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# Race against time

A committed, transparent research effort into the detection, prevention and treatment of bird flu is now critical. **Anthony S. Fauci** presents the questions that need answers.

The emergence of the highly pathogenic H5N1 influenza A virus in southeast Asia is a grim reminder of the deadly toll of flu pandemics throughout the ages. This virus has the potential to trigger the next pandemic, which, judging from history, is well overdue. We cannot predict exactly when a pandemic will occur, nor can we know for certain whether the culprit will be H5N1 or a related virus. The only certainty is that it will present extraordinary challenges. Many individuals, research and health organizations, and countries have delineated surveillance goals, are sharing information and reagents, and are asking the multiple research and logistical questions needed to develop an appropriate response. Clearly, there is much to be accomplished, and time is of the essence.

To prepare for and minimize the impact of avian viruses with pandemic potential, a multifaceted approach is essential. This includes a robust, sustained commitment to the research needed to develop new tools and strategies for influenza detection, surveillance, prevention and therapy.

Preparedness for pandemic flu is a global endeavour, with the World Health Organization (WHO) playing a pivotal role. The US contribution to the global effort involves several government agencies that operate in partnership with private industry and academic institutions. One of the main agencies, the Department of Health and Human Services (HHS), will spend about $419 million in its Influenza Preparedness and Response Plan for the fiscal year 2005. Within the HHS, the Centers for Disease Control and Prevention (CDC) has the key role of mediating disease surveillance and the public-health response. In addition, the National Institutes of Health (NIH) conducts basic research on viral pathogenicity and molecular evolution. The NIH also carries out research to identify drug targets and new technologies for vaccine production, as well as clinical research to test the safety and efficacy of new diagnostics, vaccines and antivirals (see www2.niaid.nih.gov/Newsroom/FocusOn/Flu04). The NIH's flu research budget for 2005 is approximately $119 million; it supports work that complements the efforts of the CDC and the Food and Drug Administration (FDA).

## Watch and learn

A timely response to a potential flu pandemic requires diligent surveillance as well as an understanding of how flu viruses evolve, spread and cause disease. The NIH Influenza Genome Sequencing Project aims to provide complete sequence data for selected human and avian influenza isolates. When the project began in November 2004, only seven human influenza H3N2 isolates had been completely sequenced and deposited in the NIH's GenBank database. Six months later, the sequences of 150 human H3N2 isolates had been determined and made available. Information now deposited in GenBank from various sources includes sequences of 110 complete H5N1 genomes, 4 complete H2N2 genomes, 4 complete H7N3 genomes and 30 complete H9N2 genomes (see www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html). These data are invaluable for tracking viral evolution and transmission, and for developing new drugs, vaccines and diagnostics.

Adding to our understanding of the molecular mechanisms driving flu virus emergence in animals and their spread to humans is a project carried out by investigators from St. Jude Children's Research Hospital, Tennessee. These researchers traced the current H5N1 outbreak in Asia back through a series of genetic reassortment events to a human outbreak that occurred in Hong Kong in 1997 (ref. 1). The genetic reassortments resulted in a dominant H5N1 genotype infecting chickens and ducks in 2003 and 2004. Domestic ducks in southern China were central players in the generation and maintenance of the virus, with migratory birds possibly contributing to the spread of the virus throughout southeast Asia.

It is crucial to continue surveillance studies of this type in order to monitor the spread of flu viruses from animal to animal, animal to human and from human to human. If a virus acquires the ability to transmit efficiently among humans, a pandemic is likely, whereupon aggressive intervention measures will be needed.

Vaccination and the use of antivirals are two of the most important response measures to a flu pandemic. H5N1 viruses are sensitive to the neuraminidase inhibitors oseltamivir (an oral

drug) and zanamavir (an inhalable powder). The HHS and the CDC have created an initial stockpile of 2.3 million treatment courses of oseltamivir, to which more doses will be added. More research and discussion are needed to prioritize the distribution of stockpiled anti-influenza drugs in case of a pandemic.

The NIH currently funds projects to develop and test other flu inhibitors, including CS-8958, a long-acting next-generation neuraminidase inhibitor. Other studies are directed towards identifying and evaluating new viral drug targets.

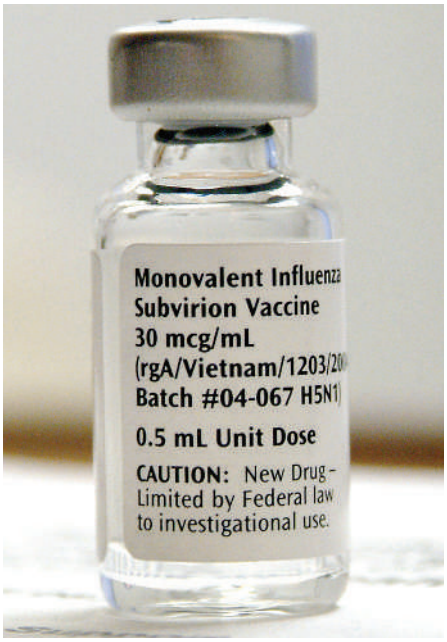
## Ramping up vaccines

Controlling an emerging flu pandemic will require a rapid and aggressive response: considerable efforts are being channelled into finding ways to streamline vaccine manufacture to allow for greater flexibility and surge capacity. The first step in vaccine preparation requires the generation of a 'reference virus' — generally a time-consuming process. A new technique called reverse genetics can be used to generate, relatively quickly, reference viruses that precisely match a target flu strain[2]. Using this technique, an H5N1 reference virus was produced within weeks and used to develop an inactivated H5N1 vaccine. A phase I clinical trial is currently under way to test the safety, immunogenicity (ability to stimulate an immune response), and appropriate dosage of an inactivated H5N1 vaccine manufactured by Sanofi Pasteur. The first phase of the trial will enroll 450 healthy adults, aged 18 to 64 years, at three sites in the United States. If the vaccine is shown to be safe, it will be tested in the elderly and in children (see www2.niaid.nih.gov/Newsroom/FocusOn/Flu04/).

The HHS has awarded a contract to Sanofi Pasteur to produce 2 million doses of inactivated H5N1 vaccine to create a stockpile as part of the HHS influenza preparedness plan. This effort will ensure that, should the need arise, the manufacturing techniques, procedures, and conditions for large-scale production are already in place. The movement to large-scale vaccine production in parallel with clinical trials indicates the urgency with which H5N1 vaccine development must be addressed. Waiting for the results of initial trials is normal procedure, but this would significantly delay production of large quantities of vaccine that might be needed to vaccinate health workers, researchers, and possibly the public, in affected areas.

To further broaden the pandemic vaccine portfolio, NIH has initiated the production and clinical testing of H9N2 candidates. The H9N2 influenza virus, although not highly pathogenic to humans, has been the most prevalent subtype of avian flu circulating among birds in Hong Kong and China[3], infecting at least eight individuals in the region. The results of phase I safety trials to evaluate the H9N2 vaccine are expected this year.

Immune responses generated by live attenuated vaccines develop more quickly and are more robust than those triggered by inactivated vaccines, such as those described above; they also tend to be more cross-protective against related variants of the same virus[4]. Live-attenuated H9N2 and H5N1 vaccine candidates have been generated and their safety, infectivity and immunogenicity will be tested in phase I clinical trials, probably later this year.

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**Protective potion: research into vaccines is urgently needed to deal with a flu pandemic.**

All licensed flu vaccines rely on the traditional method of vaccine production: the virus is grown inside chicken eggs. But this method does not readily allow for adjustments to increase output or to change the formulation for a newly emerging virus. The HHS and other organizations worldwide are supporting efforts to develop cell-culture methods for vaccine production. Replacing the traditional method, and providing the capacity for rapid scale-up, could allow vaccine manufacturers to keep pace with evolving flu viruses.

A long-term project at the NIH has been initiated to develop live-attenuated vaccines for each of the known avian flu virus subtypes. This effort, the first of its kind, represents a large-scale, long-term commitment to develop a rapid response capacity to emerging pandemic flu viruses.

Clinical lots will be generated from each reference virus and evaluated in humans for safety, infectivity and immunogenicity. Such an approach will, in principle, allow the rapid production of an avian flu vaccine against any known avian influenza subtype. In the event of a pandemic, vaccine production could theoretically commence almost immediately upon identification of a pre-tested, pandemic seed virus that most closely matched the newly emerged pandemic virus. The timetable for bringing such a vaccine to the market would depend on the pre-existing guidelines for safety testing.

In addition, NIH-supported researchers and others are attempting the difficult challenge of developing a flu vaccine based on antigens that are conserved across several influenza A strains. Such a vaccine could be more broadly protective against whatever strain an individual might encounter[5].

Prophylactic vaccination with 'prototype' antigens might provide partial protection against a pandemic strain[6]. This concept has been referred to as 'pre-priming', and may offer a way to integrate seasonal flu preparedness with pandemic flu preparedness by adding a fourth strain, such as an H5 or H7 subtype, to the familiar annual trivalent flu vaccine. Of course, these ideas are exploratory and preliminary; studies and discussion are essential to discern whether this approach makes sense from scientific, safety and logistical perspectives.

## Fragile enterprise

Strong collaborations between governments, academic institutions, and industry are needed to ensure a reliable vaccine supply. At present, pharmaceutical companies are reluctant to enter or remain in the business of manufacturing vaccines — unpredictable consumer demands and lack of financial incentives make vaccine manufacture a risky business. The biomedical research community can help by developing state-of-the-art technologies. These should be shared with industry to streamline the manufacturing process and make it more flexible, predictable and able to adapt to evolving viruses. Financial and economic incentives (including fair pricing, guaranteed purchase of unsold supplies, tax incentives, a streamlining of the complex regulatory processes needed for vaccine licensure, liability protection), and a vigorous public education effort are under consideration to ensure a steady supply and demand for vaccines.

The evolving situation in Asia offers an unprecedented opportunity to prepare for avian viruses with pandemic potential. Unlike the situation before previous flu pandemics, we now have the knowledge and technology to develop countermeasures for this deadly disease. However, unless we improve our capacity to produce such countermeasures, we may experience again the devastation of past pandemics. ■

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**Acknowledgement:** The author thanks N. Touchette, H. Harvey, G. Folkers, B. Gellin, B. Murphy, K. Subbarao, L. Lambert, M. Giovanni, B. Mulach and S. Foster for helpful discussions.