

James M. Hughes and Mary E. Wilson, Section Editors

The Origin and Prevention of Pandemics

Brian L. Pike,¹ Karen E. Saylors,¹ Joseph N. Fair,¹ Matthew LeBreton,¹ Ubald Tamoufe,¹ Cyrille F. Djoko,¹ Anne W. Rimoin,² and Nathan D. Wolfe¹

¹Global Viral Forecasting Initiative, San Francisco, and ²Department of Epidemiology, University of California–Los Angeles School of Public Health, California

Despite the fact that most emerging diseases stem from the transmission of pathogenic agents from animals to humans, the factors that mediate this process are still ill defined. What is known, however, is that the interface between humans and animals is of paramount importance in the process. This review will discuss the importance of the human-animal interface to the disease emergence process. We also provide an overview of factors that are believed to contribute to the origin and global spread of emerging infectious diseases and offer suggestions that may serve as future prevention strategies, such as social mobilization, public health education, behavioral change, and communication strategies. Because there exists no comprehensive global surveillance system to monitor zoonotic disease emergence, the intervention measures discussed herein may prove effective temporary alternatives.

Contemporary pandemics and outbreaks of disease, such as the current H1N1 influenza pandemic, as well as the emergence of H5N1 influenza virus and severe acute respiratory syndrome (SARS)–associated coronavirus, serve as poignant reminders of our global vulnerability to emergent threats to human health and our current inability to predict or prevent such events. However, despite the seemingly unpredictable nature of disease emergence, there are lessons to be learned from the origins of recently emerged diseases as well as those that have their origins in the more distant past, lessons that may offer clues as to how future infectious disease outbreaks and pandemics may be prevented. The challenge lies in using the accumulated, albeit incomplete, knowledge gained from emergent diseases of our past to identify practical solutions and strategies aimed at detecting and halting future threats.

Here, we review the field's current understanding of the origins of infectious diseases and the factors that contribute to their emergence. In particular, we highlight the importance of the zoonotic transmission of pathogenic agents from animals to humans, the favored mechanism by which emergent diseases have come to afflict humans throughout history [1–3]. Indeed, one key lesson from past pandemics is the pivotal importance of the human-animal interface. Improving our understanding

of this interface will be crucial to future pandemic prevention efforts.

ZOONOTIC DISEASE EMERGENCE

The majority of all human infectious diseases and pandemics have originated through the cross-species transmission of microorganisms from animals to humans, overwhelmingly in the Old World [1, 3]. However, because most animal pathogens are not readily transmitted to humans [4, 5], it follows that for an animal pathogen to become a specialized pathogen in humans, multiple variables must combine in a dynamic and as yet not fully understood process of cross-species transmission. For an animal pathogen to become a successful human pathogen, it must evolve into a pathogen capable of not only infecting humans, but maintaining long-term human-to-human transmission without the need for reintroduction from the original animal host. This process can be categorized into five progressive stages (reviewed by Wolfe et al [3]). Stage 1 involves animal microbes that are not present in humans under natural conditions, such as most malarial plasmodia. When a pathogen evolves such that it can be transmitted to a human under natural conditions but cannot support sustained human-to-human transmission, it has entered stage 2. Examples of such pathogens include tularemia bacilli, Nipah, rabies, and West Nile viruses. Transition from stage 2 and into stage 3 is defined by secondary transmission between humans. Stage 3 includes pathogens that undergo only a few cycles of secondary transmission between humans, such as Ebola, Marburg, and human monkeypox viruses, whereas stage 4 includes diseases that exist

Received 3 December 2009; accepted 20 February 2010; electronically published 7 May 2010.

Reprints or correspondence: Dr Nathan D. Wolfe, Global Viral Forecasting Initiative, 1 Sutter, Ste 600, San Francisco, CA 94104 (nwolfe@gvfi.org).

Clinical Infectious Diseases 2010;50(12):1636–1640

© 2010 by the Infectious Diseases Society of America. All rights reserved.

1058-4838/2010/5012-0014\$15.00

DOI: 10.1086/652860

in animals but which undergo long sequences of secondary human-to-human transmission without the involvement of animal hosts, such as influenza A, *Vibrio cholerae*, and dengue virus. Stage 5, in contrast, represents diseases that are exclusive to humans. Agents responsible for some of history's most troubling diseases belong to stage 5 and include pathogens such as human immunodeficiency virus (HIV) infection, smallpox, and tuberculosis [3].

THE HUMAN AND ANIMAL INTERFACE

The disease emergence model above provides a construct for how pathogens emerge from animals and illustrates the continuum of animal pathogen infectivity in the human population. However, relatively little is known about the factors that mediate transition from one stage to the next as a pathogen of animal origin scales the stages of this paradigm (Figure 1), ever increasing its ability to reside in the human population and be transmitted throughout it. What is known, however, is that the interface between humans and animals is of paramount importance in the process. As we increase our interactions with animals through hunting, the trading of animal foods, animal husbandry practices, wet markets, and the domestication of animals or exotic pets, the probability of cross-species transmission dramatically increases.

It is now generally accepted that the hunting and butchering of wild nonhuman primates in the early 20th century led to the introduction of simian immunodeficiency virus into the human population, giving rise to our modern day HIV pandemic [6]. In our own work, we have demonstrated that the traditional practice of hunting and butchering nonhuman primates continues to be a gateway for the zoonotic transmission of retroviruses. For instance, among central Africans reporting contact with nonhuman primate blood and body fluids through

hunting, butchering, and keeping primate pets, we identified a wide array of primate T lymphotropic viruses [7], including 2 novel viruses: one that is distinct from all other known primate T-lymphotropic viruses, now designated human T lymphoto-tropic virus subtype 4 (HTLV-4), and a second that is similar to other nonhuman primate T lymphoto-tropic virus subtype 3 viruses that had not previously been described as infecting humans. These results demonstrate that entry of pathogens into the human population via contact with nonhuman primates is an ongoing, dynamic process. In fact, zoonotic transmission of viruses occurs on an astonishingly regular basis. In a serological survey of >1000 rural Cameroonian villagers with reported exposure to primates, we found that 1% had antibodies to simian foamy virus [8], suggesting that populations exposed to animal reservoirs of disease are constantly assailed by zoonotic agents. Presumably, the likelihood of any one zoonotic agent becoming a human pathogen is dependent upon a number of factors. Multiple introductions into the human population may be necessary before a zoonotic agent establishes itself as a human pathogen and the determinants of cross-species tropism are still ill defined, as are the factors that influence whether infection causes disease. However, the frequency with which the human population is exposed to a potential zoonotic agent is likely to be an important determinant in disease emergence.

The course that a pathogen of animal origin takes into the human population varies. The SARS outbreak originated from bats of the genus *Rhinolophus*, and its human emergence is believed to have been facilitated through intermediate hosts in the wet markets of southern China [9, 10]. The current H1N1 influenza epidemic appears to have arisen in North America primarily through the reassortment of viruses of swine origin [11, 12]. The species of animal that harbors the pathogen, the nature of human interaction with that animal, and the fre-

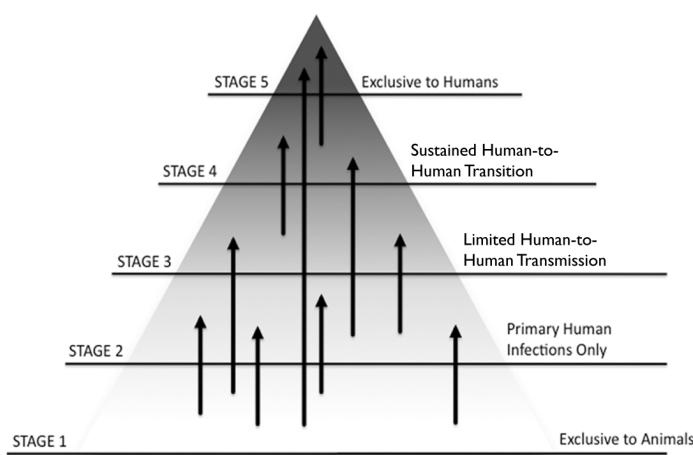


Figure 1. Zoonotic disease emergence model outlining the 5 stages of pathogen emergence from animals to humans.

quency of these interactions all likely modulate the risk of zoonotic transmission [3]. Understanding this complex process will be important to combating future disease emergence. Therefore, further investigation into the interactions that humans have with animals (as a potential reservoir of disease), and conditions that influence this interaction, is warranted. As an example, despite the fact that chimpanzees have an extremely small population size and human contact with them is infrequent, their close phylogenetic relationship to our own species likely played an important role in our acquiring HIV from chimpanzees, as did the nature of our relationship with them. Presumably, the odds of contracting HIV would have been much lower had humans not been engaged in hunting chimpanzees, a practice that offers many opportunities for exposure to zoonotic agents through contact with biological fluids and tissue.

The human-animal interface is fluid and our interaction with other species, and any potential zoonotic agents they may possess, is variable. The frequency and type of human-animal interaction fluctuates in response to other external factors that, in turn, influence the potential for transmission of zoonotic agents. For instance, socioeconomic factors are hypothesized to be a major determinant of the spatial distribution of emerging infectious disease events [1]. Socioeconomic pressures influence bushmeat hunting, a practice that is believed to be a major contributor to disease emergence [13], by obliging some populations to hunt to meet basic nutritional requirements in response to food availability [14]. Similarly, studies of Lassa fever in Guinea and Sierra Leone directly correlate the risk of infection with Lassa fever, a viral hemorrhagic fever caused by an arenavirus transmitted by rodents, with poor housing and food storage conditions in refugee camps and other desperately poor communities [15, 16]. Other factors are also thought to have the potential to influence zoonotic disease emergence. **For instance, the loss of biodiversity is believed to be an important contributing factor to zoonosis [17], and studies conducted in the Congo Basin and Rift Valley suggest that deforestation and climate change play important roles in the risk of zoonotic transmission from wildlife to humans [18].** Likewise, deforestation and climate change are hypothesized to have been causal events that led to the 1998 emergence of Nipah virus from fruit bats to pig livestock and, subsequently, to the farm workers within the Kinta district of Perak state in Peninsular Malaysia, resulting in hundreds of reported cases of acute viral encephalitis [19–22]. However, the precise causal relationship between these human-animal interface factors and how they influence the dynamics of zoonotic disease emergence is not fully elucidated, nor is the interconnectedness of the various factors (eg, socioeconomic factors and deforestation) well understood. Defining cause and effect relationships may provide

valuable clues as to how would-be emergent diseases might be prevented.

PREVENTION OF DISEASE EMERGENCE AND PANDEMICS

Current global disease control focuses almost exclusively on responding to pandemics after they have already spread globally [23]. Nevertheless, dramatic failures in pandemic control, such as the ongoing lack of success in HIV vaccine development 25 years into the pandemic, have shown that this wait-and-respond approach is not sufficient and that the development of systems to prevent novel pandemics *before* they are established should be considered imperative to human health. Had we had such mature systems in place, we may have averted the H1N1 influenza pandemic that is currently unfolding. The early detection of emergent threats to human health is all the more important given the speed with which disease causing agents are now capable of being distributed around the globe through air travel [24] and the global trade of animals as potential reservoirs of disease [25]. Because the success of a pathogen depends on its ability to spread from human to human and on the number of susceptible humans, our ability to cross continents in a single day poses a unique new challenge to emerging infectious disease control. Past studies have highlighted the importance of global travel to the spread of pandemic disease [26–28], and the recent emergence and subsequent global spread of H1N1 influenza virus eloquently illustrates how our global interconnectedness can affect the worldwide distribution of a new virus, one that may otherwise have remained a regional phenomena in an era before global transit.

The Committee on Achieving Sustainable Global Capacity for Surveillance and Response to Emerging Diseases of Zoonotic Origin was convened by the Institute of Medicine and the National Research Council to assess the feasibility, needs, and challenges of developing a future and sustainable global disease surveillance program [29]. As the committee's report comprehensively expresses, our current disease surveillance system and our ability to identify emergent diseases early are inadequate. Implementing all of the committee's recommendations would represent a significant step forward in achieving a well-integrated zoonotic disease surveillance system, but we are still far from realizing this goal. Given the fact that more than one-half of emerging infectious diseases have resulted from zoonotic transmission [1] and that the human-animal interface is so pivotal to the process of disease emergence, it stands to reason that the most effective strategy in terms of early detection of an emergent pathogenic threat would focus on conducting surveillance of humans highly exposed to animals and within the animal populations to which they are routinely exposed. Despite this, there exists no systematic global effort to monitor

for pathogens emerging from animals to humans in “at-risk” populations, and we are probably years from having such a system in place.

Although a global surveillance system for pandemic prevention is still far from reality, there may be more immediate, interim measures that may be taken to mitigate the risk of zoonotic transmission, even in the absence of a global surveillance effort. In situations where humans and animals are in close contact, behavioral change approaches may be a preventative step to reducing the risk of zoonotic transmission. Behavioral modification campaigns have previously been used in combating outbreaks of known infectious diseases [30–32]. For instance, a behavioral modification campaign was launched in Sierra Leone to reduce cases of Lassa fever [32]. The intervention involved incidence mapping, contact tracing to warn relatives of the dangers of secondary infection, and education to exposed populations in methods of avoiding exposure to rodents, the reservoir of the disease. Prevention posters included graphic depictions to instruct villagers in techniques for protecting food from rodents, trapping rodents, dealing safely with carcasses of dead rats, and symptom recognition. As part of the campaign, local musicians were even commissioned to write and perform songs about routes of transmission of Lassa fever and preventative measures. These outreach activities were an attempt to increase awareness of the disease and to promote behavior change aimed at reducing incident cases of Lassa fever through reducing the risk of exposure to animals, in this case rodents.

We have implemented similar risk-reduction measures in our own work with Cameroonian bushmeat hunters through “healthy hunter” education sessions. These sessions are designed to encourage hunters to reduce their contact with wild animal blood and body fluids. We educate hunters in this program on pathogens that can be found in wild animals, which species are believed to pose the greatest risk with regard to the transmission of zoonotic agents, and what steps can be taken to avoid possible infections. Although it is important to explain that the best way to avoid infections is to not handle animals and to limit one’s exposure to animal blood and body fluids, for many people, hunting and butchering represent an essential part of daily food preparation. Thus, the focus of this intervention is on reducing the risk of zoonotic infection and not necessarily the practice of bushmeat hunting itself. With this in mind, the interactive education sessions are meant to inform individuals of precautions that may be taken to reduce the risk of being infected with a zoonotic agent when engaged in high-risk practices such as hunting and butchering. Such precautions include avoiding the hunting of nonhuman primates, because they share many diseases and infections with humans; avoiding butchering or handling animal meat if there are injuries on the hands or arms; immediately washing any bites, scratches, cuts,

or injuries obtained during hunting or butchering, preferably with soap; and avoiding contact with animal carcasses found in the forest.

More research is needed to determine the efficacy of reducing disease spread through social mobilization, public health education, behavioral change, and communication strategies. Although it is challenging to measure behavioral change efficacy in reducing the risk of transmission of potential pathogens, program evaluation will be important in defining replicable behavioral change and communication models that are useful in emerging infectious disease “hot spots,” those regions that have disproportionately given rise to the majority of human diseases. If they prove to be effective, behavior modification measures may have an enormous impact on curtailing disease emergence and progression in conjunction with other strategies.

THE FUTURE OF PANDEMICS

The ongoing global HIV pandemic, the recent outbreaks of pathogens such as SARS and the H5N1 influenza virus, as well as the current H1N1 influenza pandemic, the global consequences of which are still to be determined, demonstrate our continued vulnerability to emerging infectious diseases. The most recent example, H1N1 influenza, and its dramatic spread also reminds us that we have entered into a new age of global pandemics, largely because of the rapidity with which newly emergent pathogens are capable of being transmitted around the world. Because of our continued vulnerability and the challenges that global travel poses to pandemic control, it is now more important than ever that we identify emerging infectious diseases early. Although it is still difficult to predict the agent that will pose the next pandemic threat, when it will occur or where it will begin, it will likely be the result of cross-species transmission from animals to humans. This likelihood argues in favor of developing a system aimed at detecting the transmission of potentially pathogenic agents from animals to humans early in the zoonotic disease emergence process and identifying ways by which we can diminish the risk of transmission, especially in populations that are highly exposed to animals and their potentially zoonotic agents.

Acknowledgments

We thank the entire staff of GVFI-Cameroon for their support as well as to Dr. Bruno Sainz for his assistance in preparing this manuscript. The authors would also like to thank Google.org and The Skoll Foundation for their continued support.

Financial support. N.D.W. was supported by awards from the National Institutes of Health Director’s Pioneer Award (DP1-OD000370), the US Military HIV Research Program, and the NIH Fogarty International Center (International Research Scientist Development Award Grant 5 K01 TW000003-05), AIDS International Training and Research Program (2 D 43 TW000010-17-AITRP), and National Geographic Society Committee for Research and Exploration (Grant 7762-04).

Potential conflicts of interest. All authors: no conflicts.

References

1. Jones KE, Patel NG, Levy MA, et al. Global trends in emerging infectious diseases. *Nature* **2008**; 451(7181):990–993.
2. Taylor LH, Latham SM, Woolhouse ME. Risk factors for human disease emergence. *Philos Trans R Soc Lond B Biol Sci* **2001**; 356(1411):983–989.
3. Wolfe ND, Dunavant CP, Diamond J. Origins of major human infectious diseases. *Nature* **2007**; 447(7142):279–283.
4. Antia R, Regoes RR, Koella JC, Bergstrom CT. The role of evolution in the emergence of infectious diseases. *Nature* **2003**; 426(6967):658–661.
5. May RM, Gupta S, McLean AR. Infectious disease dynamics: what characterizes a successful invader? *Philos Trans R Soc Lond B Biol Sci* **2001**; 356(1410):901–910.
6. Worobey M, Gemmel M, Teuwen DE, et al. Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960. *Nature* **2008**; 455(7213):661–664.
7. Wolfe ND, Heneine W, Carr JK, et al. Emergence of unique primate T-lymphotropic viruses among central African bushmeat hunters. *Proc Natl Acad Sci U S A* **2005**; 102(22):7994–7999.
8. Wolfe ND, Switzer WM, Carr JK, et al. Naturally acquired simian retrovirus infections in central African hunters. *Lancet* **2004**; 363(9413):932–937.
9. Webster RG. Wet markets—a continuing source of severe acute respiratory syndrome and influenza? *Lancet* **2004**; 363(9404):234–236.
10. Wang LF, Eaton BT. Bats, civets and the emergence of SARS. *Curr Top Microbiol Immunol* **2007**; 315:325–344.
11. Smith GJ, Vijaykrishna D, Bahl J, et al. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. *Nature* **2009**; 459(7250):1122–1125.
12. Schnitzler SU, Schnitzler P. An update on swine-origin influenza virus A/H1N1: a review. *Virus Genes* **2009**; 39(3):279–292.
13. Karesh WB, Noble E. The bushmeat trade: increased opportunities for transmission of zoonotic disease. *Mt Sinai J Med* **2009**; 76(5):429–434.
14. Brashares JS, Arcese P, Sam MK, Coppolillo PB, Sinclair AR, Balmford A. Bushmeat hunting, wildlife declines, and fish supply in West Africa. *Science* **2004**; 306(5699):1180–1183.
15. Bonner PC, Schmidt WP, Belmain SR, Oshin B, Baglole D, Borchert M. Poor housing quality increases risk of rodent infestation and Lassa fever in refugee camps of Sierra Leone. *Am J Trop Med Hyg* **2007**; 77(1):169–175.
16. Ter Meulen J, Lukashevich I, Sidibe K, et al. Hunting of peridomestic rodents and consumption of their meat as possible risk factors for rodent-to-human transmission of Lassa virus in the Republic of Guinea. *Am J Trop Med Hyg* **1996**; 55(6):661–666.
17. Maillard JC, Gonzalez JP. Biodiversity and emerging diseases. *Ann N Y Acad Sci* **2006**; 1081:1–16.
18. Martin V, Chevalier V, Ceccato P, et al. The impact of climate change on the epidemiology and control of Rift Valley fever. *Rev Sci Tech* **2008**; 27(2):413–426.
19. Chua KB, Goh KJ, Wong KT, et al. Fatal encephalitis due to Nipah virus among pig-farmers in Malaysia. *Lancet* **1999**; 354(9186):1257–1259.
20. Chua KB, Chua BH, Wang CW. Anthropogenic deforestation, El Nino and the emergence of Nipah virus in Malaysia. *Malays J Pathol* **2002**; 24(1):15–21.
21. Chua KB, Bellini WJ, Rota PA, et al. Nipah virus: a recently emergent deadly paramyxovirus. *Science* **2000**; 288(5470):1432–1435.
22. Chua KB. Nipah virus outbreak in Malaysia. *J Clin Virol* **2003**; 26(3):265–275.
23. Wolfe ND. Bushmeat hunting, deforestation, and prediction of zoonotic disease emergence. *Emerg Infect Dis* **2005**; 11(12):1822–1827.
24. Arguin PM, Marano N, Freedman DO. Globally mobile populations and the spread of emerging pathogens. *Emerg Infect Dis* **2009**; 15(11):1713–1714.
25. Arzt J, White WR, Thomsen BV, Brown CC. Agricultural diseases on the move early in the third millennium. *Vet Pathol* **2010**; 47(1):15–27.
26. Germann TC, Kadau K, Longini IM Jr, Macken CA. Mitigation strategies for pandemic influenza in the United States. *Proc Natl Acad Sci U S A* **2006**; 103(15):5935–5940.
27. Grais RF, Ellis JH, Glass GE. Assessing the impact of airline travel on the geographic spread of pandemic influenza. *Eur J Epidemiol* **2003**; 18(11):1065–1072.
28. Hufnagel L, Brockmann D, Geisel T. Forecast and control of epidemics in a globalized world. *Proc Natl Acad Sci U S A* **2004**; 101(42):15124–15129.
29. Institute of Medicine and National Research Council. Sustaining global surveillance and response to emerging zoonotic diseases. Washington, DC: The National Academies Press, **2009**.
30. Boumambouki P, Formenty P, Epelboin A, et al. Clinical management of patients and deceased during the Ebola outbreak from October to December 2003 in Republic of Congo. *Bull Soc Pathol Exot* **2005**; 98(3):218–223.
31. Kebaabetswe P, Norr K. Behavioral change: goals and means. In: Essex M, ed. AIDS in Africa. 2nd ed. New York: Kluwer Academic/Plenum Publishers, **2002**:514–526.
32. Fithen C. Social mobilisation against Lassa Fever in Sierra Leone. London, UK: Merlin, **2003**.