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Emerging zoonoses: The challenge for public health and biodefense☆

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Abstract

The concept of new and emerging diseases has captured the public interest and has revitalized the public health infectious disease research community. This interest has also resulted in competition for funding and turf wars between animal health and public health scientists and public officials and, in some cases, has delayed and hindered progress toward effective prevention, control and biodefense. There is a dynamic list of outbreaks causing substantial morbidity and mortality in humans and often in the reservoir animal species. Some agents have the potential to grow into major epidemics. There are many determinants that influence the emergence of diseases of concern that require the use of current understanding of the nature of agent persistence and spread. Additional factors that are global must be added to plans for prevention and control. To this complex mix has been added the potential for accidental or malicious release of agents. The nature of emerging infectious agents and their impact is largely unpredictable. Models that strive to predict the dynamics of agents may be useful but can also blind us to increasing disease risks if it does not match a specific model. Field investigations of early events will be critical and should drive prevention and control actions. Many disease agents have developed strategies to overcome extremes of reservoir qualities like population size and density. Every infectious agent spreads easier when its hosts are closer together. Zoonoses must be dealt with at the interface of human and animal health by all available information. Lessons learned from the emergence of and response to agents like West Nile virus, H5N1 avian influenza, SARS and bovine spongiform encephalopathy, the cause of new-variant Creutzfeldt–Jakob disease in humans, must be used to create better plans for response and meet the challenge for public health and biodefense.

Keywords: Emerging zoonoses; Control and prevention; Preparedness and biodefense

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1. Introduction

Since the publication in 1992 of the Institute of Medicine (IOM) report, Emerging Infections – Microbial Threats to Health in the United States, and its update in 2003, Microbial Threats to Health – Emergence, Detection and Response, the concept of new and emerging diseases has captured the public interest and has revitalized the public health infectious disease research community (Lederberg et al., 1992; Smolinski et al., 2003). We have seen the concept generate substantial political clout, which has led to new public funding. We have seen the concept change over time as different forces have controlled national priorities—the balance has been skewed several times, not so much in the name of research needs or prevention and control priorities, but in the name of funding the home turf. Within this changing scene, how have the zoonoses fared? The answer differs according to whether one comes to the question from the perspective of the animal disease or human disease community (Murphy, 1998, 2001).

Some zoonotic infectious agents have largely been in the hands of scientists and public officials associated with animal health and agriculture. These shared agents include: (1) agents that cause substantial morbidity or mortality (or diagnostic difficulty) in livestock or poultry, especially the agents that cause ‘‘foreign animal diseases’’; (2) certain classic agents, such as *Mycobacterium bovis* and *Brucella abortus*; and (3) bacteria of concern in pre-harvest food safety, such as *Salmonella* and *Campylobacter* spp. The prions also hold a unique place in this context. Still, it would seem that although some of the agents dealt with by the animal health community are emergent, the emerging disease concept has not been embraced by this community, and little change in funding over the past several years is evident.

Other zoonotic infectious agents have largely been in the hands of scientists and public officials associated with public health. These include, for example: (1) the rabies virus, which has served as the founding basis for veterinary public health infrastructure development; (2) the many arthropod-borne viruses, bacteria and protozoa; (3) several rodent-borne viruses and bacteria; (4) primate-borne agents; (5) prions; and (6) agents considered bioterrorism threats. All of the agents dealt with by this community are the subject of increasing research funding and a barrage of public ‘‘information.’’ Most of the effort to obtain new funding has come under the emerging diseases flag, or the flag that brings emerging diseases and biodefense together.

Finally, zoonotic infectious agents have seemingly always been ‘‘in between,’’ often involved in foolish turf wars between scientists and public officials from the animal health and public health communities. These shared agents include, for example: (1) avian influenza viruses; (2) *Salmonella enteriditis*; (3) *Listeria monocytogenes*; and (4) to some extent, West Nile virus. It would seem that progress is being made here, partly because competition between the agriculture and public health sectors results in additional funding, but usually only after turf-based delays.

Despite all this, it seems that the concept of new and emerging zoonotic diseases has not been fully exploited—especially given the overriding realization that nearly all of the emergent disease episodes that have caught public attention in the past 15 years have involved zoonotic infectious agents (King and Hamburg, 2005; Womack, 2005).

2. The importance of zoonoses and zoonotic infectious agents

One needs only to scan the long list of the new, emerging and re-emerging diseases and pathogens, and the outbreaks and epidemics in the past few years to make the point that these diseases are important. This list would not simply be composed of the ‘‘diseases of the week’’ from the public media; rather, it would be a long, dynamic list of outbreaks causing substantial morbidity and mortality in humans and in many cases reservoir animal species. Moreover, a few of the agents or diseases present the continuing threat of major epidemic incidents. For example: influenza viruses cause thousands of deaths every winter in the elderly and caused the single most deadly epidemic ever recorded (the pandemic of 1918–1919 during which 40–100 million people died). Since 1997, emerging zoonotic, highly pathogenic avian influenza viruses have caused great losses to the poultry industries in many countries and caused great worry about the next human pandemic.

The Nipah virus, the zoonotic etiologic agent (with its reservoir in fruit bats) of severe, often fatal encephalitis, caused an epidemic in the Malaysian peninsula in 1999 during which more than 100 humans died. This virus has also caused outbreaks with high fatality rates in India and Bangladesh since 2003.

Rift Valley fever virus is a mosquito-borne etiologic agent of a classical disease in sheep and a febrile disease with hepatitis and hemorrhagic fever in humans. It is the cause of one of the most explosive epidemics of zoonotic disease ever seen in Africa.

Ebola and Marburg viruses, the etiologic agents of the most lethal hemorrhagic fevers known, are zoonotic, but their natural reservoir(s) in fruit bats is still not fully proven. These viruses have caused several recent and substantial epidemics of Ebola and Marburg hemorrhagic fevers in central Africa.

Japanese encephalitis virus, the mosquito-borne etiologic agent of severe, often lethal, encephalitis is now spreading across southern Asia and has the potential for great epidemic and geographic expansion, even to North America.

SARS coronavirus, the etiologic agent of severe acute respiratory distress syndrome (ARDS) caused a worldwide epidemic originating in China in 2002, with more than 8000 cases and 800 deaths.

Sin Nombre and other New World hantaviruses are the rodent-borne etiologic agents of hantavirus pulmonary syndrome (HPS). Since its discovery in 1993, over 438 cases of HPS have been reported in the United States, with a 36% case-fatality rate.

The prion that causes bovine spongiform encephalopathy and variant Creutzfeldt–Jakob disease has been the cause of great economic loss in the cattle industry of the United Kingdom and several other European countries as well as a cause of great public concern.

West Nile virus, the mosquito-borne etiologic agent of febrile disease and encephalitis was introduced into New York in 1999 and has now spread throughout the U.S., north into Canada, and south into Mexico. The virus has caused over 18,000 cases, 800 human deaths, and a large but indeterminate number of equine deaths.

3. Determinants contributing to the emergence of zoonotic disease agents

- Microbial/viral determinants (mutation, natural selection, and evolution).
- Determinants pertaining to the host (natural resistance, innate and acquired immunity).
- Natural determinants (ecologic, environmental, and zoonotic influences).
- Determinants pertaining to human activity (personal behavior, societal, commercial, and iatrogenic factors).
- Accidental or malicious release.

Rarely do these determinants act singly – in the 2003 IOM Report, *Microbial Threats to Health – Emergence, Detection and Response*, a ‘‘Convergence Model’’ was developed to emphasize the complexity of interacting determinants favoring the emergence of pathogens

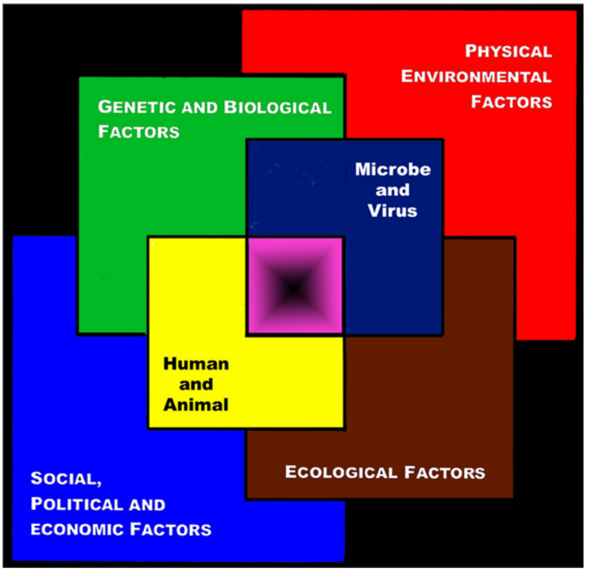

Fig. 1. Convergence model developed to emphasize the complexity of interacting determinants favoring the emergence of pathogens (Smolinski et al., 2003).

(Fig. 1) (Smolinski et al., 2003). Of all these interacting determinants, those that contribute to the emergence of host range extensions, that is ‘‘species jumping’’ events leading to new zoonoses, may be the most important.

It is highly unlikely that there will be any way to predict when or where the next important, new zoonotic pathogen will emerge; nor will there likely be any way to predict a new pathogen's ultimate importance from its early behavior. Although predictive models may be useful – this has been done again recently for influenza – most are untested, and the next genetic shift, or the next major genetic drift, yielding the next pandemic influenza virus, will most likely not be as predicted. Of course, the danger here is that our enthusiasm for computer-based modeling may prevent us from recognizing the significance of an emergence that does not match with a specific model. A greater danger may be that as a new pandemic emerges, too many epidemiologists might be sitting at their computers instead of being in the field investigating early events that drive prevention and control actions.

4. Determinants pertaining to the reservoir hosts of zoonotic infectious disease agents

Qualities of reservoir host populations, *per se*, that may affect the success of transmission of zoonotic viruses in nature include population size, density, age distribution, behavior (seasonal, hormonal), nutritional status, immune status (herd immunity), and the like. Particular zoonotic agents have developed survival strategies to deal with the extremes in host population qualities—of the viruses transmitted from human to human, most thrive in the largest, densest populations or when introduced into an isolated non-immune human population. However, many of the zoonotic infectious agents seem to thrive where there is a minimum density of susceptible animal reservoir hosts, just enough to sustain the transmission chain. Zoonotic transmission chains involving arthropod vectors are subject to very complex, multifactorial, and usually unpredictable patterns. It might seem that such transmission chains are fragile, subject to interruption by minimal human intervention, but in most cases this has not been the case. Mutation and selection work well in the circumstances of ‘‘thready’’ transmission chains: variants with improved ‘‘fit’’ have great survival advantages when added onto ancient transmission and survival patterns. For example, the several rabies virus variants that have become adapted to particular reservoir hosts must have evolved in this way.

Most changes in reservoir host populations that can affect the emergence of zoonotic infectious agents are caused by human activities. Most important, in this regard, is the ever-increasing density of human populations, the increasing density of monotypic domestic animal and crop plant populations, and the crowding together of wildlife into limited areas as habitat disappears. These population densities present grand opportunities for the selection, penetrance and continued evolution of viral variants. Regardless of the specific mode of transmission, every infectious agent spreads easier when its hosts are closer together. Next most important are the incredible changes occurring in ecosystems themselves, brought about by human occupation of every corner of the planet and the consequent forced adaptation by every other species. This is the sphere that includes uncontrolled urbanization and the relentless spread of primitive agriculture. Because of these trends, it is possible that far into the future, most new emerging disease threats to humans could come from zoonotic agents.

For example, consider the potential for the emergence of new mosquito-borne zoonoses. The many factors that are involved are in a state of flux. Climate, weather, rainfall, and temperature (global warming) changes can lead to adaptation. Population movements result in the intrusion of humans and domestic animals into previously isolated arthropod habitats such as tropical rainforests. This population movement leads to deforestation and settlement of new tropical forest/farm margins, which may in turn lead to expanding primitive irrigation systems that make no attempt to control mosquito breeding. The opening up of isolated ecosystems such as remote tropical islands, and increased long-distance air travel could introduce populations to new agents and make spreading them easier. Increased long-distance livestock and other animal transportation could carry infectious agents, vectors and even reservoir hosts around the world. New routings of long-distance bird migrations, often caused by new water impoundments, place these birds in contact with new species. In addition to all this, uncontrolled urbanization and environmental pollution favor a great increase in mosquito breeding sites.

Other changes deriving from human activities serve to amplify the risk of the emergence of new zoonotic agents. For example, the rise of the threat of bioterrorism adds yet another dimension to the risk equation (Moon, 2002); and some people think that xenotransplantation adds yet another level of risk. The focus of public attention on remote econiches and exotic wildlife hosts, that is, ‘‘The Ebola Mystique,’’ needs to be redressed. More pertinent is the example of the not-so-exotic reservoir host population represented by the cattle herd of the United Kingdom, in which the spread of the bovine spongiform encephalopathy prion put millions of people at risk and caused more than 160 human deaths.

Zoonoses must be dealt with at the interface between human public health and veterinary public health—often this interface occurs as a crack in the façade of governmental responsibilities, a crack in which human public health and veterinary/animal health agencies do not venture without turf-battling or turning a blind eye. For example, rabies still causes 40,000–70,000 human deaths worldwide each year, mostly in Asia and Africa, and 30–50% in children. More than 10 million people receive post-exposure treatment each year, and most cases are still caused by the bite of a rabid dog. Even more alarming, most children who die from rabies do not receive post-exposure treatment: a vaccine and rabies immunoglobulin. There is a notorious lack of surveillance data and a notorious failure to use any such data to drive prevention and control programs. On top of this is a failure to deal with the historic belief in several rabies-endemic countries that "rabies has always been with us and always will be with us." For example, after two human rabies deaths in Kerala State, Southern India, in 2006, the respected rabies expert, T. Jacob John, Professor of Clinical Virology, Christian Medical College, Vellore, wrote (ProMed 28 April 2006): "*The adage 'familiarity breeds contempt' is apt here. Dogs are common, dog-bites are also common. People often do not take bites seriously. There are several factors involved in such negligent behavior: belief in pre-destiny or fatalism; non-perception of personal risk; lack of authentic information from Public Health agencies; availability of non-scientific remedies; inadequate health education in schools, etc. Needless to say, such tragic deaths are preventable.*" Under-estimating the importance of rabies leads decision-makers to perceive rabies as a rare disease, resulting from the bite of an economically unimportant animal (the dog). In many countries, rabies control is lacking and falls in the crack between departments/ministries of health and agriculture because neither takes full responsibility for its prevention.

One reason for this disparity is that the research base for dealing with the zoonoses extends incredibly far, involving disciplines in which scientists often do not otherwise know each other or work with one another. The interface extends from virology, bacteriology, protozoology (biologic and molecular biologic), immunology, and pathology, to ecology, animal biology, wildlife biology, mammology, ornithology, and entomology, to meteorology, climatology, geography, sciences pertaining to societal and commercial risk factors, economics, government, biodefense, etc., as well as to the medical and veterinary sciences.

5. The relationship between the evolution of zoonotic infectious agents and the emergence of zoonotic diseases

If the relationship between zoonotic infectious agents and their reservoir hosts were static, or even evolved very slowly, we could plan accordingly—it is change and the threat of more change that underpins our concern. This has been clearly understood in the development of the concept of new and emerging diseases. Even if we cannot predict change, we must better appreciate the first signs of change. To do this we need to better integrate various disparate "databases." First, we must integrate information on just how potential zoonotic agents are changing in nature and in their reservoir hosts. This change, that is, the evolutionary progression of infectious agents, especially viruses, is in the nature of the beast. Second, we must integrate information coming from viral/microbial genomic sequencing, employing for other agents the same kind of molecular epidemiology that has been applied to endemic infectious agents, such as polioviruses, dengue viruses, and foot-and-mouth disease viruses. Third, we must integrate information from representative animal model studies—this is a key intermediate stop between basic research and disease control actions, the place occupied by the fields of pathogenesis and pathophysiology, within the field of comparative medicine. We must also integrate information coming from studies of population biology, another key intermediate stop occupied by the fields of basic epidemiology and related statistical sciences. Lastly, we must integrate information coming from clinical human, veterinary, and wildlife medicine. Most importantly, within these three areas is where we must test new approaches for intervening in the course of emerging diseases which is at the level that the public understands best.

6. Strategies for the prevention and control of zoonoses

Over the past 15 years, many documents have been published outlining traditional infectious disease prevention and control strategies and tactics. These documents apply the same strategies to emerging diseases, and they are all similar in calling for more and better surveillance and laboratory diagnostics, as well as prevention and control actions in the field. However, we need a venue for considering new, complementary, integrative approaches that are especially pertinent to the zoonotic diseases. Zoonotic diseases require substantially different prevention and control strategies than is the case when the etiologic agent has long employed only human-to-human transmission for its survival. Acute infectious disease prevention and control strategies used in public health agencies were largely developed from experiences with the vaccine-preventable childhood diseases, sexually transmitted diseases, hepatitis, etc. With these diseases, traditional, clinically based or laboratory-based surveillance has provided the foundation for intervention activities such as vaccination or antimicrobial chemotherapy. For the zoonoses, prevention and control strategies have come from other amazingly diverse bases. At the heart of these strategies have been individual scientists who have spent whole careers accumulating highly specialized knowledge and experience. In fact, the work of these scientists might best be described as basic research—research that aims to understand the full context, the full ecology of the zoonotic disease of interest, while at the same time seeking the means for its control and prevention. Several National Academies of Sciences/National Research Council reports provide an introduction to this subject (see references).

7. Conclusions

The zoonoses are likely to become even more important in the future. Strategies for their prevention and control are distinct, often making new research necessary before designing appropriate prevention and control actions. The kind of interdisciplinary research called for often requires specialists who are in short supply. Therefore, long-term planning that takes into consideration the unique nature of zoonoses is needed, and this planning must involve the entire interested scientific community. Planning must not be biased by the most recent or trendy zoonotic disease episode. Because of current interest and perceived problems, the West Nile virus emergence in the northeastern U.S. in 1999 as the ideal model or the more recent cases of human disease caused by H5N1 avian influenza might be taken as an even better basis for developing an overall model. These public health problems are certainly important enough, the impediments realistic enough, the exercise difficult enough, but why not use an even more complex model, one that would test all facets of candidate plans? The ultimate model, the ultimate test of candidate plans may be the zoonosis bovine spongiform encephalopathy, the cause of new-variant Creutzfeldt–Jakob disease in humans. Today, with the wisdom of hindsight, it might be said that the ministries of agriculture and health in the United Kingdom failed to react in timely fashion and with proper scope and scale of actions to deal with what was clearly a great risk to the public health (and to the livestock economy)—every element of the disease prevention/control responsibilities of both ministries have been called into question. This zoonosis may be instructive in a larger sense also, especially in its easy extension into the worlds of macroeconomics, international trade, and national politics. This zoonosis may be instructive in regard to the take-home message from the 2004 IOM report, *Learning from SARS: Preparing for the Next Disease Outbreak* (Knobler et al., 2004). This report concludes that if we are to improve the public health response to future outbreaks of infectious diseases, we must:

1. Anticipate the emergence of new zoonoses—after all, the most recent episodes of emerging diseases have involved zoonotic agents, so why not anticipate a continuation of this phenomenon?
2. Understand that strategies for containing known zoonoses may provide models for containing new ones.
3. Improve early detection/diagnostic systems.
4. Communicate better with the public.
5. Promote applicable research.
6. Develop new strategies for containment and decontamination.
7. Assure better multinational cooperation and collaboration.

Then, we must turn plans into action by moving beyond meetings, conference calls, reports, etc., and reach a level of stand-by readiness appropriate to the scale of episodes that have occurred naturally in recent years. Finally, given the long-term view required here, we must assure an appropriate level of advanced training and career path development that will carry the experience and expertise of the current generation over to the next generation of scientists and human and veterinary public health professionals.

8. Conflict of interest statement

Dr. Murphy does not have a financial or personal relationship with other people or organisations that could inappropriately influence or bias the paper entitled ‘‘Emerging zoonoses: the challenge for public health and biodefense.’’

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