American Enterprise Institute for Public Policy Research

November–December 2005

Is H5N1 the One? Avian Flu Facts and Fiction

By Laura M. Kelley

On November 1, 2005, President George W. Bush outlined the principal elements of the *National Strategy for Pandemic Influenza*[1] that will be constructed by the White House in the coming months. This was followed, on November 2, by the release of the Department of Health and Human Services's *HHS Pandemic Influenza Plan*.[2] The strategy calls for Congress to appropriate $7.1 billion dollars in emergency funds to purchase vaccines and antiviral medications, bolster national and international disease surveillance, and prepare federal, state, and local response measures. A whopping $5 billion will be used to build domestic state-of-the-art vaccine production capabilities and purchase vaccines and treatments for the U.S. National Stockpile.

Remarkable though it may seem, all of this spending and activity is based on the deaths of fewer than seventy-five people, caused by a viral strain that has little or no person-to-person transmissibility. There is, in fact, very little scientific evidence to support assertions that H5N1 is a good candidate virus to cause an influenza pandemic. There are also few facts available to suggest that the drugs and vaccines being purchased will control the spread of the disease. In the meantime, the manufacturers of the few available antivirals are reaping substantial and unexpected profits.

Unfortunately, far too much of the strategy is over-medicalized with policy resulting in large sums spent for antiviral magic bullets and vaccine production plants—all of which are quick fix palliatives and unlikely to be successful in stopping the spread of disease. Subsequently, far too little attention is being given to the broad-based planning and implementation of measures that will save lives, keep the engines of global commerce turning in the event of a worldwide outbreak of disease, and possibly even prevent the emergence of future pandemics.

Is H5N1 the One?

An H5N1 pandemic is not imminent. Furthermore, it is impossible to tell whether H5N1 will ever acquire the genotypic and phenotypic characteristics necessary to produce a pandemic. The strain is indeed virulent when inhaled or ingested at what are likely very high doses, but it is not efficiently transmissible between people. Given the unpredictable nature of viral shift and reassortment, if it ever becomes transmissible, it could lose all or most of its virulence, and the possibility of it fueling a deadly pandemic would remain remote.

Since the emergence of H5N1 in southern China in 1997, scientists and international health organizations have been tracking the evolution and spread of the strain across Eurasia along the flyways of wild birds. As the virus has swept across Asia to Europe, millions of wild and domestic birds have fallen victim to it, or have been killed in futile efforts to contain its spread. Some of the most recent likely cases have been noted in Nepal and Iraq, and we should soon expect the disease

Laura M. Kelley is an associate of the National Intelligence Council in Infectious Disease and Public Health. The views expressed in this essay are her own and not those of the U.S. government.

An Influenza Primer

There are three main types of influenza viruses: A, B, and C. Influenza C causes only mild disease and has not been associated with widespread human outbreaks. Influenza types A and B, however, cause epidemics nearly every year. Influenza B viruses are not divided into subtypes, but influenza A viruses are divided into subtypes, based on differences in two surface glycoproteins: hemagglutinin (H or HA), which helps the virus attach to the host cell, and neuraminidase (N or NA), which helps to release newly replicated viruses called virons from the host cell. There are currently sixteen H subtypes and nine N subtypes, and each type-A virus may have the surface glycoproteins in any combination.

The molecular structure of influenza viruses frequently "drifts," or changes slightly, producing the different epidemic strains that circulate each year. Sometimes, however, the structure changes dramatically. This can produce an influenza virus with a new H or H+N configuration to which humans have little or no resistance. In addition, when viruses from two different sources (such as avian and human viruses) infect a single animal or human, the viral DNA "reassorts" to produce a recombinant virus. If the resultant shifted or reassorted virus quickly transmits from person to person, it could spread around the world, infecting millions of people.

Although water fowl are the natural reservoirs of all type-A influenza viruses, the term "avian influenza" refers to viral subtypes that principally circulate among birds and only rarely infect humans or other mammals. Most influenza viruses cause only asymptomatic or mild infection in birds; however, the range of symptoms in birds varies greatly depending on the strain of virus. Avian influenza viruses causing little or no disease (ruffled feathers, decreased egg output) are referred to as low-pathogenic avian influenza (LPAI), whereas infection with some H5 and H7 strains can cause widespread disease and death and are usually known as highly pathogenic or HPAI.

to hit flocks in western Europe and possibly sub-Saharan Africa as well. Since transmission and geographic spread of the H5N1 virus in birds yields more opportunity for the virus to interact with and swap genes with human or mammalian influenza-A viruses, concern over the spread of the disease is well-founded. However, to date, H5N1 remains a veterinary disease and does not pose a threat to the health of most people.

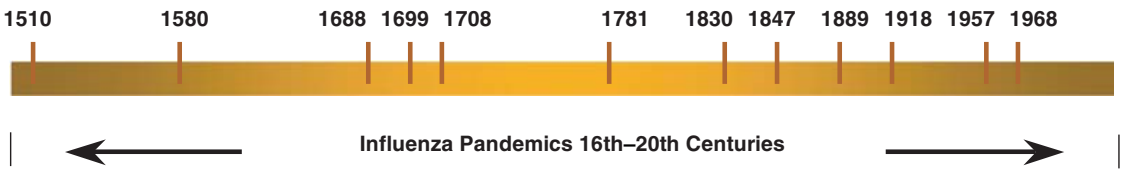
"Fowl plague" was first recognized as a serious disease of domestic birds in Italy in 1878, but it was not until the mid-1950s that the causative agents of these outbreaks were recognized as influenza-A viruses. H5N1 was first identified in birds in Scotland in 1959, which was also the year of the first recorded human case of the disease. Although there is little historical evidence, it has likely produced sub-clinical, asymptomatic, or simply untyped respiratory infections in humans since that time. In fact, studies done in Hong Kong after the 1997 reemergence of the disease found a 10 percent asymptomatic seroprevalence of the disease in poultry handlers, supporting the point that this virus has long been circulating in people with an occupational exposure to the disease, yet still has not spawned a worldwide pandemic.[3]

It may, in fact, be counterproductive to focus so much attention on H5N1 when many other influenza viruses are equally adept at swapping genetic material with other viruses and adapting to their environments. Other strains of avian influenza that have caused disease in humans include H7N7 (which caused communicable human illness in the Netherlands and one death in 2003) and H9N2 (which caused seven cases of human illness in Hong Kong and Guangdong Province in China in 1999 and has become endemic among bird populations in east and southeast Asia, India, Pakistan, Middle East, and some parts of eastern Europe.

Are We Overdue for a New Pandemic Flu?

Over the last three decades, national and international public health authorities have periodically stated that the world is "overdue" for an outbreak of pandemic disease. This view is shortsighted and only considers twentieth century outbreaks of disease. Historical records of disease pandemics likely caused by influenza go back almost 500 years, and an examination of the cadence between recorded outbreaks shows no pattern to help us predict the timing of the next one (See Figure 1). The longest interval between probable pandemics was 108 years between the 1580 and 1688 outbreaks, and the shortest was nine years between the 1699 and 1708 pandemics. Although the creation of a pandemic influenza strain is more complex than the simple passage of time,

FIGURE 1 [4]



there is clearly no periodicity to the events and we are certainly not overdue for one.

Garbage in and Gospel out: The Proliferation of Disease Models

Since pandemic planning has become the rage, most organizations involved have adopted their pet disease model to help guide their preparedness and response decision-making processes. The biggest problem is that few of these models are any good. Some of them mistakenly lead policymakers into believing that it will be possible to contain an outbreak of pandemic influenza through the use of antiviral medications and vaccines delivered to those identified at risk by epidemiological contact tracing and geographical location.[5] What is not immediately obvious to the algebraically challenged is that in order for the outbreak to be "ringed," or contained, half of all first-generation infections need to be identified within the first twenty-four to thirty-six hours of transmission. Anyone with clinical experience knows that it is impossible to do this—in any health care setting in the developed world, let alone the developing world.

Most models also concentrate on the spread or containment of the pathogen and its associated mortality; few examine the economic and social fallout from the disruption that accompanies a pandemic. However, that is where planners could really use some help to stave off likely problems. In our world of international supply chains and just-in-time production, economic impact estimates are sorely needed. Even with the few deaths—under 1,000 worldwide—caused by the Severe Acute Respiratory Syndrome (SARS) coronavirus in 2003, the economic costs of the epidemic were estimated at over $60 billion—not including the costs of health care and medical research.[6] Most of these costs were associated with sector losses in tourism, services, aviation, and restaurants and with the construction of economic stimulus packages. The economic costs of an influenza pandemic, even a relatively minor one, will surely dwarf these estimates.

The Ghosts of Pandemics Past

Too many models and scenarios constructed to inform current policy decisions conjure up images of the mass mortality associated with the 1918 pandemic that worldwide killed more than 50 million people.[7] The problem with using the 1918 "Spanish" influenza pandemic as a model for future pandemics is that it is more of an exception than the rule as flu pandemics go. The 1918 pathogen itself was almost certainly more virulent and transmissible than are other pandemic strains, as historical accounts and the recent construction of an approximate virus have suggested.[8] In addition, most of the deaths—at least those for which we have medical records—seem to have been in individuals who developed a secondary bacterial pneumonia in addition to their primary influenza infection. Today, we have a large armamentarium of broad-spectrum antibiotics with which we would have been able to treat most or all of those infections, possibly preventing a good portion of those deaths.

Far better models for anticipating impact and planning response for a future pandemic would be the 1957 Asian and the 1968 Hong Kong influenza pandemics that killed between one and two million people worldwide. In addition to the virulence and transmissibility of the pathogen posing less of a threat than the 1918 strain, the biggest factors that helped to reduce excess mortality in the later pandemics were the national and international surveillance and response networks which identified the disease in populations and moved quickly to mitigate it. These networks are more globally inclusive and likely to identify a potential pandemic closer to its start than ever before. As a result of nearly a century of technological development since the 1918 pandemic, surveillance and response capacity is now fairly good in some countries. The world no longer needs to wait for all health assistance to come from the United States or Western Europe. The ability to identify and treat disease now flows from regional fonts of expertise. That is not to say that international cooperation will not be necessary

in a future pandemic; it will just be easier to implement by interfacing with regional medical and health centers.

Antiviral Medications: No Magic Bullets

Four drugs are approved for use in the United States for the treatment of influenza: amantadine, rimantadine, oseltamivir (Tamiflu), and zanamivir (Relenza). All of them, in some way or another, act to inhibit or impair the replication of viruses. With no human clinical trial data in hand to guide purchasing and distribution of these drugs to control avian influenza, we have only a few in vitro and animal studies and a handful of treated human infections by which to judge their effectiveness. What is known, however, is that these antivirals should be taken at the onset of infection to truly be effective—a scenario that is unlikely to play out in the developing world or bureaucratic public health systems.

Disturbingly, with so little information available, resistant strains to both drug classes have already been documented and may be increasing worldwide. Isolates of avian influenza from 1979–1983 showed no resistance to the M2 inhibitor amantadine, but isolates from 2004 had resistance rates of 10 percent (H9) to 31 percent (H5).[9] Investigators are not sure why resistance is increasing in avian and human influenza strains, but one potential reason could be improper use of generic drugs to treat or prevent disease in humans and animals.

Additionally, a report was recently issued outlining an H5N1 strain that developed resistance to Tamiflu after only four days of a preventative course of medication.[10] Researchers went on to characterize the virus by demonstrating its ability to replicate efficiently, bind to human receptor sites, and to cause disease in animals. Test animals infected with the Tamiflu resistant strain could not be treated with Tamiflu and had to be treated with Relenza, demonstrating that the mutation coding for resistance was stable across several generations of viral replication.

Careful and judicious use of Tamiflu beginning with the upcoming influenza season is therefore required to keep future resistance profiles under control. If they are not, the millions spent by governments to protect and treat illness in their citizens will wind up creating pathogens that we have little or no medications to defend against. Stockpiles of drugs should also be as diverse as possible to ensure that other drugs are available in the event of rising resistance to any one medication.

Vaccines to Protect against an Unknown Virus

Vaccines approved to protect people against avian influenza viruses do not yet exist. Several candidate vaccines, however, are under development around the world. One vaccine being tested by the U.S. National Institute of Allergy and Infectious Diseases was recently found to be safe and to generate an immune response in early clinical trials. This vaccine uses more than six times the usual amount of antigen in human influenza vaccines, which may make it expensive to produce and costly to buy. Other vaccination strategies are also being investigated by private companies, and include the use of a small amount of antigen administered along with a substance called an adjuvant, which stimulates, lengthens, or increases the immune response. If vaccines using this strategy prove safe and effective, less antigen will be required per dose, which could make the vaccines inexpensive to produce. The cost of the adjuvant is, however, the wild card for estimating the cost of such a vaccine.

Since no approved human vaccine against avian influenza yet exists, the capacity of countries to produce these vaccines is irrelevant to short-term preparedness plans. It will be several years before the full effectiveness, and appropriate dosing and delivery schedules of the vaccine candidates in the pipeline are fully understood. Then licensing and approval for human use could take several additional years. Even if a vaccine candidate were known today to be safe and effective, it could take six to eight months from the appearance of the first pandemic strain to produce vaccines for only a limited portion of the population.

In an era of great scientific prowess, access to life-saving influenza vaccines is still contingent upon a time-consuming, 1940s-style manufacturing process that involves production in fertilized eggs. Low profit margins, small and unpredictable markets, and regulatory and liability hurdles have made this an exceedingly unattractive industry to be in, let alone modernize. But renewed fears of a pandemic have sparked a renewed interest in potential, yet promising, manufacturing solutions—such as cell-based, genetically engineered, or universal flu vaccines. Public-private partnerships that encourage innovation are needed to ensure the annual influenza-vaccine supply as well as to create treatments and immune-boosting preventatives for diseases of high impact but low probability, such as the pandemics and pathogens of interest to the bio-defense community.

Home Sweet Home: Community Disease Control and Prevention

If antiviral drugs will be plentiful but of unknown efficacy and vaccines may or may not be available to help to stem the tide of the next pandemic, what indeed can we do to prepare? The *HHS Pandemic Influenza Plan* declares that state, local, and tribal authorities "should be able to" isolate individuals when the viral transmission rate is low and call for and enforce voluntary quarantine measures when there is lots of virus circulating in a community. The troublesome thing about the plan is that there is little funding and specific guidance on how this massive, coordinated planning and mobilization is going to be pulled off. Lessons learned from Hurricanes Katrina and Rita have shown us that local authorities are generally not prepared to plan and implement broad-based emergency response efforts and will need a great deal of assistance from federal officials. With only $2 billion dollars of the requested emergency funds available to spend on *all* national and international surveillance and response activities, these efforts may be sorely underfunded and inadequate.

If necessary, schools and businesses may have to be closed in an attempt to break the chain of viral transmission. But again, the nearly 400-page plan is light on details of, for instance, how businesses will remain solvent under such extreme measures, how food and other supplies will be delivered and distributed, and how children will be schooled. In a Wifi-ed area some workers could telecommute and lessons could be broadcast, but this will not work in many of the more rural areas of the country. The plan also vaguely mentions that states and local authorities will need the "legal framework" to implement these measures, but it never discusses whether workers who become ill or whose places of business are closed will be paid or whether they will have a job to return to after the pandemic is over. The same goes for businesses necessary to keep global supplies of essential goods flowing—these will have to be part of massive compensation and stimulus packages. We have an awful lot of planning and testing yet to do.

Public Health Communication

Even if we purchase all the antiviral drugs and vaccines we need and do all the necessary response planning and scenario testing, the impact of the next influenza pandemic will be much greater than expected if we do not immediately begin to engage in responsible risk communication. The *HHS Pandemic Influenza Plan* states that the "timely and transparent dissemination of clear, accurate, science-based, culturally competent information about pandemic influenza and the progress of the response can build public trust and confidence."[11] HHS should indeed be applauded for including this section in their plan. One hopes that due attention will be given to constructing communication strategies with partners at all levels of the government, because risk communication can tip the scales between peace in the streets and public panic. Again, with so little funding allocated to these efforts, risk communications may be given lower priority. If so, that's a pity, because risk communication requires planning, strategizing, and frankly practice in order to make it work effectively.

Currently we have far too many voices competing against each other for airtime to deliver messages of impending pandemic gloom and doom to the general public. Ordinary people are already scared of avian influenza. Urgent efforts should be made to quell their immediate fears and convince them that those with a mandate to protect them are doing all that they can do. Ordinary people cancel travel plans and orders for durable goods and can affect industry and commerce in powerful ways if they keep their purses closed because of the fear of an infection.

Is Pandemic Prevention Possible?

A perusal of recently emerging and reemerging diseases will show that China is a hotbed of illness. Viruses and bacteria that cause respiratory diseases in particular seem to thrive in China and other East Asian countries, enormously driving up the annual burden of disease on citizens of these countries. China was also the source of the SARS coronavirus and of two of the last three pandemic influenza viruses. If there are cultural or environmental factors that predispose China to be a factory for human and veterinary diseases, an examination of common agricultural practices is certainly key.

In Asia, agricultural and animal husbandry practices are vastly different from those in the developed world. It may not be possible to prevent a future pandemic, but efforts can be made to reduce the likelihood of the emergence of animal diseases in humans and potentially pandemic influenza strains. Recent press reports have noted that over the last thirty-five years or so the population of

pigs in China has increased from 5.2 million to over 508 million, and domestic fowl numbers have climbed from 12.3 million to over 13 billion; this greatly increases the risk of diseases leaping from animals into humans. However, more important than the sheer increase in the numbers of agricultural animals is the shift from small family farms that provide food for the proprietors and local inhabitants to farms that supply food to supermarkets and wet markets throughout provinces and the country as a whole—all while still practicing the animal husbandry of the pre-industrial age. As animals are being raised in ever larger groups to meet the meat-loving demands of China's increasing middle class, modern industrial hygiene and husbandry standards are desperately needed to ensure the health and safety of the animals and their human keepers.

Keeping Avian Flu in Perspective

Fewer than seventy-five deaths from a virus with little or no person-to-person transmissibility have spurred the current wave of pandemic preparedness planning. While pandemic and other emergency planning is useful and overdue, too much emphasis has been placed on medications and vaccines, and indeed on the avian influenza itself. Most of the national and international preparedness efforts to date have been based on a pandemic of H5N1 influenza arising in southeast Asia and spreading throughout the world. Billions have been spent on medications and vaccines when a pandemic could be lurking in another outbreak of H7N7 in the Netherlands or H9N2 in India or the Middle East. Other virulent and transmissible emerging diseases are also only a plane ride away from U.S. shores. For example, the last outbreak of *Marburgvirus* came frighteningly close to a major urban area with international air connections.

We must begin to make our plans more broad-based to encompass the most threatening of pandemic scenarios. Better still would be to think strategically and work on improving regional and global disease preparedness plans instead of responding to each threat as it comes over the tactical horizon.

Notes

1. The White House, *National Strategy for Pandemic Influenza* (Washington, D.C.: National Security Council, November 2005), available at http://www.whitehouse.gov/homeland/nspi.pdf.

2. U.S. Department of Health and Human Services, *HHS Pandemic Influenza Plan* (Washington, D.C.: U.S. Department of Health and Human Services, November 2005), available at http://www.hhs.gov/pandemicflu/plan/pdf/HHSPandemicInfluenzaPlan.pdf.

3. C. Buxton-Bridges et al., "Risk of Influenza-A (H5N1) Infection among Poultry Workers, Hong Kong 1997–1998," *Journal of Infectious Diseases* 181, no. 1 (2002): 344–348.

4. Y. Ghendon, "Introduction to Pandemic Influenza through History," *European Journal of Epidemiology* 10, no. 4 (1994): 451–453; W. I. Beveridge, "The Chronicle of Influenza Epidemics," *History and Philosophy of Life Sciences* 13, no. 2 (1991): 223–234; W. I. Beveridge, *Influenza; The Last Great Plague: An Unfinished Story of Discovery* (New York: Prodist, 1977); J. Duffy, *Epidemics in Colonial America* (Baton Rouge: Louisiana State University Press, 1953); D. A. Pettit, "A Cruel Wind: America Experiences the Pandemic Influenza, 1918–1920: A Social History" (PhD dissertation, University of New Hampshire, 1976); S. Jarcho and K. M. Richards, "The Epidemic or Pandemic of Influenza in 1708–1709," *Dynamis* (1985–1986): 125–141.

5. I. M. Longini Jr. et al., "Containing Pandemic Influenza at the Source," *Science* 309, no. 5737 (2005): 1083–1087; N. M. Ferguson et al., "Strategies for Containing an Emerging Influenza Pandemic in Southeast Asia," *Nature* 437, no. 7056 (2005): 209–214.

6. National Intelligence Council, *SARS Down but Still a Threat*, Intelligence Community Assessment, September 2003.

7. N. P. Johnson and J. Mueller, "Updating the Accounts: Global Mortality of the 1918–1920 'Spanish' Influenza Pandemic," *Bulletin of the History of Medicine* 76, no. 1 (2002): 105–115.

8. J. K. Taubenberger et al., "Characterization of the 1918 Influenza Virus Polymerase Genes," *Nature* 437, no. 6 (2005); T. M. Tumpey et al., "Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus," *Science* 310, no. 5745 (2005): 77–80.

9. A. Ilyushina, E. A. Govorkova, and R. G. Webster, "Detection of Adamantine-Resistant Variants among Avian Influenza Viruses Isolated in North America and Asia," *Virology* (August 1, 2005).

10. Q. M. Le et al., "Isolation of Drug-Resistant H5N1 Virus," *Nature* 437, no. 7062 (2005): 1108.

11. U.S. Department of Health and Human Services, *HHS Pandemic Influenza Plan*, 11.