

EDITORIALS



Avian Influenza and Pandemics — Research Needs and Opportunities

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As the year 2004 progressed, so did conditions favoring the start of an influenza pandemic. The first warning came in January, when Thailand and Vietnam reported fatal human cases of avian influenza caused by the H5N1 strain of influenza A virus. That strain was already notorious for its pandemic potential, revealed during an outbreak in Hong Kong in 1997 and later in a smaller number of human cases in 2003.

With the H5N1 strain now endemic in birds in large parts of Asia, the probability that this potential for a pandemic will be realized has increased. Recent laboratory and epidemiologic studies have yielded disturbing evidence that the H5N1 virus has become progressively more pathogenic in poultry, has increased environmental resistance, and is expanding its mammalian host range. In 2004, H5N1 caused 44 human cases of avian influenza, of which 32 were fatal. Two features are striking: the overwhelming concentration in previously healthy children and young adults and the very high mortality rate. The risk that more people will be affected is now firmly entrenched in rural areas in Asia, where most households maintain free-ranging poultry flocks and depend on them for income and food. Outbreaks under such conditions may escape detection, are difficult to control, and increase the opportunity for human exposure, especially in situations where children play near poultry and families slaughter birds for food.

Since the beginning of this year, all prerequisites for the start of a pandemic have been met save one — namely, genetic changes in this virus that would allow it to achieve efficient human-to-human transmission. Will the recent changes in the ecology

of the disease and the behavior of the virus lead to this last step, or will they prove irrelevant? No one can say with certainty. Nonetheless, the warning signal has been clearer than ever since 1968, when the last pandemic occurred, and thus there is an unprecedented opportunity to intensify worldwide preparedness. Fortunately, scientific understanding of influenza, including the origins of pandemics, has progressed enormously since 1933, when an infected ferret sneezed in the face of a scientist and a virus was eventually identified as the cause of the scientist's subsequent influenza-like illness. Recent studies of the H5N1 strain of avian influenza A virus, conducted by laboratories in the World Health Organization Global Influenza Surveillance Network, have shown the power of molecular epidemiology to contribute to the monitoring of an outbreak and its evolving threat. But substantial gaps in knowledge remain, making the ability of science to guide policy imperfect at a critical time.

Information is urgently needed, in the short term, in five research areas: case management and hospital infection control; clinical research on the immunogenicity of vaccines for pandemic influenza; early interventions to slow down the spread of emerging pandemic viruses; the role of various animal and bird species in the epidemiology of influenzaviruses with pandemic potential; and risk assessment. In the longer term, the development of vaccines capable of conferring enduring protection against all influenzavirus subtypes and thus of reducing death and disease from seasonal and pandemic influenza would be a breakthrough. Furthermore, studies of the ecology and molecular biology of influenzaviruses could uncover the genetic foun-

dation of influenzaviruses' host specificity and pathogenicity.

The most pressing question is the following: Why has H5N1 not reassorted with a human influenza virus? It certainly has had ample opportunity to do so. The world has never before seen outbreaks of avian influenza on the scale of those that have swept through large parts of Asia, including densely populated China. From January through March 2004, more than 120 million poultry birds died or were destroyed as part of massive control efforts. Unprotected workers had intense exposures, as did health care workers. Virologic surveillance has demonstrated the concurrent circulation of human viruses. Hence, one conclusion is tempting: if H5N1 could reassort, it should have done so by now. The explanation may lie in sheer statistical luck. It could also be that reassortment has occurred but has resulted in viruses that are not viable, not pathogenic, or not more easily transmitted among humans than H5N1 currently is. If so, this news would be very good, and H5N1 could be moved a notch down on the watch list of viruses with the potential to cause a pandemic.

The only way to answer this question is to mimic reassortment in a laboratory under appropriate biosafety conditions. The H5N1 and human influenza H3 or H1 viruses need to be sequenced and cloned, their genes and proteins expressed in cell culture by means of reverse genetics, and the resulting viruses tested for identity with the wild virus. Subsequently, both viruses would be put in cell culture bottles, and any reassorted virus would be characterized for viability and tested for pathogenicity and transmissibility in animals. Some of this work has begun in a single laboratory but may not be completed before the end of 2005.

In 2003, avian influenza A (H5N1) virus was isolated from diseased pigs on farms in southern China, marking the first documented natural infection of pigs with any virus of the H5 subtype. That finding was not a major surprise, unlike the detection of H5N1 in its highly pathogenic form in dead migratory birds. Wild waterfowl are the natural reservoir of all influenza A viruses and have historically carried these viruses in a form with low pathogenicity, in evolutionary equilibrium, without showing signs of disease. Most recently, domestic ducks without apparent illness have been found in experiments to excrete H5N1 in its highly pathogenic form. Because these ducks can excrete large quantities of virus that is lethal to other poultry

without the warning signal of visible illness, it has become difficult to give rural residents realistic advice on how to avoid exposure. The role of domestic ducks as a silent reservoir of H5N1 may help explain why several recent human cases could not be traced to contact with diseased poultry.

These hints of changes in the ecologic characteristics of H5N1 need further investigation. Data on the prevalence of H5N1 in aquatic birds and pigs are needed. We also need to know whether domestic ducks are a sustainable reservoir of the virus on their own or whether infection in other poultry is needed to maintain the transmission cycle. Pending answers to these questions, it will be difficult to introduce disease-control measures in animals that have the best chance of reducing opportunities for human exposure. Conducting serologic studies in pigs and taking samples from wild and domestic aquatic birds are relatively simple and inexpensive measures.

Although the 18 cases of avian influenza A (H5N1) virus infection that occurred in humans in Hong Kong in 1997 have been extensively investigated, there has been relatively little progress in our understanding of the natural history of the disease and its treatment. The occurrence of primary viral pneumonia in these cases, with no evidence of secondary bacterial infection, is of particular concern. Features important for case management, infection control in hospitals, and epidemiologic investigations of individual cases and clusters, but poorly understood, include the incubation period, antibody kinetics, patterns of virus excretion, the duration of infectivity, factors determining the outcome of disease, and the clinical effectiveness of various medical interventions. Should H5N1 eventually give rise to a pandemic, answers to these questions could guide the appropriate use — or nonuse — of costly and socially disruptive interventions such as social distancing, isolation and quarantine of patients and their contacts, and travel restrictions. They will also help determine the best procedures for diagnosis and sampling and for triage in hospitals, as well as the level of infection control needed to prevent nosocomial spread.

Until now, collaborative studies, such as that reported by Ungchusak et al. in this issue of the *Journal*,¹ have rarely brought clinical, epidemiologic, and virologic experts together. Collection of sequential samples from patients is often begun too late, or data from patients and epidemiologic data are not accompanied by vital complementary informa-

tion, such as information on case management and hospital infection-control measures. An international clinical-research network on avian influenza in selected countries in Asia could be the foundation for faster and more productive investigations and could serve as a nucleus for an integrated clinical, epidemiologic, and virologic network on emerging infectious diseases.

Vaccine licensing depends on clinical studies to demonstrate safety, immunogenicity, and effectiveness. In the special context of preparedness for a pandemic, in which a rapid increase in production would be required and the demand for vaccines would far exceed supply, these studies must perform a second function: to provide data that will make possible vaccine formulations that make maximal use of limited antigen. Because manufacturing capacity is finite and cannot be augmented quickly, research is necessary to establish the smallest amount of antigen per dose that will confer sufficient protection. For example, the use of certain adjuvants can reduce the antigen requirement per vaccinee by half to three quarters. There is little experience with and great variability in the immunogenicity of avian influenzaviruses in humans, so clinical trials are urgently needed to obtain answers quickly. International coordination to decide on clinical-study protocols is indispensable because of the large number of possible vaccine formulations and the many variables to consider (e.g., type of vaccine, antigen dose, number of doses, age groups, and adjuvants) and the fact that most such trials will be conducted by pharmaceutical companies on a commercial basis. Coordination of clinical trials and rapid sharing of data are required to expedite research in the face of a possible pandemic of avian influenza A due to the H5N1 strain.

A virus with the potential to cause a pandemic could emerge suddenly, by way of a single reassortment event, or more gradually, by adaptive mutations during human infections, with the virus incrementally improving its transmissibility. Should

the latter occur (and be detected by good surveillance), its detection could open an opportunity to intervene with antiviral drugs or a vaccine and thus forestall international spread or even eliminate a virus with low transmissibility. Though it is an attractive option, no attempt has ever been made to interrupt the transmission of an influenzavirus; the results of such an enormous and costly undertaking remain uncertain. The option deserves further investigation, however, particularly when viewed against the profound effect a delay in global spread and a flattening of the peak in disease prevalence could have during the initial phase of a pandemic. Its pursuit further depends on assessment of the feasibility and logistic requirements of bringing interventions to large urban populations and scattered rural residents in Asia. Without such feasibility data, any detailed planning, including funding proposals, will be severely hampered.

Past pandemics have typically hit world populations like a flash flood. They have started abruptly and explosively, swept through populations, and left considerable damage in their wake. They could not be stopped but peaked rapidly and then subsided almost as abruptly as they began. The emergence of human cases of avian influenza A (H5N1) virus infection in Asia is an unprecedented warning and has given the world more time to prepare than anyone might have expected. Given the well-documented consequences of pandemics, it seems prudent to find answers to these questions. We need to put up safeguards while the storm is still gathering.

I am indebted to the staff of the Global Influenza Programme, World Health Organization, and to Mary Kay Kindhauser for their support during the preparation of this editorial.

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1. Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). *N Engl J Med* 2005;352:333-40.

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