INFLUENZA PANDEMIC RISK ASSESSMENT AND PREPAREDNESS IN AFRICA

INFLUENZA PANDEMIC RISK ASSESSMENT AND PREPAREDNESS IN AFRICA

World Health Organization
Regional Office for Africa
Brazzaville • 2005

Printed in the Republic of Congo

Contents

Page

About influenza pandemics

Influenza pandemics are rare but recurring events that have periodically affected humanity since ancient times. They are invariably associated with a rapid surge, experienced globally, in the number of cases of respiratory illness and death. Three pandemics occurred during the previous century: in 1918 (Spanish flu), 1957 (Asian flu) and 1968 (Hong Kong flu). The 1918 pandemic is considered one of the most lethal infectious disease events in the history of humanity: it killed 40–50 million people within a year, and took its heaviest toll on young adults in the prime of life. Subsequent pandemics were much milder, with an estimated two million deaths in 1957 and one million deaths in 1968. During the past pandemics, the groups most severely affected were similar to those affected during normal seasonal influenza, i.e. the very young, elderly, chronically ill and persons with compromised immune systems.

The world may be on the brink of another pandemic. For almost two years, health experts at WHO and elsewhere have been monitoring a new and extremely severe influenza virus, the highly pathogenic H5N1 strain. Since mid-2003, this virus has caused the largest and most severe outbreaks of highly pathogenic disease ever recorded in poultry. Some 150 million domestic birds have died or been culled in nine south-east Asian nations. Losses for the agricultural sector have been estimated at US$ 10 billion.

In December 2003, infections in people exposed to sick birds were identified. Since then, at least 120 human cases have been laboratory confirmed in four Asian countries (Cambodia, Indonesia, Thailand and Viet Nam); more than half of these people have died. Unlike normal seasonal influenza, where infection causes only mild respiratory symptoms in most people, the disease caused by H5N1 follows an unusually aggressive clinical course, with rapid deterioration and high fatality. Primary viral pneumonia and multi-organ failure are common. In the present outbreak, most cases have occurred in previously healthy children and young adults. The species barrier is significant: the virus does not easily jump from birds to humans. However, a major implication for human health is that the virus will change into a form that will spread easily from person to person. Such a change could mark the start of a global outbreak (a pandemic).

In birds, the outbreaks have begun to spread from the original focus in south-east Asia to parts of Europe. Scientists are increasingly convinced that at least some migratory species are now directly spreading highly pathogenic H5N1 to new areas; spread via this vector is likely to continue. Bird experts know that parts of the Middle East and Africa lie on migratory routes and these areas, too, may be at risk. Heightened vigilance for unusual deaths in wild and domestic birds is fully justified.

Situation overview and pandemic risk assessment

A pandemic can start when three conditions are met: a virus subtype new to humans emerges; it infects humans, causing serious illness; and it spreads easily and sustainably among humans. The H5N1 virus amply meets the first two conditions: it is a new virus for humans (viruses of the H5 subtype have never circulated widely among people), and it infects humans, causing very severe disease with a high fatality. No one will have immunity should an H5N1-like pandemic virus emerge.

All prerequisites for the start of a pandemic have been met save one: the establishment of efficient and sustained human-to-human transmission of the virus. The risk that the H5N1 virus will acquire this ability is difficult to assess, but the risk will persist as long as opportunities for human infections occur. These opportunities, in turn, will persist as long as the virus continues to circulate in birds, and this situation is expected to endure for several years to come.

The virus is now considered endemic in poultry populations in large parts of Asia, and timeframes for control of the disease are now being measured in years. Moreover, the virus has changed in ways that greatly complicate control efforts. First, domestic ducks are now acting as a "silent reservoir" of the virus, perpetuating transmission to other domestic birds. They can excrete large quantities of viral pathogens yet appear to be perfectly healthy. Second, migratory birds are almost certainly now spreading the virus along their flyways; all experts agree that control of the virus in wild birds is impossible.

Wild waterfowl are the natural reservoir host of all influenza A viruses, and usually carry these viruses with no apparent signs of harm. The spring 2005 die-off of upwards of 6000 migratory birds at a nature reserve in central China, caused by highly pathogenic H5N1, was highly unusual and probably unprecedented. Beginning in late July 2005, highly pathogenic H5N1 was detected in wild and domestic birds in Siberia (Russia) and adjacent parts of Kazakhstan. Almost simultaneously, Mongolia reported H5N1 in a large number of migratory birds. In October 2005, H5N1 was confirmed in poultry in Croatia, Romania and Turkey. Outbreaks in wild and domestic birds are under investigation elsewhere. This expanding geographical presence of the virus increases opportunities for human infections to occur and for the virus to change into a form that is readily transmitted among humans.

The virus can improve its transmissibility among humans via two principal mechanisms. The first is a "reassortment" event in which genetic material is exchanged between human and avian viruses during co-infection of a human or pig. Reassortment

could result in a fully transmissible pandemic virus, announced by a sudden surge of cases with explosive spread.

The second mechanism is a more gradual process of "adaptive mutation" whereby the capability of the virus to bind to human cells increases during subsequent infections of humans. Adaptive mutation, expressed initially as small clusters of human cases with some evidence of human-to-human transmission, would probably give the world some time to take defensive action.

Risk assessment for Africa

Outbreaks in poultry: Significance for human health

The arrival of highly pathogenic H5N1 avian influenza on the African continent would be of great concern for human as well as animal health. Though the densities of human and poultry populations are generally lower in Africa than in south-east Asia, the poultry production systems have many similarities which could create multiple opportunities for human exposure, if outbreaks occur in African poultry. In Africa, many households keep backyard flocks which often mingle freely with wild birds. Most such flocks scavenge for food, often entering households or sharing outdoor areas where children play.

With few exceptions, notably in large commercial farms, surveillance for avian disease is non-existent. Nutrition of the birds is poor and high mortality is common, increasing the likelihood that outbreaks of H5N1 will be missed. Few governments are in a position to offer support for disease control or compensation for lost birds, thus further discouraging early and open reporting. As experience in Asia has shown, late detection of outbreaks increases the likelihood that the virus will become endemic. Deaths of large numbers of poultry, whether due to disease or culling for control purposes, would deprive already impoverished populations of an important source of dietary protein.

Human cases

In Africa, the risk of human infection from an avian H5N1 virus can be expected to be similar to that seen in Asia. To date, the majority of human cases in Asia have been linked to close contact with infected domestic birds, with especially high risks thought to occur during home slaughter, defeathering, butchering and preparation for cooking. Consumption of inadequately cooked poultry and poultry products (including eggs and blood) is an additional risk. African households, especially in rural areas, traditionally

slaughter and consume birds when signs of illness appear in backyard flocks. As in Asia, such practices could prove difficult to change.

The occurrence of human cases, even sporadic, would create enormous new challenges for health systems and services that are already fragile and overburdened. Early detection of human cases is unlikely. Surveillance systems are weak and unlikely to pick up cases of a disease with symptoms similar to those of common illnesses. Health service, human and financial resources have been overwhelmed by the demands of AIDS, tuberculosis and malaria. Laboratory confirmation of human H5N1 infections requires technology, finances and trained personnel.

Management of H5N1 patients is very demanding. Infection control in most hospitals is difficult to introduce and sustain. Sporadic cases of H5N1 infection and the frequent reluctance of residents to comply with recommended reporting and isolation measures during outbreaks of severe disease could push fragile health systems close to the brink of collapse. Surveillance systems are not sufficiently sensitive to clusters of human cases, although they constitute a critical early warning signal that the virus is improving its transmissibility. Africa has some well-equipped laboratories, but these might rapidly prove inadequate should large numbers of samples need to be tested rapidly.

Vaccine research and development: Current status

Vaccines are considered the first line of defence for reducing the excess morbidity and mortality that invariably accompany pandemics. For several reasons, no country will have adequate supplies of vaccine at the start of a pandemic. Large-scale commercial vaccine production is not expected to commence until about three to six months following the emergence of a pandemic virus.

Manufacturing capacity for influenza vaccines is overwhelmingly concentrated in Europe and North America. Current production capacity—estimated at around 300 million doses of trivalent seasonal vaccine per year—falls far below the demand that will arise during a pandemic.

WHO, through its network of specialized influenza laboratories, has constantly monitored the evolution of the H5N1 virus since its initial infection of humans in Hong Kong in 1997. These laboratories prepare the prototype vaccine strain that is being provided to industry as the "seed" for vaccine development. Constant molecular analyses of viruses by these laboratories ensure that work on vaccine development stays on track. This is particularly important because of the virus mutations detected during 2005.

About ten countries have domestic vaccine manufacturers, and several of these are presently working on the development of a pandemic vaccine. Some of these projects have reached the stage of clinical trails, and trials of other candidate vaccines are expected to begin shortly. One company has indicated that it will be presenting the results of its clinical trials to WHO by early December 2005. However, if a pandemic were to begin within the next few months, no company would be ready to move immediately into commercial production.

At present, little knowledge exists to guide formulation of an effective influenza vaccine that uses the antigen component that elicits the immune response. However, clinical trials are under way to test different formulations, and these trials will provide some answers. WHO has encouraged companies to test vaccine formulations that include an adjuvant. This substance boosts the immune response and theoretically could allow adequate protection with lower antigen quantities. Work on this approach is also under way.

Because a pandemic vaccine needs to be a close match to the actual pandemic virus, commercial production cannot begin prior to emergence and characterization of the pandemic virus. WHO has, however, encouraged industry and regulatory authorities to develop fast-track procedures for licensing and marketing authorization of a pandemic vaccine. Many authorities have complied.

In addition, WHO is using international meetings to urge the international community to find ways to increase manufacturing capacity and ensure that developing countries have access to an effective vaccine at affordable prices. However, most developing countries will have no access to a vaccine during the first wave of a pandemic and perhaps throughout its duration.

Antiviral drugs: Their role during a pandemic

Pending the availability of vaccines, several antiviral drugs are expected to be useful for prevention or treatment purposes. Two drugs, oseltamivir (commercially known as Tamiflu) and zanamivir (commercially known as Relenza) have been shown, in laboratory studies, to reduce the severity and duration of illness caused by seasonal influenza. The efficacy of these neuraminidase inhibitors depends on their administration within 48 hours of symptom onset. For cases of human infection with H5N1, the drugs may reduce the severity of disease and improve prospects of survival if administered early, but clinical data are limited. The H5N1 virus is expected to be susceptible to the neuraminidase inhibitors in these drugs.

Another class of antiviral drugs, the M2 inhibitors amantadine and rimantadine, could potentially be used against pandemic influenza. However, resistance to these drugs may develop rapidly and this could significantly limit their effectiveness against pandemic influenza. Some currently circulating avian H5N1 strains are fully resistant to the M2 inhibitors, while others remain fully susceptible.

For the neuraminidase inhibitors, the main constraints are substantial and involve limited production capacity and prohibitively high prices. Because of the complex and time-consuming manufacturing process, the sole manufacturer of oseltamivir is unable to meet demand and faces a backlog of orders. Present manufacturing capacity, which has recently quadrupled, would need a decade to produce enough oseltamivir to treat 20% of the world's population.

Since supplies are severely constrained, countries now stockpiling antiviral drugs need to decide in advance on priority groups for administration. Front-line health-care workers would be obvious priorities, but such decisions are the responsibility of governments. While antiviral drugs can confer some measure of protection pending the availability of vaccines, these drugs should not be used to perform the same public health role as vaccines – even if supplies would permit. Mass administration of prophylactic antiviral drugs to large numbers of healthy people for extended periods is not recommended as it could accelerate the development of drug resistance.

Following a donation by industry, WHO will have a stockpile of antiviral drugs (oseltamivir) sufficient for 3 million treatment courses by early 2006. These drugs are strictly reserved for use in the first areas affected by an emerging pandemic virus. Recent studies, based on mathematical modelling, suggest that these drugs could be used prophylactically near the start of a pandemic to reduce the risk that a fully transmissible virus will emerge or at least to delay its international spread. This would allow time to augment vaccine supplies. The drugs will be stored centrally; WHO has considerable experience in the rapid despatch of medical supplies during emergencies.

The success of this strategy, which has never been tested, depends on several assumptions about the early behaviour of a pandemic virus. Success also depends on excellent surveillance and logistics capacity in initially-affected areas combined with an ability to enforce movement restrictions in and out of affected areas. To increase the likelihood that early intervention using the WHO stockpile of antiviral drugs will be successful, surveillance in affected countries needs to improve, particularly the capacity to detect clusters of cases closely related in time and place.

Non-pharmaceutical interventions: Their role in reducing transmission and spread

At the start of a pandemic and for many months thereafter, all countries will face inadequate supplies of vaccines and antiviral drugs. WHO has therefore organized several expert consultations to explore the role of classic public health measures in reducing transmission and delaying spread. Evaluation of these measures has been based on limited experience during past pandemics and on what is known about the behaviour of normal influenza viruses.

The effectiveness of several measures will depend on the characteristics of the pandemic virus (attack rate, virulence, principal age groups affected, modes of spread within and between countries), and these cannot be known in advance. After a pandemic is declared, WHO will monitor its evolution in real time.

Recommendations about the most effective measures will therefore become more precise as the epidemiological potential of the virus unfolds. For all these reasons, the recommendations below should be taken as general guidance and not as formal WHO advice. Recommended measures are specific to the phase of alert in the WHO six-phase scale.

Phase three (current phase). The present situation is categorized as phase three: human infections with a novel virus subtype (H5) are occurring, but there is no evidence that the virus is spreading efficiently and sustainably among humans. Although the virus has demonstrated some ability to infect humans, H5N1 avian influenza remains principally a disease of birds, and not of humans. Human cases at present are isolated and rare, indicating a significant species barrier. To date, fewer than 130 human cases have been officially confirmed, despite the infection of tens of millions of birds over a wide geographical area for almost two years, in a situation with abundant opportunities for human exposure.

At this phase, WHO recommends vigilance for human cases in areas experiencing outbreaks in birds. Unaffected areas should undertake measures to prevent entry of the virus via poultry or wild birds, especially as this virus, once established in birds, has proved to be especially tenacious. For humans, no travel restrictions or screening measures at borders are recommended, as the risk that the virus will be carried by international travellers is considered negligible.

Phases four and five. Phases four and five are characterized by evidence that the virus is progressively improving its transmissibility among humans, but it is not yet spreading

efficiently and sustainably. An increase in the number of clusters, closely related in time and place, is considered the likely epidemiological signal of improved transmissibility. During these phases, when instances of human-to-human transmission remain localized, WHO may recommend, depending on the circumstances, some of the measures below. These measures aim to reduce transmission and prevent, or at least delay, further spread.

(a) Rapid detection and isolation of persons infected with H5N1;

(b) Tracing of close contacts during the patient's first two weeks of illness and voluntary quarantine of symptomatic persons for one week;

(c) Use of antiviral drugs for treatment of cases and prophylaxis of others in the initially affected area; the WHO rapid-response stockpile of antiviral drugs will be used for this purpose;

(d) Restriction on the movement of persons in and out of the initially affected area;

(e) Screening of travellers departing from areas where clusters of human cases are occurring.

Phase six: Pandemic declared (not all countries affected). At the start of a pandemic, when not all countries or areas within a country are likely to have cases, WHO may recommend, depending on the circumstances, some of the measures below.

(a) Health-care workers and first responders should be equipped with N95 respiratory masks; these should be fit-tested, and training in their use should be provided. If respiratory masks are not available, standard well-fitted surgical masks should be used.

(b) Patients and persons seeking care in areas with cases should wear surgical masks.

(c) Persons with fever and respiratory symptoms and their contacts should be asked to undergo voluntary home confinement.

(d) Populations in countries with cases should be asked to defer non-essential domestic travel to affected parts of the country.

(e) Countries with cases should provide incoming travellers with health alert notices describing symptoms and where to report should these symptoms develop.

(f) Countries with cases may introduce exit screening measures for departing travellers. However, such measures are disruptive and costly and will not be

fully efficient as influenza viruses can be carried by asymptomatic persons who will escape detection during screening.

(g) For persons known to have been exposed in an aircraft or aboard a large ship, consideration can be given to recommended daily fever checks among passengers and crew and prophylactic treatment with antiviral drugs, when available.

Phase six: Pandemic spread (all countries affected). Because influenza viruses are contagious and spread easily via coughing or sneezing, pandemics have historically encircled the globe quickly. After a new pandemic virus has spread widely within countries and internationally, WHO may recommend, depending on the circumstances, some of the measures below in all countries:

(a) Patient isolation and tracing and quarantine of contacts should cease as such measures will no longer be feasible or useful.

(b) Health-care workers and first responders should wear N95 respiratory masks or well-fitting surgical masks; patients should wear surgical masks.

(c) Should a large surge in cases occur, health-care facilities should be organized in ways that help reduce transmission (for example, by keeping a distance between patient beds or placing adjacent beds face-to-foot).

(d) "Social distancing" measures, such as the closing of schools or cancellation of large gatherings, may be recommended if evidence indicates an association of certain settings or events with amplified transmission or dispersion into the wider community.

(e) Populations should be repeatedly informed of the need for frequent hand washing with soap and water.

(f) Populations should be repeatedly informed of the need for "respiratory hygiene" (covering mouth when coughing or sneezing, careful disposal of soiled tissues or other materials).

(g) Mask wearing by the general population is not expected to have an appreciable impact on transmission, but this action should be permitted as it is likely to occur spontaneously.

WHO does not recommend, at any phase, that individual countries be quarantined or that international borders be closed.

WHO support for pandemic preparedness in Africa

The next pandemic will be the first to strike a world that has seen the emergence of HIV/AIDS and the dramatic resurgence of tuberculosis and malaria. With capacities already overburdened by these and other priority health problems, the African continent could be particularly vulnerable to high morbidity and mortality during a pandemic. Thus, preparedness is most urgently needed in Africa.

The impact on HIV-infected persons of co-infection with a pandemic virus is not known, but persons with compromised immune systems are a known risk group for severe complications during normal seasonal influenza. For tuberculosis, some experts believe that immunosuppression following infection with a pandemic virus might lead, in survivors, to an increase in cases in areas where tuberculosis infections and transmission are widespread. No reliable evidence on the significance of co-infection with pandemic influenza and malaria is presently available.

All African countries need to develop a plan for responding to a pandemic. For planning purposes, WHO uses estimates (based on the comparatively mild 1957 pandemic) that suggest that up to 20% of the world's population will need medical care. A conservative estimate of the number of deaths, worldwide, ranges from 2 million to 7.4 million. All countries should expect to see surges in cases and deaths during a pandemic that can last around two months. Historically, pandemics have spread to all continents within six to nine months, even when international travel was mainly by ship. Most experts agree that the next pandemic could spread to all parts of the world within three months.

WHO has a range of human resources and networks that can support African countries in preparing for a pandemic and responding to early cases of H5N1 infection or influenza. WHO country offices, which work closely with ministries of health, have officers responsible for disease prevention and control and for health promotion; these officers can assist in the preparation of response plans that are specific to the African context. In Africa, WHO has intercountry support teams staffed by epidemiologists, laboratory specialists and data managers posted in epidemiological blocs serving west Africa, central Africa, the Great Lakes areas, the Horn of Africa and southern Africa. To ensure rapid emergency responses to outbreaks, a regional rapid response network has recently been established. Should Africa experience sporadic human cases of H5N1 infection, all of these resources can provide rapid support. Further support comes from WHO international reference laboratories specialized in H5-subtype viruses and the

Global Outbreak Alert and Response Network which can bring international teams quickly to the scene.

WHO, through its Regional Office for Africa, is establishing a network of influenza laboratories in Africa.[1] These laboratories are being equipped to perform rapid and reliable diagnostic work on influenza viruses. The roles and responsibilities of WHO and African countries during outbreaks of epidemic-prone diseases have been defined in a series of formally adopted protocols.

WHO has issued numerous technical and practical guidelines that can assist all countries in activities ranging from the preparation and rehearsal of response plans to the collection of patient samples and their transportation to WHO reference laboratories. These guidelines can be accessed at the WHO avian influenza website.

Recommended priority actions for African nations

1. Build strong collaboration between various health service sectors

The risk that migratory birds will carry the highly pathogenic H5N1 virus to parts of Africa in the final months of 2005 creates an urgent need for formal mechanisms of collaboration between health, agricultural and veterinary health services. In Africa, 36 countries have put in place systems for the surveillance and reporting of priority diseases through district health personnel. These systems can provide the backbone for building up local surveillance and response capacity and for forming close links with local agricultural and veterinary extension services. In particular, provision should be made for closely linked surveillance, joint investigation of outbreaks, and a constant exchange of information acquired during these activities.

In some countries affected by H5N1 outbreaks in poultry and humans, the high costs to the agricultural sector have resulted in approaches that are not always compatible with the needs and priorities of public health. Given the serious consequences of human cases of H5N1 infections and the potentially catastrophic consequences of a pandemic, priority must be given to the protection of human health whenever outbreaks in poultry or other economically important animals are detected.

[1] The network currently includes the Pasteur Institute laboratories in Algeria, Central African Republic, Côte d'Ivoire, Madagascar and Senegal; the Democratic Republic of Congo's National Institute for Biomedical Research; Kenya's Medical Research Institute; Uganda's Virus Research Institute; and Zambia's Virology Laboratory and University Teaching Hospital.

2. Existing national coordinating bodies should expand their role to include pandemic influenza.

Throughout Africa, committees already exist at national, regional, and district levels to oversee preparedness for epidemics and manage responses to them. Such committees should also oversee pandemic-related activities and ensure representation from the agricultural sector; a mechanism should be introduced to ensure that each sector is aware of its responsibilities and is held accountable. Where possible, a panel of national experts should guide the work of these committees. Nongovernmental organizations and sources of bilateral and multilateral support should be involved early to allow coordinated resource mobilization and concentrated assignment of responsibilities.

3. Improve the capacity of surveillance systems to detect cases and ensure a rapid response.

H5N1-specific capacities should be developed within the existing framework of systems for integrated disease surveillance and response. With the support of the WHO Regional Office, many African countries have already strengthened their surveillance, preparedness and response capacity for outbreaks. Standard case definitions have been developed for priority diseases, including epidemic-prone diseases. Governments are encouraged to use this improved case-based surveillance system to investigate and report suspected cases of human infection with the H5N1 virus. An additional approach is to introduce an early warning system in designated "sentinel" hospitals where staff are trained and equipped to perform case detection and laboratory confirmation, and know how and where to report cases.

Recent experience shows the high level of public anxiety that accompanies the detection of H5N1 in a country, even in the absence of any evidence of human infections. For this reason, a system for rumour surveillance and verification needs to be introduced. National technical guidelines for integrated disease surveillance and response include advice on how to maintain a rumour register and when to report events to WHO. Diagnostic support will be provided by the African network of influenza laboratories and WHO international reference laboratories. Countries with inadequate laboratory capacity should include in their preparedness plans procedures for specimen collection, handling and shipment for external diagnostic confirmation. WHO guidelines are available to support this undertaking.

Timely detection calls for a timely response. African countries, supported by WHO, have considerable experience in the emergency response to outbreaks. This experience is

the basis for responding to sporadic cases of H5N1 infection and the eventual arrival of pandemic influenza. It must be appreciated that the demands placed on health services by an influenza pandemic will rapidly eclipse those seen in epidemics of any other infectious disease. Hospitals need to have crisis management plans that include, among other measures, guidance on triage and dispatch, protocols for case management and treatment, standard operating procedures for prioritization of admission (home, hospital and lazaret), and the maintenance of essential hospital functions under emergency conditions. Governments also need to plan for the establishment of temporary admission units.

4. Develop strategies for the rapid communication of information to the public and the media.

In Africa, activities that can be undertaken by individuals and communities to reduce the risk of infection or slow its spread may be the most powerful tools for reducing morbidity and mortality during a pandemic. Mechanisms need to be in place to communicate messages, based on recommended non-pharmaceutical measures, to the public via broadly accessible communication channels and in a culturally-appropriate language. Mass health promotion campaigns for other diseases in Africa may serve as models. WHO country health promotion officers can provide assistance.

WHO is developing guidelines for communicating with the media during an influenza pandemic. These guidelines should be available before the end of 2005.