

COMMENTARY

PERSPECTIVES ON AVIAN INFLUENZA

Avian influenza viruses have regularly caused illness in a range of bird species.¹ Since 1997, there has been a special public health focus on the H5N1 strain which has caused widespread epidemics in domestic poultry beginning in Hong Kong where 20 human cases and 7 deaths occurred.² In succeeding years, there have been widespread outbreaks among domestic fowl in China, Central Asia, Southeast Asia, Indonesia, Malaysia, Japan, and South Korea. More recently, H5N1 has infected turkeys in Turkey and ducks in Romania.³

The movement of the H5N1 epizootic out of Asia and into Europe, coupled with its ability to infect other animal species and to pass from domestic fowl to humans, has created increasing concerns among some scientists, public health authorities, and political leaders.⁴ This spread, however, has been primarily facilitated by migrating birds that act as carriers. Given the flyways of migratory bird species from Eastern Europe and Western Asia, it would not be unexpected to see outbreaks of H5N1 among domestic fowl in sub-Saharan Africa, especially in East Africa, in the winter of 2005–2006. A substantial risk exists that infected migratory birds from Eastern Europe and Asia will co-mingle in Africa with those arriving from Western Europe. One result of this might be the introduction of H5N1 into domestic fowl in Western Europe when migratory birds return from Africa in the spring of 2006. Similarly, birds using the flyways between Alaska and the southern hemisphere could be infected by those from Asia, and thus introduce H5N1 into domestic fowl in North America in the spring of 2006.

The importation of exotic bird species from infected areas also poses the threat of extending the pandemic of H5N1 among domestic fowl, especially when it is done clandestinely. The spread of H5N1 to domestic flocks in Western Europe could also be facilitated by the importation of birds and bird products from Eastern Europe and Asia. Aware of this possible threat, the European Union banned such imports in October 2005.

The obvious question that arises is whether the geographic spread of the H5N1 pandemic among birds could facilitate either mutation or reassortment of the virus so that it could acquire the ability to cause widespread human disease. By focusing on this geographic spread of H5N1 among birds and its possible role in producing a lethal influenza virus for

humans, one risks losing sight of the fact that the epicenter of this bird pandemic is still active in Southeast Asia and China. This is the geographic region of the world where previous pandemics of human influenza have arisen, such as those in 1957 and 1968.⁵ The reasons for this have much to do with dense human populations living in close proximity to large numbers of domestic swine, in which viral reassortment often takes place, and with domestic fowl. Half of the world's domestic swine population of approximately one billion is found in China, thus making the probability of influenza viral reassortment more likely there than anywhere else in the world. Given these facts, it is not surprising that the viruses responsible for the 1957 and 1968 influenza pandemics arose in China as did the re-appearance of the H1N1 virus in 1977.

The visibility of the epizootic of H5N1 avian influenza among domestic fowl has also been greatly facilitated by the development of a large-scale commercial poultry industry in China and Southeast Asia in recent decades. It is estimated that there are 13 billion poultry in China today compared to 12.3 million in 1968.⁶ This translates into dense concentrations of chickens and ducks in commercial settings where viral transmission is enhanced. Thus, compared to the past, there is not only greater zoonotic transmission due to crowding, but also illness and death among birds are much more evident.

Concerns about a possible human pandemic have been heightened by the long period that has elapsed since the last one of H3N2 in 1968 known as the Hong Kong Flu, and the much shorter period between it and the previous 1957 pandemic of H2N2 known as the Asian Flu. In addition, other events have contributed to increased anxiety about the pandemic potential of H5N1. These include its ability to be transmitted from domestic fowl to humans and the high mortality rate among people who contract it. For example, among 35 human cases that occurred in Thailand and Vietnam between December 30, 2003 and March 17, 2004, 23 people died, representing a mortality rate of 65.7%.⁷ Although the existing evidence indicates that most of these cases, if not all, resulted from poultry-to-human transmission, it is clear that H5N1 is especially lethal for humans.

In an atmosphere charged with anxieties about a possible human pandemic of H5N1, few have paused to consider that this virus may have reassorted its genes in the past either in humans or animals.⁸ In so doing, it did not acquire the ability to become a virus easily transmitted among humans. Well over a decade ago, Shortridge observed that many people in China had once been infected with H4 to H15 subtypes of the influenza A virus. Seroprevalence rates for H5 viruses were found to range from 2%

to 7%. The seroprevalence rates for H7, H10 and H11 viruses were respectively higher at 38%, 17%, and 15%.⁹ These data demonstrate that the avian influenza viruses regularly infect large numbers of individuals without causing worldwide pandemics. It is important to know the seroprevalence rates for H5N1 among human populations in China and Southeast Asia, especially among those in close contact with poultry. This would provide us with vital information about the true prevalence of the disease and a sense of rates of subclinical and inapparent infection. The severe cases thus far observed in hospitals may or may not represent one end of a clinical spectrum in which the majority of cases are either mild or moderate, not requiring hospitalization. Population seroprevalence studies, especially among poultry workers, would help to elucidate this issue and tell us whether this is a killer virus for most or for just a small subset of people who become seriously ill.

Wild aquatic birds are a principal reservoir for influenza viruses, and act as healthy carriers. Feral migratory ducks are especially important asymptomatic reservoirs for these viruses, which often infect other animal species.^{10,11} The monitoring of H5N1 along migratory bird flyways is an important activity that is currently being undertaken in the United States by the Department of the Interior's National Wildlife Health Center. A number of park rangers, volunteers, and veterinarians are engaged in monitoring birds shot by hunters on public land, caught in nets, and found dead in parks or on beaches.¹² In addition, samples of water from ponds and lakes are being tested for H5N1 because the virus is shed in feral bird feces. The mingling of birds from the western and eastern hemispheres in the Arctic during the summer poses the most likely risk of wider spread of the virus among wild birds. A number of birds migrating along Asian flyways are now carriers of H5N1, and may eventually pass the virus on to those from the western hemisphere that also summer in the Arctic.

Public anxieties have also been raised by press and media references to the 1918 influenza pandemic which killed an estimated 50–100 million people worldwide, and which caused some 20 million cases and 550,000 deaths in the United States.¹³ Speculation about the possible numbers of cases and deaths from an avian influenza pandemic have added to public concerns. Many of these have been based more on guesswork than credible science, and have often been revised downward in response to public and scientific skepticism. Spokespersons for the World Health Organization have often given conflicting statements about the level of threat, while the U.S. Department of Health and Human Services has released projections based on past flu epidemics.^{14–16}

Recent analogies to the 1918 pandemic were facilitated to a degree by the publication in October 2005 of the complete genome of the 1918 virus. The results of its recreation demonstrate that it was not a reassorted virus such as those that caused the more recent 1957 (H2N2) and 1968 (H3N2) pandemics, but rather an entirely avian-like virus that mutated and adapted to humans.^{17,18} These findings are relevant to the biology of H5N1 which could possibly become a human pandemic virus either through mutation or reassortment. In the latter case, the offspring virus of H5N1 and another currently active human influenza A virus might be less lethal than a mutated H5N1 virus. Whether either of these biologic events will occur is still an open question.

Even if H5N1 became a human pandemic virus through mutation, this would not necessarily result in the morbidity and mortality rates observed in 1918. Greatly improved epidemiologic surveillance and modern diagnostic laboratory facilities worldwide can significantly aid in identifying local human epidemics and serve to facilitate rapid containment and preventive interventions. The availability of a strain-specific vaccine or even one that offers partial protection would not only reduce morbidity and mortality, but also person-to-person transmission rates. Similarly, adequate supplies of antiviral agents would attenuate the severity of illness in individuals, lower potential mortality rates, and reduce transmission. Finally, the existence of antibiotics for treating the secondary pneumonias that killed many in 1918 and vastly improved medical care would greatly lessen the number of deaths.

An important recent step in efforts to deal with a possible pandemic of influenza was the publication of the *HHS Pandemic Influenza Plan* in November 2005.¹⁹ This plan includes a number of short-term and long-term objectives encompassing the stockpiling of vaccine, antiviral agents, and medical material, strengthening surveillance and the reporting of cases, initiating rapid containment measures, and investing in the development of newer vaccine production technologies. This plan will serve as a blueprint not only for addressing a possible H5N1 pandemic, but also those due to other influenza viruses in the future.

It is difficult at this time to predict the ultimate biologic and epidemiologic course of H5N1. However, public health authorities, governments, and the pharmaceutical industry can do much to combat a pandemic of any strain of influenza with a range of modern prevention, control, and treatment interventions.²⁰ What is needed now is the resolve to do so.

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