspots" and represent areas of higher EID risk. This process of identifying EID hotspots began with an exhaustive literature search to collect biological, temporal, and spatial data for EID "events" in human populations between 1940 and present. Jones et al. (2008) based their database of EIDs on previous work (Taylor et al. 2001) and updated it with additional information on microbial pathogens. All types of pathogens found in humans were entered into the database, including sexually transmitted diseases (STDs), zoonoses, drug-resistant microbes, vector-borne diseases, and food- and water-borne infections. Information on time, location, pathogen type, transmission mode, other hosts, and pathogen life history traits was added. Further, the most commonly cited causes of emergence for each pathogen were determined (Daszak et al. 2000; Smolinski et al. 2003; Morens et al. 2004; Patz et al. 2004; Weiss and McMichael 2004). Finally, shape files defining the published boundaries of the initial emergence event were created in ArcGIS (ESRI 2005).

The final published database covered global events between 1940 and 2004 and reported 335 EID events in humans. Using these 335 EID events, a risk model was constructed using logistic regression to determine the probability of an EID event in every 1-degree grid cell of the world. These estimates are based on historical patterns of EID events and their environmental and biological drivers (including human population density and growth, mammal diversity, precipitation, temperature, latitude, and reporting effort). Then, an EID risk value was calculated for every 1-degree grid cell of the world using human population density and growth, mammal density, latitude, and rainfall with the coefficients of the multivariate logistic regression model (Jones et al. 2008).

Previous efforts to understand patterns of EIDs have highlighted viral pathogens (particularly

negative-stranded RNA viruses) as a major threat because of their high rates of nucleotide substitution, often poor copy-editing, and higher capacity to adapt to new hosts (higher "evolvability"; Burke 1998). However, Jones et al. (2008) found that a majority of EID pathogens were bacterial, specifically novel drug-resistant strains. Controlling for reporting effort, the number of EIDs still showed a highly significant relationship with time (generalized linear model with Poisson errors, offset by log(JID articles) (GLM_{PJID}), $F_{1,57} = 96.4$, $p < 0.001$), supporting the widespread claim that the threat of EIDs to global health is increasing (Fauci 2001; Smolinski et al. 2003; Morens et al. 2004; King et al. 2006). Even after controlling for reporting effort, the number of EID events originating in wildlife reached the highest proportion in the most recent decade, highlighting the importance of understanding the factors that increase the contact between wildlife and humans in developing any predictive model. The strong relationship between high wildlife host biodiversity—primarily found in low-latitude developing countries—and EID events caused by zoonotic pathogens from wildlife (e.g., SARS, Ebola) suggests that these geographic regions will continue to be a key source of novel EIDs in the future. It also reinforces the need for pathogen surveillance in wild animal populations as a forecasting measure for EIDs (Karesh and Cook 2005; Kuiken et al. 2005; King et al. 2006). Jones et al. (2008) found that areas of the planet with the greatest EID risk also had the lowest levels of surveillance effort, therefore highlighting the importance of this approach for public health resource allocation.

We have since updated the driver data and spatial resolution of the risk model in Jones et al. (2008). The original spatial resolution was approximately 100-km² grid cells of the world; using the native resolution of the driver datasets, we have reduced this resolution to 1 km², allowing for country-level EID risk maps to be drawn at a resolution useful for regional-level planning. Mammal diversity per 1-km² grid cell was calculated using range maps based on Mammal Species of the World 2005. Human population density and growth were updated according to the Global Rural-Urban Mapping Project and the Gridded Population of the World (http://sedac.ciesin.columbia.edu/gpw). At the global scale, the 1-km risk map was developed using the same model coefficients as in Jones et al. (2008), but incorporates new driver datasets as described above at their native resolution, so the distribution of wildlife zoonotic EID risk (Fig. 42.1) is qualitatively comparable to that of the original risk map. At the country level, the improved datasets allow us to examine the influence of the two main drivers, mammal diversity and human population density, on EID risk.

EID risk maps can allow us to select sites for sampling that we believe to be more likely to harbor the next EID-causing pathogen in wildlife. We can also test the hotspots model by sampling in paired "hot" and "cold" sites. This allows for the constant feedback of field data into models to revise and update the prediction of EID risk.

Select Species to Target for Sampling

Life-History Traits

Species are not equal in their ability to harbor and transmit infectious diseases. For example, there is some debate as to whether certain characteristics of bats (e.g., their longevity, colonial roosting habits, and ability to fly and hibernate) may make them better viral reservoirs than other groups of mammals (see Chapter 14 in this book). A recent analysis of bat hosts and viruses (Turmelle and Olival 2009) shows that some species in a given area will be more likely to harbor a greater number of viruses than others, and that population genetic structure (F_{ST}; related to migratory capacity and mixing of genetic populations) significantly correlates with their known viral diversity. F_{ST} is a measure of the genetic mixture of individuals between populations. Turmelle and Olival (2009) used a combined model that includes F_{ST}, the International Union for Conservation of Nature (IUCN) species threat status, and a measure of research sampling bias, and found that these variables account for 33% of known viral diversity in bats ($p = 0.02$). Approaches similar to this, which account for species-specific ecological and evolutionary traits, may be useful for identifying species with the highest projected pathogen viral richness. We can combine this approach with a geographically targeted one to identify the most cost-effective species (bats and other species) and locations to target for active wildlife surveillance.

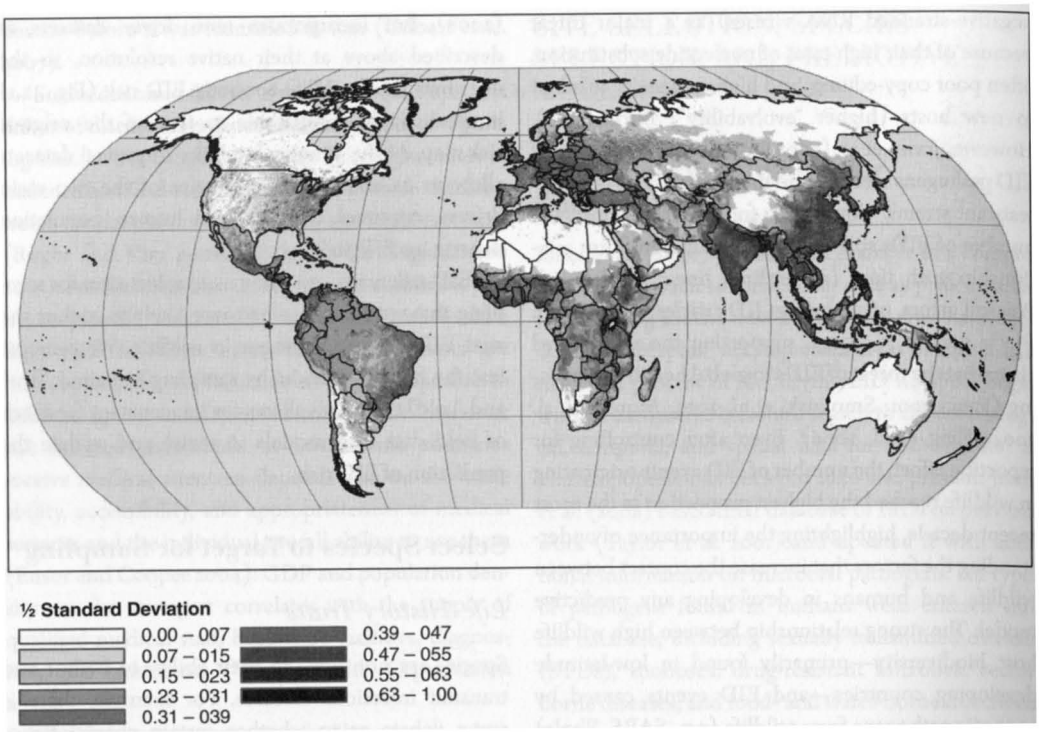

Figure 42.1:
Global map of zoonotic emerging disease hotspots risk from wildlife based on the Jones et al. (2008) model and updated mammal diversity and human population density and growth driver datasets. Risk is given by a scale from low (0.00, white) to high (1.00, black) risk.

Phylogenetic Relatedness

Another factor in the process of emergence is host relatedness with humans. Potential similarities that arise from shared ancestry, such as receptors that allow a virus to enter a cell, may play a major role in facilitating spillover of pathogens. To date, this assumption has not been explicitly tested in a phylogenetic framework, especially for viruses. Using host and pathogen data from the Jones et al. (2008) database, we have examined the distribution of wildlife and domestic hosts for pathogens known to cause human disease. Mammals appear to host the greatest proportion of pathogens emerging from wildlife to infect humans (Fig. 42.2). We constructed a database of all known mammal–virus associations to test the importance of phylogeny in estimating the probability of a virus being shared between a non-human mammalian host and humans. The final mammal–virus association database consisted of over 1,200 pairs, including over 300 unique mammal species and over 200 unique virus species. We also tested whether the probability of a virus being shared between mammal hosts and humans increased with increasing human–host contact.

After correcting for biases in reporting effort, we found that the probability of humans and non-human mammal hosts sharing a virus increased with increasing phylogenetic relatedness. Further, the probability of humans and non-human mammal hosts sharing a virus also increased with increasing contact opportunity, either through domestication or shared habitat. These results, combined with life-history trait targeting and hotspot mapping, improve our understanding of host-pathogen transmission and help to provide basic guidance in the identification of wildlife species most likely to be the source of the next EID in humans. This understanding lays the groundwork for us to begin to predict the consequences of anthropogenic activities that increase interaction between humans,

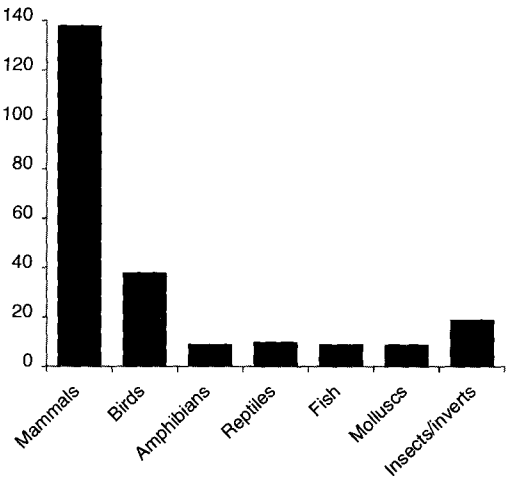

Figure 42.2:
The number of human EID events identified by Jones et al. (2008) by host species, as recorded in the original database. Mammals are responsible for by far the greatest number of human EIDs recorded thus far.

domestic animals, and wildlife, such as logging, hunting, or building roads.

Future research is also necessary to understand the relative importance of host phylogeny versus contact opportunity with humans. This will allow for a better surveillance strategy that targets wildlife and domestic host species most likely to be the source of the next EID in humans. Using the model of phylogenetic relatedness and contact opportunities described, these findings could be advanced further by using a Gap Analysis, a tool used to assess decision-making in conservation to identify areas that have been undersampled for pathogens relative to mammalian (and phylogenetic) diversity.

Contact Opportunities and Risk Interfaces

Human contact with wildlife species, both direct and indirect, is undoubtedly an important factor in the transmission and emergence of new human pathogens from wildlife. High-risk contact interfaces could be the starting point for investigating pathogen diversity and prevalence (total number of cases of a disease in a population at a given time) in wildlife. Using estimates of the range and distribution of pathogen prevalence and incidence of every known EID family, we can use power calculations to look at how many individuals of each reservoir species need to be sampled within a given set of species in a specific interface. Calculating an expected prevalence of known EID families allows us to recognize unusual events during routine sampling.

Our vision is that sampling of high-risk interfaces could be conducted over multiple seasons to obtain a baseline species diversity dataset. Then teams can determine the number of individuals per species needed for sampling to increase detection probability using estimated prevalence values for known pathogens (see Chapter 39 in this book). Next, a set of target species in the risk interface could be sampled, using the minimum number of individuals required for improved detection. Then if the prevalence is unusually high, teams could conduct follow-up sampling of species identified and appropriate potential spillover hosts, in intact or native range where possible.

Construct Predictive Models of Spread and Future Emergence

Finally, once we have a good grasp of historical disease data, current disease risk, and the socioeconomic, environmental, and biodiversity profile of a given region, we can analyze the likelihood that a given pathogen could break out and become truly pandemic (as defined by cross-continental transmission). Our group has developed a vulnerability map of this type for avian influenza (Hosseini et al. 2010) that examined travel routes, airplane travel capacity, and connections between all major airports using ten years of information from Freedom of Information Act requests to the U.S. Fish and Wildlife Service on the global wildlife trade, trade data from the United Nations Food and Agriculture Organization, and data from the International Airline Transport Alliance. Trade routes, export and import statistics, travel, and wildlife trade patterns were examined to determine how these factors increase the risk of H1N1 spreading from a hotspot region into major global population centers. This model can be generalized to the country and airport level to determine which locations are most vulnerable to importation of EIDs through trade and travel (Hosseini et al. 2010). This methodology could be crucial for identifying airports or transportation centers where pathogen monitoring and intervention will be particularly effective in preventing disease spread.

TECHNOLOGICAL ADVANCES

Recent technological advances have improved our ability to identify high-risk interfaces for disease transmission and to detect novel pathogens before widespread spillover occurs. These advances include improvements in information technology, molecular diagnostics, and risk modeling. Further advances in communications technology will serve to bring countries traditionally isolated from international health networks into the global fold. Developments over the past 15 years allow us to gather reports from disparate sources and use the Internet as a common platform for exchanging information. Examples include the Global Public Health Intelligence Network, the Program for Monitoring Emerging Diseases, and HealthMap (http://www.healthmap.org). The greatest limitations of these networks are the underlying limitations of the national reporting systems and their bias towards English-speaking countries (Keller et al. 2009). Telemedicine, or cell phone-mediated medical diagnoses, will allow technologically underserved areas to leapfrog ahead without enduring massive infrastructure changes, due in great part to the near-ubiquitous use of cell phones in much of the developing world. Systems are now being created to allow medical care providers to text coded reports to be analyzed *en masse* (Yang et al. 2009). Similarly, monitoring the frequency of specific disease-related terms in daily Internet postings, search queries, or SMS text messages is now providing alternative forms of disease surveillance (Ginsberg et al. 2009). The extent to which telemedicine and the Internet decrease the disparity between countries in regard to access to health information and capacity to detect EIDs remains to be seen, but our increased capacity to reach understudied areas suggests that this will be significant.

Platforms for pathogen discovery and our ability to follow footprints of infectious agents require the laboratory and computational infrastructure sufficiently powerful to dissect complex host–microbe interactions. For example, MassTag PCR is a multiplex platform that allows animal and human health specialists and epidemiologists to simultaneously test one sample for the presence of up to 30 different agents. MassTag PCR is a powerful tool for genomics, molecular virology, computational biology, surveillance, pathogen discovery, outbreak detection, and epidemiological investigations (Lipkin 2010).

CONCLUSIONS

EIDs are a growing and complex threat to global public health. Diseases emerge when socioeconomic or environmental changes provide the optimal conditions for pathogens to exploit new host populations, increase in pathogenicity, or otherwise amplify transmission. We present a broad-scale, strategic approach for selecting geographic sites and species for sampling and then present a framework for making predictions about the future risk of EIDs from wildlife. In our view, the best approach to detecting and preventing the next emerging infectious disease before it becomes a pandemic threat is through building a broad coalition of partners to discover, detect, and monitor diseases at the wildlife–human interface using a localized, risk-based approach. These efforts can integrate predictive modeling, digital sensing, on-the-ground surveillance, and advanced molecular techniques at critical points for disease emergence, which then feed back to models for testing and refinement.

ACKNOWLEDGMENTS

We wish to acknowledge the Research and Policy for Infectious Disease Dynamics (RAPIDD) program of the Science and Technology Directorate, U.S. Department of Homeland Security, and the Fogarty International Center, NIH and the generous support of the American people through the United States Agency for International Development (USAID) Emerging Pandemic Threats PREDICT. The contents are the responsibility of the authors and do not necessarily reflect the views of USAID or the United States Government.

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