Published in final edited form as:
JAMA. 2007 May 9; 297(18): 2025–2027.

The Next Influenza Pandemic: Can It Be Predicted?

Jeffery K. Taubenberger, MD, PhD, **David M. Morens, MD**, and **Anthony S. Fauci, MD**
National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD.

Although most experts believe another influenza pandemic will occur, it is difficult to predict when or where it will appear or how severe it will be. Neither is there agreement about the subtype of the next pandemic influenza virus. However, the continuing spread of H5N1 highly pathogenic avian influenza A (HPAI) among poultry on several continents, associated with an increasing number of severe and fatal human infections, has raised the pandemic stakes.[1] Genetically and antigenically divergent H5N1 HPAI strains appeared in 1997 and have been spreading globally since 2003.[2-3] To date, epizootics in approximately 60 countries have caused a reported 291 human cases with 172 deaths.[4]

Although overshadowed by H5N1, at least 8 other poultry epizootics have recently occurred, some involving human infections and, uncommonly, human deaths.[5] H5N1 epizootics are unique, however, in causing mortality in wild birds, occasional infections in mammals, severe human infections, and in rare instances possible human–to–human transmission.[6]

Do these unique features predict an impending H5N1 pandemic? Despite significant research, fundamental questions about how influenza A viruses switch hosts from wild birds and adapt to domesticated poultry, pigs or horses, and subsequently to humans, remain unanswered, especially those regarding the changes that allow human–to–human transmissibility.[7] Given the potential for high morbidity and mortality, an approximation of the risk that H5N1 viruses will adapt to efficient human–to–human transmission would be extremely helpful for pandemic preparedness planning; despite the apparent inevitability of influenza pandemics, data accumulated over the past decade do not necessarily indicate pandemic emergence of H5N1.

How the H5N1 Virus May Be Evolving

H5N1 viruses are evolving rapidly; however, the direction of their evolution, driven by incompletely understood selection pressures, is unclear. Although current H5N1 HPAI viruses are descendants of the 1997 epizootic virus, significant genetic and antigenic evolution has since occurred, involving drift in the H5 hemagglutinin (HA), mutations in other genes, and reassortment with other avian influenza viruses.5 It is not yet clear which of these changes is associated with lethality in wild birds or with pathogenicity and transmissibility in poultry and other species. Asymptomatic endemic H5N1 HPAI circulation in domestic ducks maintains a pool of pathogenic viruses to which poultry are continually exposed,[8] suggesting that the current H5N1 situation will likely persist.

There are limited data indicating whether any H5N1 influenza strain is evolving in the direction of human adaptation. Some H5N1 viruses exhibit a change in the polymerase protein complex PB2 that has been associated with increased H5N1 virulence in mice and ferrets, and adaptation of other avian influenza viruses to humans.[9-12] It remains unclear, however, whether this or

Corresponding Author: David M. Morens, MD, Bldg 31, Room 7A-10, 31 Center Dr, MSC 2520, National Institutes of Health, Bethesda, MD 20892-2520 (dmorens@niaid.nih.gov)..

Financial Disclosures: None reported.

any other mutation is associated only with increased mammalian virulence or provides an independent evolutionary advantage in birds.

The pathogenicity of influenza viruses for their different hosts is related to complex viral and host factors and remains to be fully characterized. Experimental animal data with both the H5N1 viruses and the 1918 influenza viruses suggest that virulence is polygenic and depends on a complementary relationship among viral gene segments.[13-14] In mammals, H5N1 viruses exhibit variable pathogenicity depending on the H5N1 strain and host. HPAI viruses are pathogenic in poultry principally because of a polybasic amino acid insertional mutation in the HA cleavage site, conferring an ability to replicate systemically. The role of systemic viral replication in humans or experimental mammals remains unclear and most likely also varies with viruses and hosts.[15]

Biological barriers to viral fitness based on gene segment combination are not well understood; however, pathogenicity, host adaptation, and host–to–host transmissibility are likely independent properties associated with different, and possibly competing, mutational changes. Pandemic viruses of comparatively low (eg, 1968 [H3N2] influenza pandemic), intermediate (eg, 1889 [data suggest a possible H3N8] and 1957 [H2N2] influenza pandemics), and high (eg, 1918 [H1N1] influenza pandemic) pathogenicity have all adapted to humans and exhibited efficient transmissibility.

To cause a pandemic, an avian virus would have to at least adapt to human HA receptors and acquire human transmissibility. History suggests that this may be a difficult challenge for influenza viruses. Despite human and mammalian exposures to countless avian viruses over many decades, the last 2 pandemics have resulted from reassortment of preexisting human–adapted viruses containing imported genes derived from avian influenza viruses, not from de novo adaptation of avian viruses to humans. When genes from a 1997 H5N1 virus were experimentally reassorted in various combinations with those from a human H3N2 virus, none were efficiently transmitted between ferrets,[16] raising questions about whether H5N1 viruses may be inherently limited in their potential to adapt to, and be transmitted between, humans.

Can the H5N1 Virus Become Adapted to and Transmissible Between Humans?

Mutational changes associated with binding of influenza viruses to receptors on different hosts are complex.17 Adaptation of the viral HA receptor–binding site from a form optimized for binding the avian receptor to a form efficiently binding the human receptor seems to require some loss of specificity for {alpha}2,3–linked sialic acids in favor of increased specificity for {alpha}2,6–linked sialic acids.[17] Experiments suggest that only 2 mutations in the receptor–binding site convert the H1, H2, and H3 HAs of the past 3 influenza pandemic viruses from an avian to a human receptor–binding pattern. Several mutations have been reported to enhance H5 binding to the human form of the receptor; however, none has been reported to induce a complete switch in specificity. While it is possible that additional unknown mutations could result in a complete switch, there is no evidence that this has occurred after 11 years of H5N1 exposure to at least thousands of humans, nor is there evidence that it has occurred after human exposure to other H5 subtype viruses over many decades. HA receptor–binding changes during host adaptation differ from subtype to subtype, and H5 viruses may well face unappreciated biological barriers in achieving human receptor binding efficiency.

Although the current number and severity of clinical H5N1 cases make the ongoing situation highly unusual, H5N1 viruses are not unique among avian influenza viruses in their ability to cause human infections and even limited human transmission. For example, since the mid 1990s, strains of H9N2 avian influenza viruses have become widely enzootic in poultry and

have caused a small number of human cases. Some H9N2 viruses have even acquired enhanced specificity for the human form of the HA receptor.5 In 2003, an H7N7 HPAI virus caused a poultry epizootic in the Netherlands and spread regionally. Before the epizootic was contained, at least 86 poultry workers and 3 contacts had become infected and developed conjunctivitis with or without an influenza–like illness; there was 1 fatality.[18] Similarly, 2 persons developed influenza conjunctivitis during a 2004 H7N3 HPAI outbreak in Canada.[19]

Several case clusters of H5N1 infections have been reported.6 While epidemiologic information has been sparse, limited person–to–person transmission of H5N1 has been suggested in a few instances, usually involving family members. It is unknown whether this represents infection associated with particularly intimate or prolonged contact or shared but unidentified host factors affecting either infection risk or virus transmissibility. Separating host susceptibility factors from shared exposures or prolonged contact is difficult but crucially important in assessing viral evolution toward human adaptation. Also important will be comprehensive serologic surveys to assess population experience with H5 and other influenza subtypes in places where exposure to domestic poultry or wild birds is common.

What Has Been Learned From Past Pandemics

Data suggest that the 1918 virus was avian–like prior to human adaptation,[11, 20] after which it eventually reassorted with a different avian virus to acquire 3 new genes and caused the 1957 H2N2 pandemic. A second reassortment, adding 2 additional avian genes, caused the 1968 H3N2 pandemic.[21-22]

Serologic and epidemiologic data suggest that the 1889 pandemic virus was of an H3 subtype (conceivably with an N8 gene), and that the 1847 pandemic virus could have been of either the H1 subtype, neuramindase (NA [N1]) subtype, or both.7 It may thus be likely that viruses causing 5 pandemics during a 175–year span have been limited to only a few of the known avian HA and NA subtypes (H1, H2, H3; N1, N2, and possibly N8). Since 16 HA subtypes and 9 NA subtypes have been found in avian influenza viruses, to which humans have been exposed to varying degrees, a question arises as to whether unappreciated biological barriers may restrict other subtypes from incorporation into transmissible human viruses. Moreover, since only H5 and H7 viruses have been shown to acquire the HA cleavage site mutation that makes them highly pathogenic to poultry, the last 3 pandemic viruses, containing avian–like HA genes of H1, H2, and H3 subtypes were not HPAI viruses like H5N1. Furthermore, there is no evidence that a human pandemic or even an epidemic has been caused by any previous HPAI virus reported in poultry for more than 125 years. None of the last 4 pandemics is known to have been temporally associated with a poultry or wild bird epizootic, leaving no historical data to support the possibility that poultry are capable of serving as intermediate hosts in pandemic development.

The Next Pandemic

It is currently impossible to predict the emergence of a future pandemic other than to strongly suspect that one will eventually occur, or to predict when or where a future pandemic will occur, what subtype it will be, and what degree of morbidity and mortality it will produce. Even though concern over the emergence of an H5N1 pandemic is clearly warranted, if for no other reason than its current high case–fatality rate, experts must also anticipate and plan for many other possibilities for pandemic emergence.

Since 1977, H1N1 and H3N2 viruses have both circulated globally to produce seasonal epidemics, causing approximately 36 000 US deaths annually.[23] Evolution has occurred not only by gradual antigenic drift but also by intra–clade reassortment to import new HAs to which there is lesser population immunity, simultaneously creating novel constellations of gene

segments.[7] It is unclear whether such continuing co–circulation, coupled with the increasing use of influenza vaccines, will increase or decrease pandemic risk or influence the subtype of the next pandemic virus.

If only H1, H2, or H3 viruses have pandemic potential, the question arises whether such co–circulation limits the next pandemic to only H2 viruses in the near future. The majority of the world's population (younger than 40 years) has no protective immunity to H2 subtype influenza viruses that circulated between 1957 and 1968. Isolates of H2N2 viruses from this era are still maintained in virology laboratory freezers throughout the world, while circulating human H3N2 viruses presumably remain susceptible to avian H2 importation by reassortment; this suggests obvious potential sources of future pandemics. H9N2 viruses, some with the ability to bind to human receptors and capable of causing human disease, are another potential source.

The past decade has demonstrated the difficulty of containing HPAI outbreaks given high–intensity poultry production and international shipping of poultry. H5N1 viruses are likely to remain indefinitely enzootic in domestic birds in many countries, posing agricultural and economic challenges while providing opportunities for H5N1 viruses to acquire—if such acquisition is possible—either efficient human–to–human transmissibility or better adaptation to poultry and wild birds, the chief spill–over hosts. The use of antiviral drugs in agricultural settings has made many H5N1 viruses resistant to adamantanes, while there has also been evidence for H5N1 resistance to neuraminidase inhibitors.[24] The evolution of H5N1 into antigenically distinct clades, probably driven in part by the use of poultry vaccines, greatly complicates the situation and makes it more difficult to predict where H5N1 evolution is going, what to expect next, and how to plan for it.[25]

Conclusions

To improve the ability to predict influenza pandemics, it is necessary to increase knowledge of the basic biology and ecology underlying host–switching events. The genetic changes that are needed to convert an influenza virus from one that has adapted to the enteric tract of wild waterfowl into a respiratory virus of horses, pigs, or humans are not fully understood. Enhanced surveillance and prospective study at the human–animal interface are crucial for understanding viral movement and evolution in an extraordinarily complex ecosystem. The H5N1 panzootic is a potent reminder of the constant and constantly changing risk posed by influenza A viruses. It is unknown whether H5N1 viruses will be able to adapt to humans and cause efficient person–to–person transmission; however, preparation for future influenza pandemics caused by H5N1 and any number of other viral possibilities is important.

Thus, it is essential that while carefully monitoring current and identifiable risks, pandemic prevention strategies must also be based on expecting the unexpected and being capable of reacting accordingly. In addition to enhanced surveillance, it will be important to expand research on vaccine design, accelerated development of new classes of antiviral drugs, and improved diagnostics. These efforts will be of immediate benefit in the control of seasonal influenza and will simultaneously help to preemptively prepare for the next pandemic.

REFERENCES

1. Guan Y, Poon LL, Cheung CY, et al. H5N1 influenza: a protean pandemic threat. Proc Natl Acad Sci U S A 2004;101:8156–8161. [PubMed: 15148370]
2. WHO. Evolution of H5N1 avian influenza viruses in Asia. Emerg Infect Dis 2005;11:1515–1521. [PubMed: 16318689]
3. Chen H, Smith GJ, Li KS, et al. Establishment of multiple sublineages of H5N1 influenza virus in Asia: implications for pandemic control. Proc Natl Acad Sci U S A 2006;103:2845–2850. [PubMed: 16473931]

4. World Health Organization Global Influenza Program Surveillance Network. Confirmed human cases of avian influenza A (H5N1). http://www.who.int/csr/disease/avian_influenza/country/en/index.html
5. Alexander, DJ. An overview of the epidemiology of avian influenza [published online ahead of print]. Vaccine: 2006.
6. Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person–to–person transmission of avian influenza A (H5N1). N Engl J Med 2005;352:333–340. [PubMed: 15668219]
7. Taubenberger JK, Morens DM. 1918 Influenza: the mother of all pandemics. Emerg Infect Dis 2006;12:15–22. [PubMed: 16494711]
8. Sturm-Ramirez KM, Hulse-Post DJ, Govorkova EA, et al. Are ducks contributing to the endemicity of highly pathogenic H5N1 influenza virus in Asia? J Virol 2005;79:11269–11279. [PubMed: 16103179]
9. Subbarao EK, Kawaoka Y, Murphy BR. Rescue of an influenza A virus wild–type PB2 gene and a mutant derivative bearing a site–specific temperature–sensitive and attenuating mutation. J Virol 1993;67:7223–7228. [PubMed: 8230444]
10. Hatta M, Gao P, Halfmann P, Kawaoka Y. Molecular basis for high virulence of Hong Kong H5N1 influenza A viruses. Science 2001;293:1840–1842. [PubMed: 11546875]
11. Taubenberger JK, Reid AH, Lourens RM, Wang R, Jin G, Fanning TG. Characterization of the 1918 influenza virus polymerase genes. Nature 2005;437:889–893. [PubMed: 16208372]
12. Govorkova EA, Rehg JE, Krauss S, et al. Lethality to ferrets of H5N1 influenza viruses isolated from humans and poultry in 2004. J Virol 2005;79:2191–2198. [PubMed: 15681421]
13. Kash JC, Tumpey TM, Proll SC, et al. Genomic analysis of increased host immune and cell death responses induced by 1918 influenza virus. Nature 2006;443:578–581. [PubMed: 17006449]
14. Kobasa D, Jones SM, Shinya K, et al. Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. Nature 2007;445:319–323. [PubMed: 17230189]
15. Maines TR, Lu XH, Erb SM, et al. Avian influenza (H5N1) viruses isolated from humans in Asia in 2004 exhibit increased virulence in mammals. J Virol 2005;79:11788–11800. [PubMed: 16140756]
16. Maines TR, Chen LM, Matsuoka Y, et al. Lack of transmission of H5N1 avian-human reassortant influenza viruses in a ferret model. Proc Natl Acad Sci U S A 2006;103:12121–12126. [PubMed: 16880383]
17. Taubenberger JK. Influenza hemagglutinin attachment to target cells: “birds do it, we do it.”. Future Virol 2006;1:415–418.doi:10.2217/17460794.1.4.415.
18. Fouchier RA, Schneeberger PM, Rozendaal FW, et al. Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. Proc Natl Acad Sci U S A 2004;101:1356–1361. [PubMed: 14745020]
19. Tweed SA, Skowronski DM, David ST, et al. Human illness from avian influenza H7N3, British Columbia. Emerg Infect Dis 2004;10:2196–2199. [PubMed: 15663860]
20. Reid AH, Taubenberger JK, Fanning TG. Evidence of an absence: the genetic origins of the 1918 pandemic influenza virus. Nat Rev Microbiol 2004;2:909–914. [PubMed: 15494747]
21. Scholtissek C, Rohde W, von Hoyningen V, Rott R. On the origin of the human influenza virus subtypes H2N2 and H3N2. Virology 1978;87:13–20. [PubMed: 664248]
22. Kawaoka Y, Krauss S, Webster RG. Avian-to-human transmission of the PB1 gene of influenza A viruses in the 1957 and 1968 pandemics. J Virol 1989;63:4603–4608. [PubMed: 2795713]
23. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003;289:179–186. [PubMed: 12517228]
24. Le QM, Kiso M, Someya K, et al. Avian flu: isolation of drug-resistant H5N1 virus. Nature 2005;437:1108. [PubMed: 16228009]
25. Webster RG, Govorkova EA. H5N1 influenza–continuing evolution and spread. N Engl J Med 2006;355:2174–2177. [PubMed: 17124014]