ABSTRACT

The threat of a human influenza pandemic has greatly increased over the past several years with the emergence of highly virulent avian influenza viruses, notably H5N1 viruses, which have infected humans in several Asian and European countries. Previous influenza pandemics have arrived with little or no warning, but the current widespread circulation of H5N1 viruses among avian populations and their potential for increased transmission to humans and other mammalian species may afford us an unprecedented opportunity to prepare for the next pandemic threat. The US Department of Health and Human Services is coordinating a national strategy to respond to an influenza pandemic that involves multiple agencies, including the Centers for Disease Control and Prevention, the Food and Drug Administration, and the National Institutes of Health (NIH). Within NIH, the National Institute of Allergy and Infectious Diseases (NIAID) conducts basic and clinical research to develop new vaccine technologies and antiviral drugs against influenza viruses. We describe recent research progress in preparing for pandemic influenza.

Keywords: pandemic influenza; threat; human influenza

1. INTRODUCTION

This document sets out activities that can be undertaken by individual countries, the international community, and WHO to prepare the world for the next influenza pandemic and
mitigate its impact once international spread has begun. Recommended activities are specific to the threat posed by the continuing spread of the H5N1 virus. Addressed to policy-makers, the document also describes issues that can guide policy choices in a situation characterized by both urgency and uncertainty.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
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<tr>
<td>Phase 1</td>
<td>No animal influenza virus circulating among animals have been reported to cause infection in humans.</td>
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<td>Phase 2</td>
<td>An animal influenza virus circulating in domesticated or wild animals is known to have caused infection in humans and is therefore considered a specific potential pandemic threat.</td>
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<td>Phase 3</td>
<td>An animal or human-animal influenza reassortant virus has caused sporadic cases or small clusters of disease in people, but has not resulted in human-to-human transmission sufficient to sustain community-level outbreaks.</td>
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<td>Phase 4</td>
<td>Human to human transmission of an animal or human-animal influenza reassortant virus able to sustain community-level outbreaks has been verified.</td>
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<td>Phase 5</td>
<td>The same identified virus has caused sustained community level outbreaks in two or more countries in one WHO region.</td>
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<td>Phase 6</td>
<td>In addition to the criteria defined in Phase 5, the same virus has caused sustained community level outbreaks in at least one other country in another WHO region.</td>
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<td>Post Peak Period</td>
<td>Levels of pandemic influenza in most countries with adequate surveillance have dropped below peak levels.</td>
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<tr>
<td>Post Pandemic Period</td>
<td>Levels of influenza activity have returned to the levels seen for seasonal influenza in most countries with adequate surveillance.</td>
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Recommendations are phase-wise in their approach, with levels of alert, and corresponding activities, changing according to epidemiological indicators of increased threat. In view of the immediacy of the threat, WHO recommends that all countries undertake urgent action to prepare for a pandemic. Advice on doing so is contained in the recently revised WHO global influenza preparedness plan 1 and a new WHO checklist for influenza pandemic preparedness planning. To further assist in preparedness planning, WHO is developing a model country plan that will give many developing countries a head start in assessing their status of preparedness and identifying priority needs. Support for rehearsing these plans during simulation exercises will also be provided.

Influenza pandemics have historically taken the world by surprise, giving health services little time to prepare for the abrupt increases in cases and deaths that characterize these events and make them so disruptive. Vaccines – the most important intervention for reducing morbidity and mortality – were available for the 1957 and 1968 pandemic viruses, but arrived too late to have an impact.

Map 1. Pandemic influenza

As a result, great social and economic disruption, as well as loss of life, accompanied the three pandemics of the previous century. The present situation is markedly different for several reasons. First, the world has been warned in advance. For more than a year, conditions...
favouring another pandemic have been unfolding in parts of Asia. Warnings that a pandemic may be imminent have come from both changes in the epidemiology of human and animal disease and an expanding geographical presence of the virus, creating further opportunities for human exposure.

While neither the timing nor the severity of the next pandemic can be predicted, evidence that the virus is now endemic in bird populations means that the present level of risk will not be easily diminished. Second, this advance warning has brought an unprecedented opportunity to prepare for a pandemic and develop ways to mitigate its effects. To date, the main preparedness activities undertaken by countries have concentrated on preparing and rehearsing response plans, developing a pandemic vaccine, and securing supplies of antiviral drugs.

Because these activities are costly, wealthy countries are presently the best prepared; countries where H5N1 is endemic – and where a pandemic virus is most likely to emerge – lag far behind. More countries now have pandemic preparedness plans: around one fifth of the world’s countries have some form of a response plan, but these vary greatly in comprehensiveness and stage of completion.

Map 2. Pandemic influenza
Scheme 1. *Dear spread pandemic influenza*

Scheme 2. *Dear spread pandemic influenza*
Access to antiviral drugs and, more importantly, to vaccines remains a major problem because of finite manufacturing capacity as well as costs. Some 23 countries have ordered antiviral drugs for national stockpiles, but the principal manufacturer will not be able to fill all orders for at least another year. Fewer than 10 countries have domestic vaccine companies engaged in work on a pandemic vaccine.

A November 2004 WHO consultation reached the stark conclusion that, on present trends, the majority of developing countries would have no access to a vaccine during the first wave of a pandemic and possibly throughout its duration. Apart from stimulating national preparedness activities, the present situation has opened an unprecedented opportunity for international intervention aimed at delaying the emergence of a pandemic virus or forestalling its international spread.

Doing so is in the self-interest of all nations, as such a strategy could gain time to augment vaccine supplies. At present capacity, each day of manufacturing gained can mean an additional 5 million doses of vaccine.

International support can also strengthen the early warning system in endemic countries, again benefiting preparedness planning and priority setting in all nations. Finally, international support is needed to ensure that large parts of the world do not experience a pandemic without the protection of a vaccine. Pandemics are remarkable events in that they affect all parts of the world, regardless of socioeconomic status or standards of health care, hygiene and sanitation.

Once international spread begins, each government will understandably make protection of its own population the first priority. The best opportunity for international collaboration – in the interest of all countries – is now, before a pandemic begins.
2. PANDEMIC INFLUENZA PREPAREDNESS

Vaccine development is a critical component of pandemic influenza preparedness. In this regard, the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) in April 2005 initiated a phase I clinical trial to assess the safety and immunogenicity of different doses of an inactivated H5N1 influenza vaccine manufactured by Sanofi Pasteur. In this study, 451 healthy adult volunteers were vaccinated at 3 sites in the United States.

Preliminary evaluation indicates the vaccine is safe and able to stimulate an immune response that may be protective. The vaccine is currently being tested in the elderly, and testing in children is expected to begin by January 2006. The H5N1 seed virus used to make this vaccine was developed in a matter of weeks through the use of reverse genetics, whereas the traditional process of genetic reassortment usually requires a longer period of time and is less predictable. Additional pilot lots of inactivated vaccine are being produced by another manufacturer, Chiron Corporation, and are expected to undergo testing by early 2006. Chiron also has produced 40,000 doses of an inactivated H9N2 influenza vaccine formulated with and without MF59 adjuvant. Clinical trials to test the safety and immunogenicity of the inactivated H9N2 vaccine are underway, with promising preliminary results.

In addition, the US Department of Health and Human Services (HHS) has awarded several contracts to pharmaceutical companies to produce large quantities of bulk H5N1 vaccine as part of the HHS Pandemic Influenza Preparedness Program. These contracts are a critical step toward pandemic influenza preparedness because they pave the way for the manufacturer to commence efficient, large-scale production of any pandemic vaccine if or when it is needed.

HHS has also awarded a separate contract to Sanofi Pasteur to accelerate the development of cell culture– based technologies for influenza vaccine production. Other research efforts are focused on medications to treat influenza infection. Unfortunately, most currently circulating H5N1 influenza viruses are resistant to 2 inexpensive antiinfluenza drugs, rimantadine and amantadine, that target the viral M2 protein.
Scheme 5. *Dear spread pandemic influenza*
Newer drugs such as oseltamivir phosphate and zanamivir that target the influenza neuraminidase protein appear to be effective against most current H5N1 strains. HHS and the Centers for Disease Control and Prevention have begun developing a stockpile of antiinfluenza drugs that includes oseltamivir phosphate, zanamivir, and rimantadine for future use should pandemic influenza occur. Numerous other projects are under way to identify novel drug targets and develop compounds that inhibit viral entry, replication, and maturation. Underpinning these efforts are basic research studies. For example, NIAID coordinates the Influenza Genome Sequencing Project, a collaborative effort to create complete genetic blueprints of known human and avian influenza viruses.

![Scheme 6. Dear spread pandemic influenza](image)

As of December 7, 2005, a total of 559 influenza genome sequences have been made publicly available in GenBank by the NIAID project. In a separate but related contract awarded to researchers at St. Jude Children’s Research Hospital, animal influenza viruses from wild birds, live bird markets, and pigs in Hong Kong and North America are being sequenced, and surveillance has expanded to include additional sites in Asia.

The goal of these projects is to rapidly sequence influenza genomes derived from a variety of human and animal sources to enable scientists to understand how the viruses evolve, spread, and cause disease. The long-term goal is improving methods of prevention and treatment.
3. SITUATION ASSESSMENT

The risk of a pandemic is great. Since late 2003, the world has moved closer to a pandemic than at any time since 1968, when the last of the previous century’s three pandemics occurred. All prerequisites for the start of a pandemic have now been met save one: the establishment of efficient human-to-human transmission.

During 2005, ominous changes have been observed in the epidemiology of the disease in animals. Human cases are continuing to occur, and the virus has expanded its geographical range to include new countries, thus increasing the size of the population at risk. Each new human case gives the virus an opportunity to evolve towards a fully transmissible pandemic strain.

4. THE RISK WILL PERSIST

Evidence shows that the H5N1 virus is now endemic in parts of Asia, having established an ecological niche in poultry. The risk of further human cases will persist, as will opportunities for a pandemic virus to emerge. Outbreaks have recurred despite aggressive control measures, including the culling of more than 140 million poultry.
Wild migratory birds – historically the host reservoir of all influenza A viruses – are now dying in large numbers from highly pathogenic H5N1.

Domestic ducks can excrete large quantities of highly pathogenic virus without showing signs of illness. Their silent role in maintaining transmission further complicates control in poultry and makes human avoidance of risky behaviours more difficult.

5. EVOLUTION OF THE THREAT CANNOT BE PREDICTED

Given the constantly changing nature of influenza viruses, the timing and severity of the next pandemic cannot be predicted. The final step – improved transmissibility among humans – can take place via two principal mechanisms: a reassortment event, in which genetic material is exchanged between human and avian viruses during co-infection of a human or pig, and a more gradual process of adaptive mutation, whereby the capability of these viruses to bind to human cells would increase during subsequent infections of humans. Reassortment could result in a fully transmissible pandemic virus, announced by a sudden surge of cases with explosive spread.

Adaptive mutation, expressed initially as small clusters of human cases with evidence of limited transmission, will probably give the world some time to take defensive action. Again, whether such a “grace period” will be granted is unknown.

6. THE EARLY WARNING SYSTEM IS WEAK

As the evolution of the threat cannot be predicted, a sensitive early warning system is needed to detect the first sign of changes in the behaviour of the virus. In risk-prone countries, disease information systems and health, veterinary, and laboratory capacities are weak. Most affected countries cannot adequately compensate farmers for culled poultry, thus discouraging the reporting of outbreaks in the rural areas where the vast majority of human cases have occurred. Veterinary extension services frequently fail to reach these areas. Rural poverty perpetuates high-risk behaviours, including the traditional home-slaughter and consumption of diseased birds.

Detection of human cases is impeded by patchy surveillance in these areas. Diagnosis of human cases is impeded by weak laboratory support and the complexity and high costs of testing. Few affected countries have the staff and resources needed to thoroughly investigate human cases and, most importantly, to detect and investigate clusters of cases – an essential warning signal. In virtually all affected countries, antiviral drugs are in very short supply. The dilemma of preparing for a potentially catastrophic but unpredictable event is great for all countries, but most especially so for countries affected by H5N1 outbreaks in animals and humans.

These countries, in which rural subsistence farming is a backbone of economic life, have experienced direct and enormous agricultural losses, presently estimated at more than US$ 10 billion. They are being asked to sustain – if not intensify – resource-intensive activities needed to safeguard international public health while struggling to cope with many other competing health and infectious disease priorities.
7. PREVENTIVE INTERVENTION IS POSSIBLE, BUT UNTESTED

Should a pandemic virus begin to emerge through the more gradual process of adaptive mutation, early intervention with antiviral drugs, supported by other public health measures, could theoretically prevent the virus from further improving its transmissibility, thus either preventing a pandemic or delaying its international spread. While this strategy has been proposed by many influenza experts, it remains untested; no effort has ever been made to alter the natural course of a pandemic at its source.

8. REDUCTION OF MORBIDITY AND MORTALITY DURING A PANDEMIC WILL BE IMPEDED BY INADEQUATE MEDICAL SUPPLIES

Vaccination and the use of antiviral drugs are two of the most important response measures for reducing morbidity and mortality during a pandemic. On present trends, neither of these interventions will be available in adequate quantities or equitably distributed at the start of a pandemic and for many months thereafter.

9. STRENGTHEN THE EARLY WARNING SYSTEM

Events unfolding in parts of Asia for more than a year have sounded a general warning that a pandemic may be imminent. If this warning is to become precise enough to guide national and international actions, surveillance and reporting in affected countries must improve. The present inadequacy of surveillance has several sources. Some countries lack the requisite epidemiological and laboratory capacity for responding to any emerging disease. For H5N1, conclusive diagnostic tests are technically difficult and costly, and can be conducted safely only in specially equipped facilities. Surveillance is impaired by the fact that most cases have occurred in rural areas.

Case detection is complicated by the frequent high prevalence in affected countries of other severe respiratory diseases having similar symptoms. Many activities defined in global and national pandemic response plans are triggered by changes in the behaviour of the virus. Detection of these changes and interpretation of their significance depend on timely and reliable epidemiological, clinical, and virological data. Every single human case yields evidence essential for risk assessment.

The investigation of clusters of cases, closely related in time and place, provides the first alert to improved transmissibility of the virus. Serological surveys in close contacts of patients, communities where clusters of cases have occurred, and high-risk populations, such as health care workers, also provide early alerts to changes in the behaviour of the virus. Information on the clinical course of cases is an equally vital signal, as milder disease with lower fatality is expected to coincide with improved transmissibility.

Analyses of viruses, collected during surveillance, by WHO and FAO/OIE reference laboratories can detect changes in the virus and likewise determine whether these indicate improved transmissibility, thus working to substantiate clues gleaned from epidemiological and clinical observations. Equally important, studies of recently collected viruses are needed to ensure that work on vaccine development stays on course.
10. STRATEGIC ACTIONS

10.1. Improve the detection of human cases

WHO will provide the training, diagnostic reagents, and administrative support for external verification needed to improve the speed and reliability of case detection. To date, the vast majority of cases have been detected following hospitalization for respiratory illness. Hospitals in affected countries need support in case detection, laboratory confirmation, and reporting.

Apart from its role in an early warning system, rapid laboratory confirmation signals the need to isolate patients and manage them according to strict procedures of infection control, and can thus help prevent further cases. Diagnostic support continues to be provided by laboratories in the WHO network. However, because the initial symptoms of H5N1 infection mimic those of many diseases common in these countries, accurate case detection requires the testing of large numbers of samples. Improved local capacity is therefore a more rational solution.

10.2. Combine detection of new outbreaks in animals with active searches for human cases

Using epidemiologists in its country offices and, when necessary, external partners, WHO will ensure that detection of new outbreaks of highly pathogenic H5N1 in poultry is accompanied by active searches for human cases. Surveillance in several countries where H5N1 is considered endemic in birds is inadequate and suspicions are strong that human cases have been missed. Cambodia’s four human cases were detected only after patients sought treatment in neighbouring Viet Nam, where physicians are on high alert for cases and familiar with the clinical presentation.

10.3. Support epidemiological investigation

Reliable risk assessment depends on thorough investigation of sporadic human cases and clusters of cases. Guidelines for outbreak investigation, specific to H5N1 and to the epidemiological situation in different countries, are being developed on an urgent basis for use in training national teams. These guidelines give particular emphasis to the investigation of clusters of cases and determination of whether human-to-human transmission has occurred. Teams assembled from institutions in the WHO Global Outbreak Alert and Response Network (GOARN) can be deployed for rapid on-site investigative support.

10.4. Coordinate clinical research in Asia

Clinical data on human cases need to be compiled and compared in order to elucidate modes of transmission, identify groups at risk, and find better treatments. Work has begun to establish a network of hospitals, modelled on the WHO global influenza surveillance network, engaged in clinical research on human disease. The network will link together the principal hospitals in Asia that are treating H5N1 patients and conducting clinical research. Technical support will allow rapid exchange of information and sharing of specimens and research results, and encourage the use of standardized protocols for treatment and standardized sampling procedures for investigation.
10. 5. Strengthen risk assessment

WHO’s daily operations need to be strengthened to ensure constant collection and verification of epidemiological and virological information essential for risk assessment. Ministries of health and research institutions in affected countries need to be more fully engaged in the collection and verification of data. Ministries and institutions in non-affected countries should help assess the significance of these data, and the results should be issued rapidly.

These activities, currently coordinated by WHO, need to escalate; influenza viruses can evolve rapidly and in unexpected ways that alter risk assessment, as evidenced by the recent detection of highly pathogenic H5N1 viruses in migratory birds. Functions of the WHO network of laboratories with expertise in the analysis of H5N1 viruses can be improved through tools, such as a genetic database, and a strong collaboration with veterinary laboratory networks to ensure that animal as well as human viruses are kept under constant surveillance.

10. 6. Strengthen existing national influenza centres throughout the risk-prone region

Many existing national influenza centres, designated by WHO, already possess considerable infrastructure in the form of equipment and trained personnel. Additional support, particularly in the form of diagnostic reagents, could help strengthen the early warning system in risk-prone countries and their neighbours.

10. 7. Give risk-prone countries an incentive to collaborate internationally

The promise of assistance is a strong motivation to report cases and share clinical specimens internationally. A high-level meeting should be convened so that heads of state in industrialized countries and in risk-prone countries can seek solutions and reach agreement on the kinds of support considered most desirable by individual countries.

11. CONCLUSIONS

Recent experience with an outbreak of severe acute respiratory syndrome (SARS) serves as an instructive example in preparing for a potential influenza pandemic (38,39). In 2002, the deadly respiratory disease emerged and rapidly spread to Canada, Vietnam, Hong Kong, and other sites in China, ultimately resulting in 8,098 cases and 774 deaths. The outbreak, which elicited a classic study in epidemiologic investigation with regard to identifying the point source, tracking the spread, and instituting containment measures, taught us many important lessons.

Academic scientists, public health officials, and commercial pharmaceutical companies acted together in an unprecedented way, leading to the development of promising vaccine candidates in record time. The etiologic agent of SARS, a previously unrecognized coronavirus, was identified in March 2003 and sequenced within 2 weeks, and a vaccine candidate was developed by the following March. In December 2004, a clinical trial of a candidate SARS vaccine began at the NIH Vaccine Research Center (40).
Because the SARS coronavirus is not as easily transmitted as influenza viruses, we do not know whether the actions that led to the containment of SARS would be as successful if an avian influenza virus acquired the ability to spread efficiently from person to person.

However, we have an added advantage in bracing for pandemic influenza that we did not have with SARS. As noted, SARS is caused by a coronavirus that was unknown before the 2003 outbreak. In the current situation, we have identified the H5N1 virus as a likely candidate for triggering a pandemic.

We cannot be certain when the next influenza pandemic will emerge, or even whether it will be caused by H5N1 or an unrelated virus. However, we can be certain that an influenza pandemic eventually will occur. The efforts currently under way to monitor the evolution and spread of H5N1 and other influenza viruses and to develop candidate vaccines and appropriate countermeasures will help in developing the infrastructure and manufacturing capacity that will be required to scale up vaccine and antiviral production when the pandemic occurs.

Because quantities of vaccine and antiviral drugs against a pandemic influenza virus will be limited, deciding beforehand how to best use our resources throughout the world to minimize the impact of pandemic influenza is critical. Global cooperation will be vital. During the SARS epidemic, the World Health Organization created an outstanding network of laboratories and public health agencies from countries around the globe that were indispensable in identifying and ultimately containing the spread of the virus.

To adequately address the many research issues surrounding avian influenza and other potential pandemic pathogens, NIAID’s Office of Clinical Research is establishing a Southeast Asia Clinical Trials Network to evaluate influenza interventions. This network builds upon existing infrastructure where possible and will be a true partnership between the investigators and the healthcare leadership of the target countries. Such international teamwork is essential as we prepare for an influenza pandemic.

References


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(Received 19 May 2015; accepted 08 June 2015)